



# The New England Journal of Medicine

Formerly the Boston Medical and Surgical Journal

Established 1828

Published by the Massachusetts Medical Society under the Jurisdiction of  
The Committee on Publications

VOLUME 239

JULY-DECEMBER, 1948

# MASSACHUSETTS MEDICAL SOCIETY

## OFFICERS AND STANDING COMMITTEES

<b>President</b> Daniel B Reardon Quincy	<b>Secretary</b> H Quimby Gallupe Waltham	<b>Delegates to American Medical Association</b> Charles J Kichham Brookline Leland S. McKittrick Brookline Patrick J Sullivan Dalton John J Curley Leominster Walter G Phippen Salem Frank W Snow Newburyport
<b>President-Elect</b> Arthur W Allen Boston	<b>Treasurer</b> Elliot Hubbard Jr Cambridge	<b>Director of Medical Information and Education</b> John F Conlin Boston
<b>Vice-President</b> Donald Munro Boston	<b>Assistant Treasurer</b> Norman A Welch West Roxbury	<b>Executive Secretary</b> Robert St. B. Boyd Boston
<b>Committee on Publications</b> Chairman Richard M Smith Oliver Cope John Fallon, James P O'Hare, Conrad Wesselhoeft	<b>Orator</b> C Sidney Burwell Brookline	<b>Executive Offices, 8 Fenway, Boston 15, Telephone KE 6-5162</b>
<b>Committee on Arrangements</b> Chairman Harold G Giddings John W Norcross Franklin G Balch Jr, Gordon Donaldson Albert Ehrenfried	<b>Committee on Public Health</b> Chairman Roy J Ward John J Poutas Warren R Sisson Lawrence J Smith Conrad Wesselhoeft	
<b>Committee on Ethics and Discipline</b> Chairman Ralph R Stratton William J Brickley Archibald R Gardner, Fred R Jovett Allen G Rice	<b>Committee on Medical Defense</b> Chairman Horatio Rogers Edwin D Gardner Charles J Kichham John E Moran, William R Morrison	
<b>Committee on Medical Education</b> Chairman Chester S Keefer James M Faulkner, George D Henderson Isaac R. Jankelson Robert T Monroe	<b>Committee on Society Headquarters</b> Chairman Frank R Ober Albert A Hornor Walter G Phippen George L. Steele	
<b>Committee on Membership</b> Chairman Lewis S Pilcher William A R Chapin Perce H Leavitt, Francis P McCarthy Samuel A Vose John E Moran Kathleen S Snow * Bancroft C Wheeler *	<b>Committee on Finance</b> Chairman Robert W Buck Francis C Hall Fabian Packard Bancroft C Wheeler Charles F Wilensky	
*Representing the supervising censors	<b>Committee on Industrial Health</b> Chairman Daniel L Lynch Joseph C Aub Louis R Daniels John G Downing Harold R Kurth Frederic N Manley Henry C Marsh	

## OFFICERS OF THE SECTIONS

<b>Medicine</b> Chairman Laurence B Ellis Cambridge vice chairman, Allen S Johnson, Longmeadow secretary James A. Halsted Dedham	<b>Radiology</b> Chairman Albert M. Moloney Boston secretary Lawrence Robbins Boston
<b>Surgery</b> Chairman Robert E. Gross Boston secretary Franklin G Balch Jr Boston EXECUTIVE COMMITTEE — J Hartwell Harrison Brookline	<b>Physical Medicine</b> Chairman David C. Ditmore Boston secretary Arthur L. Watkins Boston
<b>Pediatrics</b> Chairman W Bradford Adams Springfield secretary Gerald N. Hoeft Boston	<b>Dermatology and Syphilology</b> Chairman Francis P McCarthy Boston secretary Alfred Hollander Springfield
<b>Obstetrics and Gynecology</b> Chairman James F Conway Brookline vice chairman Daniel J McSweeney Boston and Milton secretary Duncan E Reid Boston	<b>Anesthesiology</b> Chairman Morris J Nicholson Boston secretary Jacob Fine Beverly
	<b>Physiology and Pathology</b> Chairman Monroe J Schlesinger Newton secretary Donald A. Nickerson Melrose

## OFFICERS OF THE DISTRICT MEDICAL SOCIETIES FOR 1948-1949

<b>BARNSTABLE</b> — President Henry P Hopkins Chatham vice president Arthur J. DeLoa Harwichport secretary Frederick Sanborn Osterville treasurer Frank Travers Barnstable librarian Carroll H Keene Chatham executive and public relations councilor Paul P Henson Hyannis legislative councilor Julius G Kelley Pocasset.	<b>MIDDLESEX EAST</b> — President Milton J Quinn Winchester vice-president Ira W Richardson Wakefield secretary Roy W Layton Melrose treasurer Charles W DeWolf Wakefield librarian Angelo L. Majetta Winchester executive councilor Kenneth L. MacLachlan Melrose public relations councilor Milton J Quinn Winchester legislative councilor Justin L. Anderson Reading
<b>BERKSHIRE</b> — President George S Reynolds Pittsfield vice president N B McWilliams Williamstown secretary Daniel N Beers Pittsfield treasurer Theodore W Jones Pittsfield executive councilor Helen M Scoville Pittsfield public relations councilor Patrick J Sullivan Dalton legislative councilor John Hughes Pittsfield	<b>MIDDLESEX NORTH</b> — President James Y. Rodger Lowell vice president Harry Coburn Lowell secretary Brendan D. Leahy Lowell treasurer Mason D. Bryant Lowell executive councilor William M. Collins Lowell public relations councilor Samuel A. Dibbins Lowell legislative councilor Joseph Sweeney Lowell
<b>BRISTOL NORTH</b> — President Joseph V. Cbatigny Taunton vice-president James H. Brewster Attleboro secretary William E. Dawson Taunton treasurer Charles E. Hoyer Taunton executive councilor Joseph L. Murphy Taunton public relations councilor Milton E. Johnson Attleboro legislative councilor William M. Stobbs Attleboro	<b>MIDDLESEX SOUTH</b> — President John F. Casey Allston vice president James Marvin Baty Belmont secretary Alexander A. Levi Newton treasurer Fabian Packard Belmont orator Alfred O. Ludwig Belmont executive councilor Joseph C. Merriam Framingham public relations councilor Ralph H. Wells Lexington legislative councilor Kenneth J. Tillotson Belmont
<b>BRISTOL SOUTH</b> — President Aubrey J. Pothier New Bedford vice-president John S. Fielden Fall River secretary and treasurer James E. Fell Fall River executive councilor Richard B. Butler Fall River public relations councilor Harold E. Perry New Bedford legislative councilor Curtis C. Tripp New Bedford	<b>NORFOLK</b> — President George W. Papen Brookline vice president W. Richard Obler Jamaica Plain secretary Basil E. Barton West Roxbury treasurer Albert Ehrenfried Brookline executive councilor Charles J. E. Kichham Jamaica Plain public relations councilor Dean S. Luce Canton legislative councilor Solomon L. Skvirsky Brighton
<b>ESSEX NORTH</b> — President Robert E. Blais Amesbury vice president Z. William Celson Lawrence secretary and public relations councilor Harold R. Kurth Lawrence treasurer J. Leroy Wood Lawrence librarian Frank W. Stockwell Newburyport executive councilor Rolf C. Norris Methuen legislative councilor Nicandro F. DeCesare Lawrence	<b>NORFOLK SOUTH</b> — President Frederick Hinchliffe Cohasset vice president Edmund B. FitzGerald Wollaston secretary and librarian Ebenezer K. Jenkins South Braintree treasurer Raymond G. Vinal Norwell executive councilor Robert L. Cook Quincy public relations councilor Henry A. Robinson Hingham legislative councilor David L. Belding Hingham
<b>ESSEX SOUTH</b> — President Edward L. Peirson Salem vice president Burlingh B. Mansfield Ipswich secretary Henry D. Stebbins Salem treasurer Andrew Nichols and Danvers executive councilor Albert E. Parkhurst Beverly public relations councilor Bernard Appel Lynn legislative councilor Lonor Grimes Swampscott	<b>PLYMOUTH</b> — President George A. Buckley Brockton vice president Mildred L. Ryan Brockton secretary Samuel Gale Brockton treasurer Henry Rahnowitz Brockton librarian John H. Weller Bridgewater executive councilor George A. Moore Brockton public relations councilor Charles D. McCann Brockton legislative councilor Alfred L. Duncombe Brockton
<b>FRANKLIN</b> — President and executive councilor Lawrence R. Dame Greenfield vice president Fernand Freeman Greenfield secretary and treasurer Milton M. Sisson Greenfield public relations councilor John E. Moran Greenfield legislative councilor Harold R. Mahar Orange	<b>SUFFOLK</b> — President Alexander J. A. Campbell Brighton vice president Lawrence J. McCarthy Chelsea secretary Charles G. Shedd Wellesley treasurer Sidney C. Wiergo Waban executive councilor Harvey A. Kelly Winthrop public relations councilor Howard F. Root Boston legislative councilor William E. Browne Boston
<b>HAMPDEN</b> — President Robert Hildreth Westfield vice president and legislative councilor Arthur Riordan Springfield secretary and treasurer Walter Williams Springfield executive councilor Archibald Doug as Westfield public relations councilor Frederic Haer Springfield	<b>WORCESTER</b> — President John J. Dumphy Worcester vice-president Bancroft C. Wheeler Worcester secretary Donald Hirsch Worcester treasurer Arthur D. Ward Worcester librarian Philip H. Cook Worcester executive councilor John Fallon Worcester public relations councilor Nicholas S. Scarcello Worcester legislative councilor John B. Butts Worcester
<b>HAMPSHIRE</b> — President Edward J. Manwell Northampton vice president Henry Tadeell Belchertown secretary and treasurer F. Mary P. Snook Worthington librarian Abbie M. O'Keefe Northampton executive councilor Maurice Kennedy Hadley public relations councilor Joseph R. Hobbs Williamsburg legislative councilor Justin E. Hayes Northampton	<b>WORCESTER NORTH</b> — President Donald B. Cheatham Athol vice president and legislative councilor C. Bertram Gay Fitchburg secretary James G. Simmons Fitchburg treasurer Frederick H. Thompson Jr Fitchburg executive councilor John J. Curley Leominster public relations councilor James V. McHugh Leominster

# INDEX TO The New England Journal of Medicine

Volume 239, July 1, 1948 to December 30, 1948

## PAGES ACCORDING TO WEEKLY ISSUES

PAGES	No	DATE	PAGES	No	DATE
1-34	1	July 1	493-530	14	Sept. 30
35-74	2	July 8	531-564	15	Oct. 7
75-106	3	July 15	565-604	16	Oct. 14
107-158	4	July 22	605-644	17	Oct. 21
159-212	5	July 29	645-692	18	Oct. 28
213-244	6	Aug. 5	693-728	19	Nov. 4
245-282	7	Aug. 12	729-762	20	Nov. 11
283-316	8	Aug. 19	763-800	21	Nov. 18
317-352	9	Aug. 26	801-844	22	Nov. 25
353-382	10	Sept. 2	845-902	23	Dec. 2
383-418	11	Sept. 9	903-944	24	Dec. 9
419-452	12	Sept. 16	945-984	25	Dec. 16
453-492	13	Sept. 23	985-1020	26	Dec. 23
			1021-1060	27	Dec. 30

## BOOK REVIEWERS

Allen, Frank N	Fitz, Reginald	Murphy, Rosemary A
Anderson, James O	Friedman, Emerick	Nathanson, Ira T
Appel, Bernard	Goldberg, Bernard I	Nowak, Stanley J G
Ballard, James F	Goodale, Robert L	O'Brien, Frederic W
Benda, Clemens E.	Gould, L V	O'Hara, Dwight
Bland, Edward F	Green, Robert M	Phaneuf, Louis E
Brown, Ethan A	Hayden, E Parker	Pippitt, Richard B
Brues, Austin M	Hirsch, Oskar	Pope, Alton S
Buck, Robert W	Hooker, Sanford	Quigley, Thomas B
Carbone, Hubert A	Joslin, Elliott P	Resnik, Joseph
Castleman, Benjamin	Kazanjian, Varaztad H	Robey, William H
Christian, Henry A	Kelemen, George	Root, Howard F
Chute, Richard	Kettle, Ronald H	Savitz, Harry A
Cogan, David C.	Konikow, William M	Shattuck, George C
Colby, Fletcher H	Krumbhaar, George D	Smith, George G
Colcock, Bentley P	Kuhns, John G	Smith, Richard M
Colett, Ilse V	Lahev, Frank H	Sosman, Merrill C
Daland, Ernest M	Lanc, C Guy	Spector, Benjamin
Dameshek, William	Leavitt, Peirce H	Sprague, Howard B
Dearborn, Lester W	Lever, Walter F	Stetson, Charles G
Deutsch, Emmannel	Lombard, Herbert L.	Stone, Moses J
Di Cori, Ferruccio	Lowry, Franklin P	Viets, Henry R
Dodge, Carroll V	Ludvig, Elek J	Waite, J Herbert
Downing, John G	Lurie, Moses H	Warren, Kenneth W
Edwards, Edward A.	Marble, Alexander	Wesselhoeft, Conrad
Farber, Sidney	McCarthy, Francis P	Wheeler, Ralph E
Faulkner, James M	Meigs, Joe V	White, Franklin W
Faxon, Nathaniel W	Meltzer, Philip E	White, Paul D
Feemster, Roy F	Milone, Joseph E	Wiggin, Sidney C.
Fine, Jacob	Moore, Merrill	Wittenberg, H W
Finland, Maxwell	Morrison, Hyman	

## KEY TO ABBREVIATIONS

c — correspondence  
cr — case record  
e — editorial  
ma — medicolegal abstract

mdph — Massachusetts Department of Public Health  
mms — Massachusetts Medical Society  
mp — medical progress  
misc — miscellany

ness — New England Surgical Society  
n — notice  
o — obituary  
\* — original article

## SUBJECT INDEX

## A

- ABSCESS Amebic [Drake & Warthin] 45\*  
 ACCIDENTS 1055 - c  
 ACTINOMYCOSIS [Pittman] 558 - cr  
 ADDISON'S DISEASE [Aub] 935 - cr  
     [Ravreby & Sawyer] 110\*  
 ADENOMA [Souder & Kingsley] 459\*  
 ADOPTION [Jones] 242 - c  
 ALCOHOLISM Chronic Therapy [O'Hollaren & Lemere] 551  
 ALLERGY Instruction 981 - c  
     Prophylaxis [Shulman] 591\*  
 ALIARENGA prize 548 - misc  
 AMERICAN ACADEMY OF DERMATOLOGY AND SYPHILOLOGY,  
     Dec. 4-9, 728 - n  
 AMERICAN ACADEMY OF GENERAL PRACTICE, Mar 7-9,  
     728 - n  
 AMERICAN ASSOCIATION FOR ADVANCEMENT OF SCIENCE  
     415 - c  
 AMERICAN ASSOCIATION OF SCHOOLS OF SOCIAL WORK,  
     Jan 27-29, 984 - n  
 AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY, Inc.,  
     Feb 4, 1949, 244 550 984 - n  
 AMERICAN BOARD OF OPHTHALMOLOGY 492 - n  
 AMERICAN BOARD OF SURGERY [Harvey] 159 - nss  
 AMERICAN CANCER SOCIETY, Incorporated, Nov 6-7, 644 - n  
 AMERICAN COLLEGE OF CHEST PHYSICIANS (president)  
     242 - misc  
 AMERICAN COLLEGE OF PHYSICIANS, Mar 28-Apr 1, 158 - n  
     Research fellowships 158 - n  
 AMERICAN COLLEGE OF SURGEONS, Oct. 18-22, 54, 417 - n  
 AMERICAN FEDERATION FOR CLINICAL RESEARCH, Dec. 4,  
     644 - n  
 AMERICAN PUBLIC HEALTH ASSOCIATION, Nov 8-12 725 - c  
 AMERICAN SOCIETY OF ANESTHESIOLOGISTS, Inc., Oct. 1-2,  
     382, Nov 4-6, 418 - n  
 AMERICAN SOCIETY FOR STUDY OF ARTERIOSCLEROSIS,  
     Oct 31-Nov 1, 550 - n  
 AMERICAN TRUDEAU SOCIETY, Oct. 15 418 - n  
 AMINO ACIDS Injection [Eckhardt & Davidson] 164\*  
 AMPOTILES Siliform 552 - n  
 ANEMIA Pernicious [Berk & others] 911\*  
 ANESTHESIA Transtracheal [Harken & Salzberg] 585\*  
 ANNOUNCEMENTS  
     Abbott, Richard N. 492  
     Aranson, Albert 212  
     Bloomenthal, H Myer 550  
     Courtiss, Morris 800  
     Davis, William L. 844  
     Holden, Robert B. 244  
     Horwitz, William H. 212  
     Inman, W. Charles 551  
     Israelhau, A. G. 550  
     Kaufman, Manuel 800  
     Kennard, Harrison E. 417  
     Lendgren, Carl V. 762  
     Leonard, Field C. 944  
     McKittick, John B. 551  
     McKittick, Leland S. 551  
     Miller, Harold I. 985  
     Pilcher, Lewis S. 644  
     Quigley, Thomas B. 282  
     Risley, Thomas S. 551  
     Rowland, William D. 244  
     Rubin, Abraham L. 550  
     Ryan, William F. 551  
     Sagall, Elliot L. 844  
     Sieve, Benjamin F. 692  
     Snedeker, Lendon 642 - misc  
     Stone, Edward S. 985  
     Thomas, Jackson M. 604  
     Thurman, Aaron 417  
     Tullis, James L. 604  
 ANTIBIOTICS [Kuffel & others] 107\*  
 ANUS Sphincter Diseases [Newton & Macgregor] 113\*  
 ARMY Rations 209 - c  
 ARTERIES Diseases [Edwards] 362\*  
 ARTERIOSCLEROSIS Coronary [Ellis] 589 - cr  
     Necrotic lesions [Edwards] 571\*  
 ARTHRITIS AND RHEUMATISM FOUNDATION 452 - misc

- ARTHRITIS Rheumatoid [Jacobson] 1047 - cr  
 ASTHMA In children [Hill] 1039\*  
 ATOMIC age 278 - c  
     Energy Medical aspects [Warren] 765 - mms

## B

- BAL [Randall & Secler] 1004, 1040 - mp  
 BARUCH COMMITTEE report 414 - c  
 BEHAVIOR Aggressive [Alexander] 10\*  
 BERGWELL, WALTER [Gallupe] 105 - c  
 BLOOD [Gibson] 544, 579 - mp  
     Tests 542 - mdph  
 BLUE CROSS 1016 - c  
     British Columbia 642 - misc  
 BLUE CROSS-BLUE SHIELD  
     Blue Cross 529  
     Blue Shield Costs 602  
     Infants Premature 691  
     Obstetrics Coverage 452  
     Secretary meetings 642  
 BLUE SHIELD 52 - misc, 1016 - c  
     Infant Premature 450 - c  
 BOOK REVIEWS  
     Andrews, E. 35  
     Bancroft, F. W. 74  
     Bartley, S. H. 349  
     Beach, F. A. 727  
     *Biochemistry of Cancer* [Greenstein] 645  
     *Brief Psychotherapy* [Frohman] 942  
     Brown, E. L. 941  
     *Case Histories in Clinical and Abnormal Psychology* 727  
     Chute, E. 549  
     Clark-Kennedy, A. E. 35  
     Colwell, A. R. 945  
     *Congenital Malformations of Heart* [Tausig] 105  
     Copeman, W. S. C. 727  
     *Diabetes Mellitus in General Practice* [Colwell] 945  
     *Diagnosis and Treatment of Dental Disease* [Fradkin] 157  
     *Diseases of Joints and Rheumatism* [Stone] 549  
     Ehrenwald, J. 799  
     *Emotional Maturity* [Saul] 35  
     *Epithelia of Woman's Reproductive Organs* [Papanicolaou  
         & others] 1020  
     *Fatigue and Impairment in Man* [Bartley & Chute] 349  
     Follis, R. H., Jr. 942  
     Fradkin, W. Z. 157  
     Frohman, B. S. 942  
     *Gastritis* [Schindler] 348  
     Geckeler, G. D. 242  
     Goldberger, E. 1020  
     Greenstein, J. P. 645  
     Hamilton, W. F. 549  
     *Heart* [Luisada] 602  
     *History of Scientific Ergonomics* [Andrews] 35  
     *Hodgkin's Disease and Allied Disorders* [Jackson & Parker]  
         901  
     *Hormones and Behavior* [Beach] 727  
     *Human Gastric Function* [Wolf & Wolf] 242  
     Jackson, H., Jr. 901  
     Lehtinen, L. E. 645  
     Luisada, A. A. 602  
     Marchetti, A. A. 1020  
     *Medicine* [Clark-Kennedy] 35  
     *Nursing for Future* [Brown] 941  
     Papanicolaou, G. N. 1020  
     Parker, F., Jr. 901  
     *Pathology of Nutritional Disease* [Follis] 942  
     *Psychopathology and Education of Brain-Injured Child*  
         [Strauss & Lehtinen] 645  
     *Radium Dosage Manchester System* 35  
     Saul, L. J. 35  
     Schindler, R. 348  
     *Stethoscopic Heart Records* [Geckeler] 242  
     Stone, K. 549  
     Strauss, A. A. 645  
     *Surgical Treatment of Abdomen* [Bancroft] 74  
     Tausig, H. B. 105  
     *Telepathy and Medical Psychology* [Ehrenwald] 799  
     *Textbook of Human Physiology* [Hamilton] 349

Traut, H F 1020  
*Treatment of Rheumatism in General Practice* [Copeman] 727  
*Unipolar Lead Electrocardiography* [Goldberger] 1020  
 Wolf, S 242  
 Wolff, H G 242  
 BOSTON CITY HOSPITAL [McSweeney & Hassett] 254\*  
     House Officers' Association, Nov 16, 23 and 30, 762,  
     Dec 14, 902 - n  
 BOSTON MEDICAL LIBRARY 490  
     Librarian's report [Viets] 84\*  
     President's report [Phippen] 83\*  
 BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY, Nov 18,  
     762, Dec 15, 944 - n  
 BOSTON STATE HOSPITAL. Psychiatric seminar schedule,  
     Nov 17-Jan 26, 762 - n  
 BOSTON UNIVERSITY SCHOOL OF MEDICINE, 1848-1948, 639 - o  
 BRAIN Tumors. Diagnosis [Redlich & others] 945\*  
 BRONCHIAL ABSCESS [Simmons] 443 - cr  
 BRONCHI Tumors [Schier] 592 - cr  
     [Souders & Kingslev] 459\*  
 BRONCHOSCOPY. Anesthesia [Harkcn & Salzberg] 383\*  
 BRUCE memorial lecture and medal 212 - misc

C

CALCULI. Urinary [Cristol & others] 427\*  
 CANCER. Free monographs 692 - n  
 CARCINOMA [Bauer] 894 - cr  
     [Chapman & others] 145 - cr  
     [Cogan] 837 - cr  
     [Culver] 231 - cr  
     [Faxon] 506 - cr  
     [Gaudrault] 56\*  
     [Hopkins & Tate] 501\*  
     [McKittrick] 95 - cr  
     [Schier] 592 - cr  
     [Smith] 64 - cr  
     [Sosman] 834 - cr  
     [Sweet] 720 - cr  
     [Townsend] 274 - cr  
 CARDIOVASCULAR defects. Arterial grafts [Gross & others]  
     578\*  
 CASTLE, WILLIAM B. 212 - misc  
 CESAREAN section. Statistics [McSweeney & Hassett] 254\*  
 CHILD safety 525 - e  
 CHILDREN. Crippled 451 - mdph  
 CHILDREN'S BUREAU. Advisory committee 797 - misc  
 CHISHOLM, BROCK 450 - e  
 CHLOROMYCETIN 239 - e  
 CHRISTMAS seals 840 - e  
 CLUTE MEMORIAL 691 - misc  
 COLD. Common 563 - e  
 COLITIS [Short] 635 - cr  
 COLLEGE OF AMERICAN PATHOLOGISTS, Sept. 18, 418 - n  
 COLON. Obstruction [Gaston & Costin] 705\*  
     Tumors [Welch] 897 - cr  
 COLORADO STATE MEDICAL SOCIETY, Sept. 22-25, 418 - n  
 COMA. Hepatic [Murphy & others] 605\*  
 CONNECTICUT. Postgraduate medical education, 451 - e  
 CORBETT, JOHN R. [Gallupe] 105 - c  
 COREA, ARTHUR G. [Gallupe] 105 - c  
 COUNCIL, Oct. 6, 688 - e  
 COUNCILMAN, W T [Christian] 74 - c  
 COUNTRY doctor 312 - e  
     [Chase] 283 - mms

D

DEAFNESS. Fenestration treatment [Johnson] 619\*  
 DEATH. Causes 71 - e  
     Medicolegal 1017 - e  
 DEATHS  
     Allen, William H 691  
     Appel, Bernard H 488  
     Barnes, Henry 842  
     Barton, Robert B 983  
     Capeles, Thomas F 348  
     Carroll, Henry G 348  
     Crotty, Martin F 30  
     Dahlen, Carl A 941  
     Denn, Francis P 488  
     Doucett, Frederick L 103  
     Dunphy, Henry A 691

Elkavich, Frank D 348  
 Faunce, Calvin B 691  
 Felch, Carrie I 103  
 Flagg, Elisha 73  
 Glassman, Nathan B 842  
 Grainger, Edward J 348  
 Holt, Earl K 941  
 Houghton, Henry L 103  
 Klein, George 691  
 Ledbury, John W 241  
 Lindsay, Joseph I 103  
 Lubinski, Henry 691  
 MacCorison Carl C 103  
 Mailey, H Douglas 842  
 Marsh, Arthur W 348  
 Myerson, Abraham, 488, 982 - o  
 Paine, N Emmons 983  
 Pare, Francis M 103  
 Pratt, William P 382  
 Raymond, Loring H 941  
 Rosmarin, Ernest 315  
 Schwager, Solomon 983  
 Small Albert E 73  
 Stratton Harold L 211  
 Strong, Richard P 241, 489 - o  
 Torner, George H 103  
 DENVY-BROWN, DEREK [Gallupe] 105 - c  
 DEPRESSION. Mental treatment [Altschule & Tillotson] 1036\*  
 DIABETES 795 - e  
     [Root] 797-c  
     Amputation [Root] 453\*  
     Mellitus [Beaser] 765\*  
     Surgery [Kuffel & others] 107\*  
 DIBENAMINE. Diagnostic agent [Spear & Griswold] 736\*  
 DICUMAROL [Palmer & Gundersen] 818\*  
     Therapy [Wishart & Chapman] 701\*  
 DIPHTHERIA. Therapy [Crawford] 220\*  
 DISEASES. Reporting 1058 - mdph  
 DIVERTICULITIS [LeRover & White] 245\*  
 DRAFT. Physicians [Brun] 983 - c  
 DRUG. Advertisement 900 - e  
 DUODENUM. Carcinoma [Chapman] 145 - cr

E

ECHINOCOCCUS cyst [Kranes] 205 - cr  
 EDEMA [Peters] 353\*  
 EDITORIALS  
     Accidents 1055  
     Allergy. Instruction 981  
     American Association for Advancement of Science 415  
     American Public Health Association Nov 8-12, 723  
     Army medical training program 597  
     Army. Rations 209  
     Atomic age 278  
     Baruch Committee report 414  
     Blue Cross and Blue Shield 1016  
     Blue Shield. Premature infant 450  
     Boston University School of Medicine, 1848-1948, 639  
     Child safety 525  
     Chloromycetin 239  
     Christmas seals 840  
     Cold. Common 563  
     Connecticut. Postgraduate medical education 451  
     Council, Oct. 6, 688  
     Country doctor 312  
     Death. Causes 71  
     Medicolegal 1017  
     Diabetes 795  
     Drug. Advertisements 900  
     Embryonic infections 281  
     Eskimos. Tuberculosis 725  
     Eye bank. Boston 239  
     Fee-splitting. Prescriptions. Eye glasses 102  
     Geniatrics 154, 487  
     Gesell, Arnold 1057  
     Gonorrhea. Penicillin-resistant 411  
     Grafts. Arterial 595  
     Great Britain. National Health Service Act 72  
     Greater Boston Community Fund 595  
     Health bills. National 102  
     Health programs. International 563

Health services 899, 982  
Hepatitis Syringe-transmitted 70  
Hospitals Voluntary 28  
India Public health 757  
Influenza and pneumonia 959  
*Japanese Medical Journal* 758  
Legs Artificial 311  
Leptosy Treatment 580  
Life Insurance Medical Research Fund 564  
Life Philosophy 315  
Lung Military lesions 155  
Mamm crypts Medical 721  
Massachusetts General Hospital Case Records 690  
Massachusetts Medical Benevolent Society 899  
Massachusetts Physicians Committee 981  
Medical care Costs 211  
Medical service 640  
Medicine Practice Moral status 1017  
Social 562  
Neuburger, Max 581  
New England Heart Association Pencilin fund 901  
New England Postgraduate Assembly Nov 25 611  
New York 1055  
Nursing 958  
History 725  
Nutrition 100  
Oysters Pollution 210  
Parenthood Planned 347  
Pencilin 811  
Dose 756  
Pencilin in syphilis 526  
Pennsylvania State Medical Society 186  
Philosophy and medicine 155  
Physicians Draft 755  
Physicians Society members 842  
Physicians Status 640  
Pickle, William N 149  
Polymyxin 315  
Population 186  
Practitioner General 791  
Price 889 525  
*Providence Evening Bulletin* 208  
Public relations 188  
Q fever and raw milk 29  
Railway car sanitation 527  
Reading Disability 210  
Red Cross 691  
Rehabilitation 795  
Respiratory infections and handkerchiefs 1057  
Rubella and pregnancy 347  
Rutland State Sanatorium 689  
Sherrington Neurophysiology History 101  
Smallpox to tetanus 70  
Statistics Medical 596  
Storlow House 582  
Streptomycin 279  
Thorndike Memorial Laboratory 345  
Thyroid Nodule 238  
Trichinosis 114  
Tropical diseases in New England 29  
Tuberculosis Increase 796  
Vaccination Compulsory 379  
Vaginal smear 316  
Veterans Administration Educational program 152  
*Los Populi* 540  
Washington Hospital 1018  
White Pencil 910  
World Health Organization 30 450  
World relief 980  
Electroconvulsive therapy [Kaldick & others] 773\*  
Epilepsy Surgery [Towne] 225\*  
Eris Ricketts [Gallup] 105 - c  
Eris disc [Crosby] 212 - c  
Eris infections 281 - c  
EMC Program Reimbursement 642 - mdph  
Erysipelas [Adams & Weinstein] 865 - mp  
Erysipelas Bacterial [Kraus] 716 - cr  
Subacute bacterial [Ripport & Ellis] 951\*  
[Mencely] 708\*  
Treatment [Cressy & others] 497\*  
Erysipelas 379 - c  
Erimology [Pickle] 119\*

Enthesis Local [White & others] 1 - mm  
Erythematous Lupus [Warran & Badger] 565\*  
Erysipelas Tuberculosis 725 - c  
Erysipelas Ulcer [Scannell] 752 - cr  
Essay Price 525 - c  
Erythrasma 1017 - c  
Eye bank Boston 259 - c  
Glasses Prescriptions 102 - c

## I

Iatrogenic tubes [Uffelder] 67 - cr  
Iatrogenic [Rosen & Scannell] 367\*  
Iatrogenic Bureau of Investigation 282 492 - n  
Iatrogenic 102 - c  
Iatrogenic [Cattell] 972 - cr  
Iatrogenic 726 - mm  
Iatrogenic 212 - mm  
Iatrogenic 418 - n  
Iatrogenic [Downing & Becker] 862\*

## G

Gay Bladder Carcinoma [Townsend] 274 - cr  
Gastritis [Mekutrick] 95 - cr  
Garcia R Rivas (License Deprivation) [Schadt] 845 - c  
Gastritis Chronic [Hale] 406 - cr  
Geriatrics 154 187 - c  
Gestalt Arnold 1057 - c  
Ginsburg David (License Restoration) [Schadt] 602 - c  
Giovannetti, Humbert [Gallup] 105 - c  
Gonorrhea Nodular [Anglem & Bradford] 217\*  
Gonorrhea Pencilin-resistant 411 - c  
Gonorrhea Arthur M [Gallup] 105 - c  
Gratton State Hospital 490 - mm  
Gratton Artificial 595 - c  
[Gross & others] 578\*  
Great Britain National Health Service Act 72 - c  
Greater Boston Community Fund 595 - c  
Greater Boston Medical Society Nov 16 762 Dec 21, 954 - n

## H

Hamden District Medical Society Program 492 - n  
Harvard Medical Society Oct 12 550 Nov 9, 728, Dec 14 902 Jan 11 1060 - n  
Hawaii bills National 102 - c  
Education 281 - mm  
Programs International 565 - c  
Services 899 982 - c  
[Archibald & others] 858\*  
Haver Congestive Failure [Wishart & Chapman] 701\*  
Diseases 31 - mdph  
[Adams] 680 - cr  
[Archer] 375 - cr  
[Spray] 685 - cr  
Hartman Treatment [Kardon] 575\*  
Hematomas Subdural [Hale & Gardner] 495\*  
Hemochromatosis [Hamer & Bowen] 995\*  
[Townsend] 1000 - cr  
Hematuria [Taylor] 1012 - cr  
Syringe-transmitted 70 - c  
Viral [Gillis & Janeway] 305 - mp  
Hodgkin's Disease [Jackson] 1059 - c  
Hospitals  
Boston City Hospital House Officers Association Nov 16 25 and 30 762 Dec 14 902 - n  
Boston State Hospital Psychiatric seminar schedule Nov 17-Jan 26 762 - n  
Gratton State Hospital 490 - mm  
Metropolitan State Hospital 550 Oct 1-May 20 418 - n  
Mount Auburn Hospital Tumor clinic 544 - n  
New England Hospital for Women and Children Nov 4 692 Dec 2 84 Jan 6, 1060 - n  
New York Post-Graduate Hospital 316 - n  
[Joseph H] Pratt Diagnostic Hospital medical conference program Oct 8 29 564 Dec 5-24 902 Jan 4-28, 1060 - n  
Hospitals Administration [Bluestone] 258\*  
Care 281 - mdph  
[Gettling & others] 1028\*

Patient costs 528 - mdph  
Students 212 - misc  
Voluntary 28 - c  
OOK, MARION [Gallupe] 105 - c  
UBSCH, HUGO BOB 282 - n  
UNDREN YEARS AGO 315  
HYPERTENSION [Burgess] 75\*  
Essential prognosis [Palmer & others] 990\*  
[Palmer & others] 322\*  
Paroxysmal [Thompson & Witham] 291\*  
Rice diet [Contratto & Rogers] 531 - mms  
Treatment [London & London] 491 - c

## I

ILEUM Tumors [Schatzki] 632 - cr  
IMMUNIZATION 70 - c  
INDIA Public health 757 - c  
INDIANA STATE MEDICAL ASSOCIATION, Oct 26-28, 418 - n  
INFANTILE PARALYSIS Fellowships 984 - n  
INFANTS Care program 528 - mdph  
Premature 450 - c  
Tumors [Kirkirk & Hudson] 468\*  
INFECTIONS [Heusner] 845\*  
INFLUENZA 939 - c  
INSURANCE Medical research fund 564 - c  
INTER-AMERICAN CONGRESS OF RADIOLOGY, Nov 11, 1949,  
158 - n  
INTERSTATE POSTGRADUATE MEDICAL ASSOCIATION OF  
NORTH AMERICA Nov 9-12, 644 - n  
INTESTINES Deformities [Burgin] 97 - cr  
INTUBATION Miller-Abbott [Caruolo] 596\*  
INTUSSUSCEPTION [Gross & Ware] 645\*  
ISOLATION 1058 - mdph

## J

*Japanese Medical Journal* 758 - c

## K

KALA-AZAR [Wilner & Haedickel] 250\*  
KENTUCKY STATE MEDICAL ASSOCIATION, Sept. 27-30, 418 - n  
KIDNEY Biopsy [Castleman & Smithwick] 729\*  
Cyst [Chute] 790 - cr  
Diseases [Hall & Luetscher] 621 - mp

## L

LAKEVILLE STATE SANATORIUM 415 - mdph  
LEARY, ALFRED (License Deprivation) [Schadt] 602 - c  
LEGS Artificial 314 - c  
LEPROSY Treatment 580 - c  
LEVER BROTHERS COMPANY Medical director 564 - misc  
LEUKEMIA Bone and joint pain [Wolfson & Aisner] 156 - c  
LICENSES Deprivation [Schadt] 602, 843 - c  
Restoration [Schadt] 602 - c  
LIFE Philosophy 515 - c  
LIPEMIA [Lenzner & Bowen] 998\*  
LIVER Abscess [Drake & Warthin] 45\*  
Cirrhosis [Ropes] 519 - cr  
Cyst [Robbins] 517 - cr  
Hepatoma [Reyersbach] 339 - cr  
Injury Treatment [Papen & Mikal] 920\*  
LOBECTOMY [Holmes] 539\*  
LUNGS Abscess [Brailey] 482 - cr  
Carcinoma [Sosman] 834 - cr  
[Franseen] 787 - cr  
Military lesions 155 - c  
Tumors [Chapman] 408 - cr  
LYMPHOXIA Malignant [Davenport] 25 - cr  
[Taylor] 254 - cr  
LYNCH, WILLIAM M [Gallupe] 105 - c

## M

MacKNIGHT, RICHARD P 156 - mdph  
MAINE MARITIME ACADEMY 984 - n  
MALARIA [Geiman] 18, 58 - mp  
Vivax [Jordan] 397\*

MALPRACTICE 796 - mms 1018 - ma  
MANUSCRIPTS Medical 724 - c  
MARKLE FOUNDATION grants 352 - n  
MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH  
Blood tests 842  
Children Crippled 451  
Crippled children clinics, Oct 1-28, 490, Nov 1-22, 642,  
Dec 1-27, 843, Jan 3-24, 1059  
Diseases, communicable May 73, June 211, July, 415,  
Aug, 601 Sept., 726, Oct., 941  
Diseases Reporting 1058  
EMIC program Reimbursement 642  
Heart disease 51  
Hospital care 281  
Hospitals Division director 156  
Hospitals Patient costs 528  
Infant-care program 528  
Isolation 1058  
Lakeville State Sanatorium 415  
Maternal and infant care program 528  
Patients Cost of care 526  
Quarantine 1058  
Rheumatic fever Fellowships 241, 415  
Rice diet 759  
Rocky Mountain spotted fever 103  
Vaccine 642  
Tick survey [Ayres & Feemster] 760  
Typhoid vaccine 797  
Wood-tick study 348  
MASSACHUSETTS Diseases [Horton & Rubenstein] 169\*  
MASSACHUSETTS GENERAL HOSPITAL Case records 690 - c  
Health services [Archibald & others] 858\*  
Hospital facilities [Getting & others] 1028\*  
Research Council, Dec 1 844 - n  
MASSACHUSETTS MEDICAL BENEVOLENT SOCIETY 899 - c  
MASSACHUSETTS MEDICAL SOCIETY  
Applicants for fellowship 597  
Atomic energy Medical aspects [Warren] 763  
Council, Oct. 6, 688 - c  
Council and committee meetings Attendance 796  
Council proceedings, May 24, 127, Oct. 6, 876  
Country doctor [Chase] 283  
Epilepsy Focal [White & others] I  
Hampden District 940  
Malpractice 796  
Medicine Industrial [Shipman] 615  
Membership Deprivations 527  
Military service Classification 156  
Physicians Society members 842 - c  
Poliomyelitis [Lawson] 994  
Proceedings of one hundred and sixty-seventh anniversary,  
May 25-27, 183  
Rice diet [Contratto & Rogers] 531  
Veterans Administration 240  
Fee guides 758  
MASSACHUSETTS MEDICO-LEGAL SOCIETY Program 604 - n  
MASSACHUSETTS PHYSICIANS COMMITTEE 981 - c  
MASSACHUSETTS PUBLIC HEALTH ASSOCIATION, Nov 8,  
692 - n  
MASSACHUSETTS TRULIEU SOCIETY, Dec. 15, 944 - n  
MASTECTOMY [Pollock] 366\*  
MATERNAL-CARE program 528 - mdph  
McPHERSON, SIDNEY H [Gallupe] 105 - c  
MEDICAL CARE [Weinerman] 810\*  
Costs 211 - c  
Voluntary 1016 - c  
MEDICAL examiner [Ford] 1001\*  
MEDICAL officer positions Examination 644 - n  
Service 640 - c  
Training program 597 - c  
MEDICINE Industrial [Shipman] 615 - mms  
Practice 208 - c  
Practice Moral status 1017 - c  
Social 562 - c  
[SPERRY] 985\*  
MENICOLEGAL ABSTRACT Malpractice 1018  
Narcotics Legal aspect 1018  
Nurse dismissal Legal aspect 51  
MELANOMA [Chapman] 408 - cr  
MENINGITIS [Riley] 386\*  
MENTAL HEALTH Act. National 726 - misc  
METHEMOGLOBINEMIA [Finch] 470 - mp

METROPOLITAN STATE HOSPITAL 530, Oct 1-May 20, 418 - n  
 MICHIGAN STATE MEDICAL SOCIETY, Sept 22-24, 418 - n  
 MIDDLESEX EAST DISTRICT MEDICAL SOCIETY Program 644 - n  
 MIDDLESEX SOUTH DISTRICT MEDICAL SOCIETY, Oct. 20, 604 - n  
 MISSISSIPPI VALLEY MEDICAL SOCIETY, Sept 28-30, 1060 - n  
 MITRAL stenosis Surgery [Harken & others] 801\*  
 MONKEYS 212 - misc  
 MONONUCLEOSIS Infectious [Timmes & others] 173\*  
 [Raymond & Williams] 542\*  
 MOUNT AUBURN HOSPITAL Tumor clinic 844 - n  
 MUNTZ, GLENN F (License Deprivation) [Schadt] 843 - c  
 MUSCLES Necrosis [Pearson & others] 213\*  
 MYELOMA [Cope] 376 - cr  
 MYERSON, ABRAHAM 982 - o  
 MYOCARDITIS Diphtheritic [Boyer & Weinstein] 913\*

N

NAILES Symptomatology [Edwards] 362\*  
 NARCOTICS Legal aspect 1018 - ma  
 NATIONAL COMMITTEE FOR MENTAL HYGIENE, INC, Nov 3 and 4, 282 - n  
 NATIONAL GASTROENTEROLOGICAL ASSOCIATION Award contest 902 - n  
 NATIONAL HEART INSTITUTE 416 - misc  
 NATION's health 692 - misc  
 NEOPLASTIC disease Chemotherapy [Karnofsky] 226, 260, 299 - mp  
 NEPHRITIS Glomerulus [Jacobson] 271 - cr  
 [Harwood] 308 - cr  
 NEPHROSIS [Bruno] 769\*  
 [Strauss] 693\*, 761 - c  
 NEUBURGER, MAX 381 - c  
 NEUROPHYSIOLOGY History 101 - c  
 NEUROSYPHILIS [Kopp] 1021\*  
 NEVADA STATE MEDICAL ASSOCIATION, Sept 24-25, 418 - n  
 NEW ENGLAND CONFERENCE OF INDUSTRIAL PHYSICIANS AND SURGEONS, Sept 22, 244, Nov 10, 728 - n  
 NEW ENGLAND DERMATOLOGICAL SOCIETY, Oct. 20, 530, Dec 1, 800 - n  
 NEW ENGLAND DIABETES ASSOCIATION, Oct. 20, 530, 564, Dec 6, 902 - n  
 NEW ENGLAND HEART ASSOCIATION, Nov 8, 692, Dec 6, 844, Jan 10, 1060 - n  
 Penicillin fund 901 - c  
 NEW ENGLAND HOSPITAL FOR WOMEN AND CHILDREN, Nov 4, 692, Dec 2, 844, Jan 6, 1060 - n  
 NEW ENGLAND PEDIATRIC SOCIETY, Oct. 27, 530, Jan 26, 1060 - n  
 NEW ENGLAND POSTGRADUATE ASSEMBLY, Nov 3-5, 641 - c  
 NEW ENGLAND SOCIETY OF ANESTHESIOLOGISTS, Sept 14, 316, Oct 18, 564, Nov 23, 762, Dec 14, 844, Jan 11, 1060 - n  
 NEW ENGLAND SURGICAL SOCIETY  
 American Board of Surgery [Harvey] 159  
 Prostatectomy Retropubic [Austen & Quinby] 35  
 Spinal-cord injuries [Horne & others] 959  
 [Alunro & others] 903  
 NEW ENGLAND TELEPHONE AND TELEGRAPH COMPANY  
 Medical director 726 - misc  
 NEW ENGLAND TROPICAL DISEASES 29 - c  
 NEW HAMPSHIRE MEDICAL SOCIETY  
 Death  
 Elkavich, Frank D 348  
 One Hundred and Fifty-Seventh Anniversary, June 1-3, 510, 671, 828  
 NEW YEAR 1055 - c  
 NEW YORK ACADEMY OF MEDICINE, Oct 4-15, 492 - n  
 NEW YORK POST-GRADUATE HOSPITAL 316 - n  
 NEW YORK STATE SOCIETY OF ANESTHESIOLOGISTS, Dec 9-10, 34 - n  
 NEW YORK UNIVERSITY 281 - misc  
 NORFOLK DISTRICT MEDICAL SOCIETY, Sept 28, 452, Nov 23, 800 - n  
 NURSE dismissal Legal aspect 31 - ma  
 NURSING 938 - c  
 History 723 - c  
 NUTRITION 100 - c  
 Child [Talbot & others] 79\*  
 NIE MEMORIAL FUND 758

O

OAKLEY, GERALDINE [Gallupe] 105 - c  
 OBSTETRICS Coverage 452  
 Anesthesia [Hershenson] 429\*  
 OPERATION mush ox 209 - c  
 OREGON STATE MEDICAL SOCIETY, Sept. 15-18, 382 - n  
 OSTEOMA [Barr] 931 - cr  
 OTOLARYNGOLOGY [Flake] 819 - mp  
 OVARIES Cysts [Ncikirk & Hudson] 468\*  
 OVARY Tumors [Gaudrault] 56\*  
 [Oliver & Horne] 14\*  
 [Smith] 64 - cr  
 OVERHOLT, RICHARD H 242 - misc  
 OYSTERS Pollution 240 - c

P

PAINE, HARLAN L Resignation 490 - misc  
 PANAMA Physicians 1020 - n  
 PANCREAS Atrophy [Ross] 975 - cr  
 Carcinoma [Culver] 231 - cr  
 Tumors [Sweet] 720 - cr  
 PANCREATITIS Fibrosis [Talbot] 148 - cr  
 PARATHYROID Carcinoma [Bauer] 894 - cr  
 PARENTHOOD Planned 347 - c  
 PARKS, MARGARET [Gallupe] 105 - c  
 PATIENTS Cost of care 528 - mdph  
 PENICILLIN 526, 841 - c  
 [Crawford] 220\*  
 Dosage 756 - c  
 Fund 901 - c  
 [Hewitt & others] 286\*  
 PENNSYLVANIA Medical Society, Oct. 3-7, 486 - c, 492 - n  
 PHARMACY methods [Yellen] 32 - c  
 PHEOCHROMOCYTOMA [Spear & Griswold] 736\*  
 PHILOSOPHY and medicine 153 - c  
 PHOTOGRAPHY in medicine [Fallon & Meyers] 740\*  
 PHYSICIANS Draft 755 - c  
 Family [Thompson] 643 - c  
 Society members 842 - c  
 Status 649 - c  
 PHYSIOLOGY [Hoff & Scott] 89, 120, 176 - mp  
 PICKLES, WILLIAM N 449 - c  
 PLASTIC surgery [Cannon] 435 - mp  
 PNEUMONIA 939 - c  
 Pneumococcal Penicillin Treatment [Tumulty & Zubrod] 1033\*  
 POLAND [Segnitz] 798 - c  
 POLIOMYELITIS [Lawson] 994 - mms  
 Age distribution [Horton & Rubenstein] 169\*  
 POLLEN sensitivity [Hill] 1039\*  
 POLYMYXIN 313 - c  
 POPULATION 486 - c  
 POSTGRADUATE medical education Connecticut 451 - c  
 POUTAS, JOHN J 564 - misc  
 PRACTITIONER General 794 - c  
 (JOSEPH H) PRATT DIAGNOSTIC HOSPITAL, medical conference program, Oct. 8-29, 564, Dec 3-24, 902, Jan 4-28, 1060 - n  
 PREGNANCY Complications [Kasdon] 575\*  
 Tests [Robbins] 333, 369 - mp  
 Tubal [Parsons] 556 - cr  
 PREVENTIVE MEDICINE 525 - c  
 Qualifications 490 - misc  
 PRIZE essay 525 - c, 842 - n  
 PROCTOLOGY [Hayden] 399 - mp  
 PROGRESS, MEDICAL  
 BAL [Randall & Seeler] 1004, 1040  
 Blood [Gibson] 544, 579  
 Edephalitis [Adams & Weinstein] 865  
 Hepatitis Viral [Gelhis & Janeway] 503  
 Kidney Diseases [Hall & Luetscher] 621  
 Malaria [Geiman] 18, 58  
 Neoplastic disease Chemotherapy [Karnofsky] 226, 260, 299  
 Otolaryngology [Flake] 819  
 Physiology [Hoff & Scott] 89, 120, 176  
 Plastic surgery [Cannon] 435  
 Pregnancy tests [Robbins] 333, 369  
 Proctology [Hayden] 399

Pulmonary lesions X-ray diagnosis [Robbins] 779  
Sarcoidosis [Freiman] 664, 709, 743  
Sulfhemoglobinemia Methemoglobinemia [Finch] 470  
Thoracic surgery [Scannell] 924, 961  
PROSTATECTOMY Retropubic [Austen & Quinby] 35 - ness  
*Providence Evening Bulletin* 208 - e  
PSYCHIATRY [Tarnower] 466\*  
Neurology Residencies 351 - n  
PSYCHOTHERAPY [Levinger] 1020 - c  
Group [Terhune & Dickenson] 854\*  
PUBLIC HEALTH schools President (Simmons) 212 - misc  
[Gettung] 295\*  
PUBLIC relations 488 - e  
PULMONARY lesions X-ray diagnosis [Robbins] 779 - mp

## Q

Q fever and raw milk 29 - e  
QUARANTINE 1058 - mdph

## R

RADIOACTIVITY [Cristol & others] 427\*  
RAILWAY car sanitation 527 - e  
READING Disability 210 - e  
RECTUM Tumors [Hopkins & Tate] 501\*  
REN CROSS 691 - e  
REGISTRATION IN MEDICINE. Officers [Schadt] 282 - c  
REGISTRATIONS Suspension [Gallupe] 105 - c  
REHABILITATION 793 - e, 843 - misc  
RESPIRATORY infections and handkerchiefs 1057 - e  
RHEUMATIC DISEASES International Congress, Mar 30-  
June 3, 800 - n  
RHEUMATIC FEVER. Acute. Therapy [Wégria & others] 117\*  
Fellowships 241, 415 - mdph  
RICE DIET 759 - mdph  
[Contratto & Rogers] 531 - mms  
ROCKY MOUNTAIN spotted fever 105 - mdph  
Vaccine 642 - mdph  
ROMANE, DEWITT C fellowship 104 - misc  
ROSS, ELIZABETH [Gallupe] 105 - c  
ROSS, JOHN R. [Gallupe] 105 - c  
RUBELLA and pregnancy 347 - e  
RUTLAND STATE SANATORIUM 689 - e  
[Dufault] 660\*  
[Kronick] 653\*

## S

SAFETY conference 32 - misc  
SALPINGITIS [Ulfelder] 67 - cr  
SARCOINOSIS [Freiman] 664, 709, 743 - mp  
SARCOMA [Chapman] 749 - cr  
Liver Tumors [Franssen] 787 - cr  
Retropertoneal [Young] 203 - cr  
SEAN, MILTON J E 797 - misc  
SEXUAL potency [Horne & others] 959 - ness  
[Munro & others] 903 - ness  
SHERRINGTON 101 - e  
SILVER HILL FOUNDATION MEDICAL COUNCIL, Oct. 15,  
797 - misc  
SIMMONS, JAMES S 212 - misc  
SKIN complications [Strauss] 956\*  
Diseases 32 - misc  
Ulcers Treatment [Feinberg] 613\*  
SMITH, HOWARD H [Gallupe] 105 - c  
SOCIAL SECURITY 726 - misc  
SOCIETIES  
American Association for Advancement of Science 413 - e  
American Association of Schools of Social Work, Jan 27-29,  
984 - n  
American Cancer Society, Inc., Nov 6-7, 644 - n  
American Public Health Association, Nov 8-12, 723 - e  
American Society of Anesthesiologists, Inc., Oct. 1-2,  
382, Nov 4-6, 418 - n  
American Society for Study of Arteriosclerosis, Oct. 31-  
Nov 1, 530 - n  
American Trudeau Society, Oct 15 418 - n  
Boston City Hospital House Officers' Association, Nov  
16, 23 and 30, 762, Dec 14, 902 - n

Boston Society of Psychiatry and Neurology, Nov 18,  
762 Dec 15, 944 - n  
Colorado State Medical Society, Sept 22-25, 418 - n  
Greater Boston Medical Society, Nov 16, 762 - n, Dec. 21,  
984 - n  
Hampden District Medical Society Program 492 - n  
Harvard Medical Society, Oct. 12, 530, Nov 9, 728,  
Dec 14, 902, Jan 11, 1060 - n  
Indiana State Medical Association, Oct. 26-28, 418 - n  
Interstate Postgraduate Medical Association of North  
America, Nov 9-12, 644 - n  
Kentucky State Medical Association, Sept. 27-30, 418 - n  
Massachusetts Medical Benevolent Society 899 - e  
Massachusetts Medico-Legal Society Program 604 - n  
Massachusetts Public Health Association, Nov 8, 692 - n  
Massachusetts Trudeau Society, Dec. 15, 944 - n  
Michigan State Medical Society, Sept. 22-24, 418 - n  
Middlesex East District Medical Society Program 644 - n  
Middlesex South District Medical Society, Oct. 20, 604 - n  
Mississippi Valley Medical Society, Sept 28-30, 1060 - n  
National Gastroenterological Association Award contest  
902 - n  
Nevada State Medical Association, Sept. 24-25, 418 - n  
New England Dermatological Society, Oct 20, 530, Dec 1,  
800 - n  
New England Diabetes Association, Oct 20, 530, 564,  
Dec 6, 902 - n  
New England Heart Association, Nov 8, 692, Dec. 6,  
844, Jan 10, 1060 - n  
Penicillin fund 901 - e  
New England Pediatric Society, Oct. 27, 530, Jan 26,  
1060 - n  
New England Society of Anesthesiologists, Sept. 14, 316,  
Oct. 18, 564, Nov 23, 762 Dec. 14, 844, Jan 11,  
1060 - n  
New York State Society of Anesthesiologists, Dec 9-10,  
34 - n  
Norfolk District Medical Society, Sept. 28, 452, Nov 23,  
800 - n  
Oregon State Medical Society, Sept. 15-18, 382 - n  
Pennsylvania Medical Society, Oct. 3-7 486 - e, 492 - n  
South Boston Medical Society, Oct. 4, 452 Nov 15, 762 - n  
South End Medical Club, Oct. 19, 564, Nov 16, 762 - n  
Suffolk District Medical Society, Oct. 9, 452, Dec. 2,  
492, Jan 12, 1060 - n  
Vermont State Medical Society, Sept. 15-17, 382 - n  
Virginia Medical Society, Oct. 18-20, 418 - n  
Washington State Medical Association, Oct. 3-6, 418 - n  
Wisconsin Medical Society, Oct. 4-6, 418 - n  
SOUTH BOSTON MEDICAL SOCIETY, Oct. 4, 452, Nov 15,  
762 - n  
SOUTH END MEDICAL CLUB, Oct. 19, 564, Nov 16, 762 - n  
SPECIALTY boards [Chapin] 529 - c  
SPHENOID sinus Carcinoma [Cogan] 837 - cr  
SPINAL-CORD injuries [Horne & others] 959 - ness  
[Munro & others] 903 - ness  
SPINAL epidural infections [Heusner] 845\*  
STATISTICS Medical 596 - e  
STOMACH Carcinoma [Faxon] 306 - cr  
STORROW HOUSE 382 - e  
STREPTOMYCIN 279 - e  
[Cressy & others] 497\*  
STRONG, RICHARD P 489 - o  
SUCCINATE Therapy [Wégria & others] 117\*  
SUFFOLK DISTRICT MEDICAL SOCIETY, Oct. 9, 452, Dec. 2,  
492, Jan 12, 1060 - n  
SULFHEMOGLOBINEMIA [Finch] 470 - mp  
SULFONAMIDE hypersensitivity [Straus] 956\*  
SULLIVAN, EDWARD V [Gallupe] 105 - c  
SWIMMING pools [Gallagher & Neuberger] 282 - c  
SYPHILIS Penicillin 526 - e

## T

TELANGIECTASIA Hemorrhagic [Schwartz & Armstrong] 434\*  
TESTOSTERONE. Depressions [Altschule & Tillotson] 1056\*  
TETANUS toxoid [Press] 50\*  
THOMAS, EVERETT O [Gallupe] 105 - c  
THORACIC surgery [Scannell] 924, 961 - mp  
THORACOPLASTY [Dufault] 660\*  
THORNDIKE, AUGUSTUS 104 - misc

THORNDIKE MEMORIAL LABORATORY Director 212 - misc  
 Peabody, Minot and Castle 345 - c  
 THORSON, STEPHEN B [Gallupe] 105 - c  
 THROMBOSIS Coronary [Clark] 478 - cr  
     [Mivers] 1051 - cr  
     Mesenteric [Allen] 444 - cr  
 THYROID Cancer [Anglem & Bradford] 217\*  
     Nodule 238 - c  
     Therapy [Buxton & Vann] 536\*  
 TIBIA Abscess [Simmons] 443 - cr  
 TICK survey [Avres & Feemster] 760 - mdph  
 TRACHEA Adenoma [Lerman] 341 - cr  
 TRICHINIASIS 414 - c  
 TROPICAL diseases 29 - c  
 TUBERCULOSIS [Ulfelder] 67 - cr  
     Increase 796 - c  
     Pulmonary Statistics [Kronick] 653\*  
 TYPHOID vaccine 797 - mdph

U

UNITED STATES army medical resident training program  
     492 - n  
     Army medical training program 597 - c  
     Medical officers Appointments 158 - n  
     Navy Medical training program 158 - n  
     Public Health Service Training program 643 - misc  
 UROLOGY award 452 - n  
 UTERUS Double [Vernaglia] 732\*  
     Tumors [Gregg] 23 - cr

V

VACCINATION Compulsory 379 - c  
 VAGINAL SMEAR [Lombard & others] 317\*, 346 - c  
 VAN METER PRIZE award 492 - n  
 VERMONT STATE MEDICAL SOCIETY, Sept 15-17, 382 - n

VETERANS ADMINISTRATION 240 - mms, 244, 351, 902 - n  
     Educational program 152 - c  
     [Campbell] 156 - c  
     Fee guides 758 - mms  
     Residency training program 352 - n  
 VIRGINIA MEDICAL SOCIETY, Oct. 18-20, 418 - n  
 VITAMIN B<sub>12</sub> Therapy [Berk & others] 328, 911\*  
*Vox Populi* 840 - c

W

WALKER, EDMUND EUGENE [Gallupe] 105 - c  
 WASHINGTON STATE MEDICAL ASSOCIATION, Oct. 3-6, 418 - n  
 WASHINGTONIAN HOSPITAL 1018 - c  
 WATER pollution 156, 643 - misc  
 WHITE, PAUL D 940 - c  
 WILKINS, GEORGE F 726 - misc  
 WISCONSIN MEDICAL SOCIETY, Oct 4-6, 418 - n  
     University Symposium on science and civilization, Jan 13-  
     15, 1060 - n  
 WOMEN Diseases [Buxton & Vann] 536\*  
 WOOD-TICK study 348 - mdph  
 WORLD HEALTH ORGANIZATION 30, 450 - c, program, 104 -  
     misc  
     Relief 980 - c

Y

YALE CHILD STUDY CENTER Director 797 - misc  
 YAWS [Downing] 17\*

Z

ZUNDELL, SAMUEL C (License Deprivation) [Schadt]  
     602 - c

# AUTHOR INDEX

## A

ADAMS, F D 680 - cr  
ADAMS, R D 213\*, 865 - mp  
AISNER, M 156 - c  
ALEXANDER, L 10\*  
ALLEN, A W 444 - cr  
ALTSCHULE, M D 1036\*  
ANGLEM, T J 217\*  
ANKER, R 911\*  
ARCHIBALD, R E 858\*  
ARMSTRONG, B E 434\*  
AUB, J C 933 - cr  
AUSTEN, G, JR 35 - ness  
AVERILL, J H 173\*  
AYRES, J C 760 - mdph  
AYVAZIAN, L F 563\*

## B

BADGER, T L 563\*  
BARR, J S 931 - cr  
BAUER, W 894 - cr  
BEASER, S B 765\*  
BERK, L 328, 911\*  
BILL, A H, JR 578\*  
BLUESTONE, E M 258\*  
BOTHE, A E 427\*  
BOWEN, B D 998\*  
BOYER, N H 913\*  
BRADFORD, M L 217\*  
BRAILEY, A G 482 - cr  
BRECKER, F W 862\*  
BRODT, E B 945\*  
BRUNO, M S 769\*  
BURGESS, A M 75\*  
BURGIN, L 97 - cr  
BURNS, K 983 - c  
BUXTON, C L 536\*

## C

CAMPBELL, A J A 156 - c  
CANON, B 435 - mp  
CARUOLO, J E 596\*  
CASTLE, W B 328, 911\*  
CASTLEMAN, B 729\*  
CATTELL, R B 972 - cr  
CHALMERS, T C 603\*  
CHAPIN, W A R 529 - c  
CHAPMAN, C B 701\*  
CHAPMAN, E M 145, 408, 749 - cr  
CHASE, M E 283 - mms  
CHRISTIAN, H A 74 - c  
CHUTE, R 790 - cr  
CLARK, R J 478 - cr  
COGAN, D G 837 - cr  
CONTRATTO, A W 531 - mms  
COPE, O 376 - cr  
COSTIN, M E 705\*  
CRAWFORD, J D 220\*  
CRESSI, N L 497\*  
CRISTOL, D S 427\*  
CROSBIE, G H 212 - misc  
CULVER, P 231 - cr

## D

DAVENPORT, L F 25 - cr  
DAVIDSON, C S 164, 603\*  
DENNY-BROWN, D 213, 328\*  
DICKENSON, J R 854\*  
DOERING, C R 990\*  
DOWNING, J G 17, 862\*  
DRAKE, E H 43\*  
DUFALUT, P 660\*  
DUNSMORE, R H 945\*

## E

EDWARDS, E A 362, 571\*  
ECKHARDT, R D 164, 605\*  
ELLIS, D S 589 - cr  
ELLIS, L B 801, 951\*  
EPSTEIN, M 911\*

## F

FALLOU, J 740\*  
FARBER S 373 - cr  
FAXON, H H 306 - cr  
FEEMSTER, R F 760 - mdph  
FEINBERG, A W 613\*  
FINCH, C A 470 - mp  
FINLAND, M 328\*  
FIORE, A 858\*  
FISCHEL E E 117\*  
FLAKE, C G 819 - mp  
FORD R 1001\*  
FOSTER, D P 107\*  
FRANSEEN, C C 787 - cr  
FREIMAN, D G 664, 709, 743 - mp

## G

GALLAGHER, J R 282 - c  
GALLUPE, H Q 105 - c  
GARDNER, W J 493\*  
GASTON, E A 705\*  
GATES, O 317\*  
GAUDRAULT, G L 56\*  
GEIMAN, Q M 18, 58 - mp  
GELLIS, S S 503 - mp  
GETTING, V A 295, 1028\*  
GIBSON, S T 544, 579 - mp  
GREGG, W I 25 - cr  
GRISWOLD, D 736\*  
GROSS, R E 578, 645\*  
GROTZINGER, P W 427\*  
GUNDERSEN, S M 818\*  
GURRI, J 773\*

## H

HAEDICKE, T A 250\*  
HALL, A D 621 - mp  
HALSTED, J A 406 - cr  
HARKEN, D E 383, 801\*  
HARVEY, S C 159 - ness  
HARWOOD, R 308 - cr  
HASSETT, A J 254\*  
HAYDEN, E P 399 - mp  
HEINLE, R W 911\*  
HERSHENSON, B B 429\*  
HEUSNER, A P 845\*  
HEWITT, W L 286\*  
HILL, L W 1039\*  
HOFF, H E 89, 120, 176 - mp  
HOLMES, E M 539\*  
HOOKER, D H 107\*  
HOPKINS, F S 501\*  
HORNE, E O 14\*  
HORNE, H W 903, 959 - ness  
HORTON, R J M 169\*  
HUDSON, H W, JR 468\*  
HURWITT, E S 578\*

## I

IRVIN, L N 107\*

## J

JACKSON, H, JR 1059 - c  
JACOBSON, B M 271, 1047 - cr  
JANEWAY, C A 503 - mp

JOHANSON, C I 619\*  
JONES, C C 242 - c  
JORDAN, W S, JR 597\*

## K

KALDECK, R 773\*  
KARNOFSKY, D A 226, 260, 299 - mp  
KASDON, S C 575\*  
KEEFER, C S 286\*  
KINGSLEY, J W, JR 459\*  
KOO, C C 79\*  
KOPP, I 1021\*  
KRAVES, A 205, 716 - cr  
KRONICK, M 653\*  
KUFFEL, M J 107\*  
KUNKEL, P 497\*

## L

LAHEY, W J 497\*  
LALONDE, A A 493\*  
LAWSON, R B 994 - mms  
LEMERE, F 331\*  
LENZNER, A R 998\*  
LERMAN, J 341 - cr  
LEROYER, C P, JR 245\*  
LEVINGER, E L 1020 - c  
LIU, C T 1 - mms  
LOMBARD, H L 317\*  
LONDON, R E 491 - c  
LONDON, S B 491 - c  
LOOFBOUROW, D 990\*  
LETSCHER, J A, JR 621 - mp

## M

MACGREGOR, C A 113\*  
MCKITTRICK, J B 95 - cr  
MC Laughlin, W F 773\*  
MCSWENEY, D J 254\*  
MENEELY, J K, JR, 708\*  
METCALFE, J 173\*  
MEYERS J 740\*  
MIDDLETON, M 317\*  
MIKAL, S 920\*  
MINTER, W J 1 - mms  
MUNRO, D 903, 959 - ness  
MURPHY, T L 603\*  
MYERS, G S 1051 - cr

## N

NEIKIRK, W I 468\*  
NEUBERG, H W 282 - c  
NEWTON, F C 113\*  
NORMAN, L R 801\*  
NYSENS, A F 522\*

## O

O'HOLLAREN, P 331\*  
OLIVER, H M 14\*

## P

PALMER, J L 818\*  
PALMER, R S 322, 990\*  
PAPEN, G W 920\*  
PARSONS, L 536 - cr  
PAULL, D P 903, 959 - ness  
PEARSON, C 213\*  
PEIRCE, E C, 2ND 578\*  
PETERS, J P 333\*  
PICK, W W 79\*  
PICKLES, W N 419\*

PITTMAN, H S 558 - cr  
 PHIPPEN, W G 83\*  
 POLLOCK, L H 366\*  
 PRESS, E 50\*

Q

QUINBY, W C 35 - ness

R

RANDALL, R V 1004, 1040 - mp  
 RAPOPORT, B 951\*  
 RAVREBY, L 110\*  
 RAYMOND, R W 542\*  
 REDLICH, F C 945\*  
 REYERSBACH, G C 339 - cr  
 RILEY, E A 386\*  
 ROBBINS, L L 517 - cr, 779\*  
 ROBBINS, S L 333, 369 - mp  
 ROGERS, M B 531 - mms  
 ROOT, H F 453\*, 797 - c  
 ROPES, M 519 - cr  
 ROSEN, A P 367\*  
 ROSS, R A 975 - cr  
 RUBENSTEIN, A D 169, 1028\*  
 RYDER, C F 1028\*

S

SALZBERG, A M 383\*  
 SAWYER, W H 110\*  
 SCANLAN, J J 367\*  
 SCANNELL, J G 752 - cr, 924, 961 - mp  
 SCHATZ, G L 282, 602, 843 - c

SCHATZKI, R 632 - cr  
 SCHIER, W W 592 - cr  
 SCHWARTZ, S O 434\*  
 SCOTT, H J 89, 120, 176 - mp  
 SEELER, A O 1004, 1040 - mp  
 SEGNIETZ, R H 798 - c  
 SHIPMAN, T L 615 - mms  
 SHORT, C L 635 - cr  
 SHULMAN, M H 391\*  
 SIMMONS, C C 443 - cr  
 SKVIRSKY, S L 858\*  
 SMITH, J A 64 - cr  
 SMITHWICK, R H 729\*  
 SOSMAN, M 834 - cr  
 SOUDERS, C R 459\*  
 SPEAR, H C 736\*  
 SPERRY, W L 985\*  
 SPRAGUE, H B 683 - cr  
 STRAUS, D A 956\*  
 STRAUSS, M B 693\*, 761 - c  
 SWEET, R H 720 - cr

T

TALBOT, N B 79\*, 148 - cr  
 TARNOWER, S M 466\*  
 TATE, R C 501\*  
 TAYLOR, G W 234, 1012 - cr  
 TERHUNE, W B 854\*  
 THOMPSON, C E 291\*  
 THOMPSON, M 643 - c  
 TILLOTSON, K J 1036\*  
 TIMMES, J J 173\*  
 TOWNE, C E 223\*  
 TOWNSEND, J H 274, 1009 - cr  
 TUMULTY, P A 1033\*

U

ULFELDER, H 67 - cr

V

VANN, F H 536\*  
 VERNAGLIA, J B 732\*  
 VIETS, H R 84\*

W

WARE, P F 645, 801\*  
 WARREN, S 317\*, 763 - mms  
 WARTHIN, T A 45\*  
 WASSERSUG, J I 773\*  
 WEGRIA, R 117\*  
 WEINERMAN, E R 810\*  
 WEINSTEIN, L 865 - mp, 913\*  
 WELCH, A D 911\*  
 WELCH, C E 897 - cr  
 WELLS, S L 79\*  
 WHITE, B V 245\*  
 WHITE, J C 1 - mms, 322\*  
 WHITTLESEY, P 286\*  
 WILLIAMS, R L 542\*  
 WILNER, P R 250\*  
 WILSON, P E 117\*  
 WISHART, J H 701\*  
 WITHAM, A C 291\*  
 WOLFSON, W Q 156 - c

Y

YELLEN, B L 32 - c  
 YOUNG, E L 203 - cr

Z

ZUBROD, G 1033\*

CASE RECORDS  
OF THE MASSACHUSETTS GENERAL HOSPITAL  
  
WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C CABOT

TRACY B MALLORY, M.D, *Editor*  
BENJAMIN CASTLEMAN, M.D, *Associate Editor*  
EDITH E. PARRIS, *Assistant Editor*

VOLUME 34  
1948

PITTMAN, H S 558 - cr  
 PHIPPEN, W G 83\*  
 POLLOCK, L H 366\*  
 PRESS, E 50\*

Q

QUINBY, W C 35 - ness

R

RANDALL, R V 1004, 1040 - mp  
 RAPOPORT, B 951\*  
 RAVREBY, L 110\*  
 RAYMOND, R W 542\*  
 REDLICH, F C 945\*  
 REYERSBACH, G C 339 - cr  
 RILEY, E A 386\*  
 ROBBINS, L L 517 - cr, 779\*  
 ROBBINS, S L 333, 369 - mp  
 ROGERS, M B 531 - mms  
 ROOT, H F 453\*, 797 - c  
 ROPES, M 519 - cr  
 ROSEN, A P 367\*  
 ROSS, R A 975 - cr  
 RUBENSTEIN, A D 169, 1028\*  
 RYDER, C F 1028\*

S

SALZBERG, A M 383\*  
 SAWYER, W H 110\*  
 SCANLAN, J J 367\*  
 SCANNELL, J G 752 - cr, 924, 961 - mp  
 SCHATZ, G L 282, 602, 843 - c

SCHATZKI, R 632 - cr  
 SCHIER, W W 592 - cr  
 SCHWARTZ, S O 434\*  
 SCOTT, H J 89, 120, 176 - mp  
 SEELER, A O 1004, 1040 - mp  
 SEGELITZ, R H 798 - c  
 SHIPMAN, T L 615 - mms  
 SHORT, C L 635 - cr  
 SHULMAN, M H 391\*  
 SIMMONS, C C 443 - cr  
 SKVIRSKY, S L 858\*  
 SMITH, J A 64 - cr  
 SMITHWICK, R H 729\*  
 SOSMAN, M 834 - cr  
 SOUDERS, C R 459\*  
 SPEAR, H C 736\*  
 SPERRY, W L 985\*  
 SPRAGUE, H B 683 - cr  
 STRAUS, D A 956\*  
 STRAUSS, M B 693\*, 761 - c  
 SWEET, R H 720 - cr

T

TALBOT, N B 79\*, 148 - cr  
 TARNOWER, S M 466\*  
 TATE, R C 501\*  
 TAYLOR, G W 234, 1012 - cr  
 TERHUNE, W B 854\*  
 THOMPSON, C E 291\*  
 THOMPSON, M 643 - c  
 TILLOTSON, K J 1036\*  
 TIMMES, J J 173\*  
 TOWNE, C E 223\*  
 TOWNSEND, J H 274, 1009 - cr  
 TUMULTY, P A 1033\*

U

ULFELDER, H 67 - cr

V

VANN, F H 536\*  
 VERNAGLIA, J B 732\*  
 VIETS, H R 84\*

W

WARE, P F 645, 801\*  
 WARREN, S 317\*, 763 - mms  
 WARTHIN, T A 45\*  
 WASSERSUG, J I 773\*  
 WEGRIA, R 117\*  
 WEINERMAN, E R 810\*  
 WEINSTEIN, L 865 - mp, 913\*  
 WELCH, A D 911\*  
 WELCH, C E 897 - cr  
 WELLS, S L 79\*  
 WHITE, B V 245\*  
 WHITE, J C 1 - mms, 322\*  
 WHITTLESEY, P 286\*  
 WILLIAMS, R L 542\*  
 WILNER, P R 250\*  
 WILSON, P E 117\*  
 WISHART, J H 701\*  
 WITHAM, A C 291\*  
 WOLFSON, W Q 156 - c

Y

YELLEN, B L 32 - c  
 YOUNG, E L 203 - cr

Z

ZUBROD, G 1033\*

- endocarditis, bacterial, acute, of mitral valve, 34421, 34451
  - aortic, 34441, 34451
  - subacute, aortic, 34041, 34111
  - rheumatic, acute and chronic, with stenosis of all valve 34101
- hypertrophy, 34141, 34361, 34442
- infarct, myocardial, 34051, 34242, 34391, 34421, 34442, 34532
- sclerosis, coronary, with occlusion, 34051, 34421, 34442
- stenosis, calcareous, aortic 34441
- thrombus, mural, 34051, 34242, 34361, 34391, 34442, 34532
- coronary, recent, 34391, 34532
- Hemangioma, cavernous, head of gastrocnemius muscle, 34232
- Hemochromatosis of liver, pancreas, skin and lymph nodes, 34521
- Hepatitis, see Liver
- Hepatoma, 34351
  - with extension into portal and hepatic veins, 34011, 34521
- Hernia, diaphragmatic, 34462
- Hodgkin's disease see Lymphoma
- Homologous serum hepatitis, 34522
- Humerus, carcinoma, metastatic renal-cell, 34162
- Hydrothorax, chylous, 34031
- Hypernephroma, see Kidney (renal-cell carcinoma)
- Hypertrophy, benign, of prostate, with obstruction, 34081
- Ileum, see Intestine
- Infarct of kidney, bilateral, cortical, 34502
  - of lung, 34172, 34361, 34391, 34442, 34532
  - of myocardium, 34051, 34242, 34391, 34421, 34442, 34532
- Infiltration, fat, of liver, 34512
- Intestine, anomaly of, duplication (terminal ileum), 34292
  - carcinoid (ileum), 34431
  - carcinoma of, adeno- (rectosigmoid), 34112
    - colon, ascending, 34172
    - duodenum, at ampulla of Vater, 34251, 34301
    - ileum, metastatic, with perforation, 34452
  - colitis of, ulcerative, chronic severe, 34432
  - cyst of (cecum), twisted, 34061
  - lipoma of, submucous (transverse colon), 34492
  - lymphoma of, giant-follicular type, 34222
  - obstruction of (ileum), 34341
  - ulcer of (duodenum), 34072, 34122
- Intoxication, carbon tetrachloride, 34221
- Kidney, adenoma of, papillary, 34041
  - amyloid degeneration of, 34261, 34531
  - carcinoma of, metastatic, 34262
  - cyst of, 34472
  - infarction of, bilateral, cortical, 34502
  - infiltration of, leukemic, 34062
  - (See also Nephritis, Nephrosis)
- Kyphoscoliosis, 34241
- Leukemia, lymphatic, 34062
- Lipoma, intradural, of sacral canal, 34131
  - submucous, of transverse colon, with previous intussusception, 34492
- Liver, adenoma of, 34402
  - amyloid degeneration of, 34531
  - carcinoma of, 34351
    - metastatic, 34031
  - cirrhosis of, biliary, 34512
  - portal, inactive, 34011
  - postatrophic type, 34402
  - toxic, 34432
  - cyst of, congenital, 34401
  - echinococcus of, 34512
  - hemochromatosis of, 34521
  - hepatitis, homologous serum, 34522
  - hepatoma, with extension into portal and hepatic veins 34011, 34521
  - infiltration of, fat, 34512
  - leukemic, 34062
  - sarcoma of (fibro-), metastatic, 34471
- Lung, abscess of, 34392, 34422
  - aspiration of amniotic fluid, massive, 34182
  - carcinoma of, metastatic, 34031
    - bronchiogenic, 34142
    - squamous-cell, 34481
  - edema of, acute, 34212, 34331
    - with massive hemorrhage, 34342
  - embolism of, multiple, 34172, 34242, 34361, 34442, 34532
  - emphysema of, 34191
  - fibrosis of, 34191
  - hemorrhage in, 34342
  - infarct of, 34172, 34361, 34391, 34442, 34532
  - infiltration of, leukemic, 34062
  - melanoma of, metastatic, 34372
  - sarcoma of (fibro-), metastatic, 34471
  - tuberculosis of, 34261, 34502
- Lymph nodes, carcinoma, metastatic, 34021, 34031
- hemochromatosis of 34521
- tuberculosis of 34502
- Lymphoma malignant giant-follicular type, 34092, 34222
- Hodgkin's type, 34272
- lymphoblastic type, 34121
- reticulum-cell type, generalized, 34032, 34322
- Mediastinum, sarcoma of (neurofibro-), 34461
- teratoma, malignant, involving pericardium, pleura and lung, 34202
- Melanoma of lung, metastatic, 34372
- Muscle, hemangioma of, cavernous, of head of gastrocnemius, 34232
  - infiltration of, leukemic (voluntary), 34062
- Nevus, multiple, 34362
- Myocardium, see Heart
- Myocardosis, 34361
- Nephritis, glomerulo-, acute, 34212, 34432, 34451
  - subacute, 34041, 34111, 34531, 34542
  - prelo- chronic, with uremia, 34131
- Nephrosis, lower-nephron (carbon tetrachloride intoxication), 34221
- Obstruction, small-bowel, 34541
- Oleothorax, 34261
- Osteoma, osteoid, 34501
- Ovary, carcinoma of (adeno-), papillary serous, 34281
  - metastatic, 34031
- Pancreas, atrophy of acinar tissue of, complete, 34512
  - carcinoma of, adeno-, 34251, 34321, 34452
  - cyst of 34082
  - fibrosis of, 34302
  - hemochromatosis of, 34521
- Parathyroid gland, carcinoma of, 34491
- Pelvis, abscess of, 34112, 34201, 34452
- Perforation of appendix, 34052, 34102
  - of gall bladder, 34071
  - of ileum, 34452
  - of pyloric stump, 34072
- Pericardium, infiltration of, leukemic 34062
- Peritonitis, general, acute, 34052, 34452
  - with fat necrosis, 34072
- Pleura, infiltration of, leukemic, 34062
- Pneumonia, see Lung
- Poisoning, carbon tetrachloride, 34221
- Pregnancy, tubal, 34411
- Prostate, hypertrophy of, benign, with obstruction, 34081
- Purpura, 34342
- Rectum, see Intestine
- Retroperitoneum fibrosarcoma of, 34311, 34511
  - ganglioneuroma 34181
- Sacrum, sarcoma of, Ewing's, 34012
- Salpingitis tuberculous, 34282
- Sarcoma of adrenal gland (fibro-), 34511
  - of liver (fibro-), metastatic, 34471
  - of lung (fibro-), metastatic, 34471
  - of mediastinum (neurofibro-), with invasion of innominate vein and superior vena cava, 34461
  - of retroperitoneal tissues (fibro-), 34311, 34511
  - of sacrum (Ewing's), 34012
- Sinus, carcinoma of (sphenoid) transitional-cell, 34482
- thrombosis of (superior longitudinal), 34182
- Skin, hemochromatosis of, 34521
  - purpura of, 34342
- Spina bifida occulta, 34131
- Spinal cord, lipoma (intradural), 34131
- Spleen, amyloid degeneration of, 34261, 34551
  - infiltration of, leukemic, 34062
- Stomach, carcinoma of (adeno-), 34082, 34341
  - mucous (signet-ring type), 34171
  - gastritis, chronic, superimposed on hypertrophic type, 34371
  - perforation of pyloric stump, 34072
- Teratoma, malignant, of anterior mediastinum, 34202
- Testicles, infiltration of, leukemic, 34062
- Tetralogy of Fallot, 34101
- Thrombophlebitis, of femoral and iliac veins and of inferior vena cava, 34172
- Thrombosis of right ventricular endocardium and left popliteal vein, 34242
  - of superior longitudinal sinus, 34182
  - mesenteric, venous, 34382
  - (See also Heart)

# INDEX

## CASE RECORDS OF THE

### MASSACHUSETTS GENERAL HOSPITAL

#### 1948

---

The date of publication of any case may be determined from the case number. The first two figures of each case number indicate the volume number, 34. The third and fourth figures give the number of the week, dating from January 1. The last figure gives the case number for the week. For example, Case 34251 is the first case for the twenty-fifth week of Volume 34.

- Abscess of brain, multiple, 34201
  - of lung, 34392, 34422
  - appendiceal, 34102
  - Brodie's, of tibia, 34381
  - pelvic, 34112, 34201, 34452
- Actinomycosis of chest wall, 34412
- Addison's disease, 34092, 34502
- Adenoacanthoma of fundus of uterus, 34271
- Adenocarcinoma, see Carcinoma
- Adenoma of kidney, papillary, 34041
  - of liver, 34402
  - of trachea, with extension into thyroid gland, 34352
- Adrenal gland, amyloid degeneration of, 34261, 34531
  - atrophy of primary (cortex), 34092
  - sarcoma of (fibro-), 34511
  - tuberculosis of, 34502
- Amyloidosis, of adrenal gland, 34261, 34531
  - of kidney, 34261, 34531
  - of liver, 34531
  - of spleen, 34261, 34531
- Aneurysm, mycotic, of coronary artery, with rupture, 34441
- Anomaly, congenital, of aorta, right-sided, with persistent truncus arteriosus, patent interventricular septum, persistent fifth aortic arch, left, 34161
  - of bile duct, 34132
  - of spine (spina bifida occulta), 34131
  - of terminal ileum (duplication), 34292
 (See also Heart)
- Aorta, anomaly of (right-sided), 34161
- Appendicitis, acute, with perforation, 34052, 34102
  - gangrenous, with abscess, 34102
- Arthritis, rheumatoid, 34531
- Ascites, chylous, 34031
- Aspiration of amniotic fluid, massive, 34182
- Atresia, congenital, of hepatic and cystic duct, 34132
- Atrophy of adrenal gland (cortex), 34092
  - of pancreas (acinar tissue), 34512
- Bile duct, atresia of, congenital, 34132
  - carcinoma of (adeno-), 34251
- Bladder, carcinoma of (papillary), 34472
- Bone, abscess of, Brodie's (tibia), 34381
  - carcinoma of, metastatic, of humerus, 34162
  - of rib, 34262
  - myeloma of, multiple, 34362
  - osteoma, osteoid of (femur), 34501
  - tumor of, Ewing's (sacrum), 34012
- Bone marrow, leukemic infiltration of, 34062
- Brain, abscess of, multiple, 34201
  - carcinoma of, metastatic, subarachnoid space, 34192
 (See also Sinus)
- Bronchiectasis, 34022
- Bronchitis, chronic, 34512
- Bronchus, carcinoma of, 34022, 34091, 34142, 34241, 34422
  - metastatic, 34021, 34151
- Carbon tetrachloride intoxication, 34221
- Carcinoid of ileum, 34431
- Carcinoma of ampulla of Vater (adeno-), 34251
  - of bile duct (adeno-), 34251
  - of bladder (papillary), 34472
  - of brain (subarachnoid space), metastatic, 34192
  - of bronchus, 34022, 34091, 34142, 34241, 34422, 34481
  - metastatic, from breast, 34021
  - from kidney, 34151
  - of colon (adeno-), 34172
  - of duodenum (adeno-), at ampulla of Vater, 34251, 34301
  - of esophagus, metastatic, from breast, 34021
  - of gall bladder, 34102, 34291, 34332
  - of humerus, metastatic, 34162
  - of kidney (renal-cell), 34262
  - of liver (hepatoma), 34351
    - with extension into portal and hepatic veins, 34011, 34521
  - metastatic, 34021, 34031
  - of lung, metastatic, 34031
  - of lymph nodes, metastatic, from breast, 34021, 34031
  - of ovary, metastatic, 34031, 34281
  - of pancreas, 34231, 34321, 34452
    - (tail) with invasion of spleen, adrenal gland and stomach, 34152
  - of parathyroid gland, 34491
  - of rib, metastatic, 34262
  - of sigmoid, with abscess formation and extension to pelvis and uterus, 34112
  - of sinus, sphenoid (transitional-cell), 34482
  - of stomach (adeno-), 34082, 34341
    - mucous (signet-ring), 34171
  - of uterus (adenoacanthoma), 34271
  - of vertebra, metastatic, 34031
  - metastatic, endobronchial, of renal-cell adenocarcinoma, 34151
    - adeno-, primary site undiscovered, 34192
- Cecum, see Intestine
- Cholecystitis, see Gall bladder
- Cholelithiasis, see Gall bladder
- Chordoma of second and third lumbar vertebrae, 34511
- Cirrhosis, see Liver
- Colitis, see Intestine
- Colon, see Intestine
- Cyst of cecum (twisted), 34061
  - of kidney, 34472
  - of liver, congenital, 34401
  - echinococcus, 34312
  - of pancreas, 34082
- Diaphragmatic hernia, 34462
- Duodenum, see Intestine
- Echinococcus cyst, 34312
- Edema, pulmonary, acute, 34212, 34331
  - with massive hemorrhage, 34342
- Embolus, pulmonary, multiple, 34172, 34242, 34361, 34442
- Emphysema, pulmonary, 34191
- Empyema, right pleural cavity, 34211
- Endocarditis, see Heart
- Esophagus, carcinoma of, metastatic, 34021
  - ulcer of, 34462
  - varix of, with rupture, 34402, 34432
- Ewing's tumor of sacrum, 34012
- Femur osteoid osteoma of, 34501
- Fibrosis pancreatic, 34302
  - pulmonary, 34191
- Gall bladder, carcinoma of, 34102, 34291, 34332
  - cholecystitis of, chronic and subacute, with perforation, 34071
  - cholelithiasis, 34291
- Ganglioneuroma, retroperitoneal, 34181
- Gastritis, chronic, superficial, superimposed on hypertrophic type, 34371
- Goiter, colloid, with cystic formation, 34252
- Heart, aneurysm, mycotic, left circumflex, of coronary artery, with rupture, 34441
  - anomaly, congenital, bicuspid aortic valve, 34111
  - patent interventricular septum, 34161
  - persistent truncus, 34161
  - tetralogy of Fallot, 34101
  - cor pulmonale, 34191, 34241

# The New England Journal of Medicine

Copyright 1948 by the Massachusetts Medical Society

Volume 239

JULY 1, 1948

Number 1

## FOCAL EPILEPSY

### A Statistical Study of Its Causes and the Results of Surgical Treatment

#### II. Epilepsy Secondary to Cerebral Trauma and Infection\*

JAMES C. WHITE, M.D.,† CHING TUNG LIU, M.D.,‡ AND WILLIAM JASON MIXTER, M.D.§

BOSTON

THIS is the second of two papers reviewing surgical experience with 240 epileptic patients at the Massachusetts General Hospital in the decade 1935 through 1944. These patients in whom the epileptogenic focus could be localized clinically and visualized at operation therefore amount to 21 per cent of the total 1130 hospital admissions for epilepsy. In the preceding paper the relation of seizures to tumor of the brain was discussed.<sup>1</sup> Tumors are the most important etiologic factor in this group of epileptic patients with a local operable condition, since approximately a third of those in whom such lesions were situated above the tentorium had convulsions. One hundred and sixty tumors made up two thirds of the total operable cases. This paper considers the role of cerebral trauma and infection, with material based on 80 patients.

The modern surgical attack on epilepsy due to focal injury of the brain dates back to the pioneer work of Professor Otfried Foerster<sup>2</sup> on gunshot injuries of the brain in German soldiers of World War I. Penfield, who studied with him in Breslau in 1927, has made the greatest advances and written the outstanding monograph on the subject with Erickson, describing the technic and results in the extensive series of cases from the Neurological Institute in Montreal.<sup>3</sup> As pointed out in the preceding paper, special interest began to be focused on this group of patients with focal epileptogenic lesions<sup>4</sup> at the Massachusetts General Hospital in 1935. Air studies, either by pneumoencephalography

or by ventriculography, have been carried out routinely throughout this period, and electroencephalography since 1937. Penfield's method of mapping the cerebral cortex of the patient under local anesthesia with the thyratron stimulator has been used in these operations. In the last year of World War II the development of a cortical electrode holder and of the technic for "activated electroencephalography" on Dr. A. Earl Walker's<sup>5</sup> service at the Cushing General Hospital has provided a still more effective method of delimiting the area from which the epileptogenic discharge originates, but it is not safe to draw conclusions from such recent operations. We have therefore selected the decade 1935-1944 for statistical review because it gives a follow-up period from a minimum of two years up to a possible maximum of twelve for the evaluation of surgical results.

#### MATERIAL

Out of the total 80 patients submitted to exploration for seizures that were believed to have resulted from trauma or infection, 62 are available for statistical study of end results. These include 49 cases of acute or chronic seizures resulting from cerebral trauma and 13 following infection (Table 1). The remaining 18 cases were excluded for various reasons. Follow-up study was inadequate in 6. Three other patients turned out to have brain tumors (these cases are described below). In 7 with previously verified abscesses, 1 with cortical resection for athetosis and 1 with a subcortical hematoma following rupture of a cerebral aneurysm, operation for complicating mild seizures was not considered necessary. Epilepsy due to widespread cortical atrophy, diffuse degenerative disease, hydrocephalus and the hereditary forms of the disease is not suitable for surgical treatment, and failure to find operable lesions in some of the cases described below was due primarily to our lack of sufficient appreciation of this fact in the

\*Presented at the annual meeting of the Massachusetts Medical Society, Boston, May 25, 1948.

†From the Neurosurgical Service, Massachusetts General Hospital.

‡Assistant professor of surgery, Harvard Medical School; chief Neurosurgical Service, Massachusetts General Hospital.

§Resident in neurosurgery, Graduate Hospital of the University of Pennsylvania; formerly research fellow in neurosurgery, Massachusetts General Hospital.

¶Member, Board of Consultation, Massachusetts General Hospital.

Although the type of epilepsy observed in the great majority of these patients was the classic Jacksonian focal seizure, some had generalized attacks and others only hallucinatory auras. The petit mal form of epilepsy, however, rarely if ever starts from a superficial focus and is therefore not amenable to surgery.

Thyroid gland, goiter of, colloid, with cystic formation, 34252  
 Tibia, abscess of (Brodie's), 34381  
 Trachea, adenoma of, with extension into thyroid gland, 34352  
 Tuberculosis of adrenal glands, 34502  
   of endometrium, 34282  
   of lung, 34261, 34502  
   of lymph nodes, 34502  
   of Fallopian tube, 34282  
 Tumor, Ewing's, of sacrum, 34012  
 Ulcer of duodenum, acute, 34122  
   chronic, 34072  
   of esophagus (peptic), 34462  
 Uterus, adenoacanthoma of fundus of, 34271  
   endometritis, 34282  
   normal, 34042  
 Varix of esophagus, with rupture, 34402, 34432  
 Vein, extension of hepatoma into (portal and hepatic), 34011, 34521  
   phlebitis of, thrombo-, 34172  
   thrombosis of (popliteal), 34242  
   mesenteric, 34382  
 Vertebra, carcinoma of, metastatic, 34031  
   chordoma of, second and third lumbar vertebrae, 34511

#### SPEAKERS IN DISCUSSION OTHER THAN TRACY B MALLORY

The numbers in heavy type refer to cases in which  
 the speaker has presented the Differential Diagnosis

Adams, F Dennette, 34211, 34441  
 Adams, Raymond D, 34201  
 Albright, Fuller, 34092  
 Allen, Arthur W, 34371, 34382  
 Aub, Joseph C, 34221, 34252, 34331, 34502  
 Baker, Myles P, 34011, 34172, 34241  
 Barney, J Dellinger, 34262  
 Barr, Joseph S, 34232, 34501  
 Bartlett, Marshall K, 34061, 34222  
 Bauer, Walter, 34111, 34152, 34491, 34502  
 Beckman, William W, 34041, 34221  
 Benedict, Edward B, 34082, 34151, 34481  
 Bland, Edward F, 34081, 34111, 34241, 34242  
 Bock, Arlie V, 34051  
 Brailey, Allen G, 34151, 34392  
 Burgin, Leo B, 34132, 34292  
 Butler, Allan M, 34132, 34182, 34512  
 Castleman, Benjamin, 34012, 34032, 34041, 34052, 34061, 34071, 34082, 34112, 34131, 34271, 34282, 34291, 34301, 34311, 34321, 34351, 34352, 34362, 34371, 34381, 34382, 34392, 34401, 34441, 34471, 34472, 34492, 34511, 34522, 34532  
 Cattell, Richard B, 34511  
 Cave, Edwin F, 34162  
 Chapman, Earle M, 34131, 34231, 34301, 34372, 34432, 34461  
 Churchill, Edward D, 34142  
 Chute, Richard, 34472  
 Clark, Lincoln, 34212  
 Clark, Richard J, 34391  
 Clark, William S, 34262  
 Cogan, David G, 34482  
 Colby, Fletcher H, 34081  
 Cope, Oliver, 34351, 34352, 34362, 34491  
 Craige, Ernest, 34261  
 Culver, Perry J, 34321, 34332  
 Daland, Ernest M, 34112, 34151  
 Davenport, Lowrey F, 34032, 34062, 34272  
 Decker, Briant L, 34212  
 Dobyns, Brown M, 34181  
 Ellis, Daniel S, 34092, 34171, 34251, 34281, 34301, 34402, 34421, 34432, 34502  
 Farber, Sidney, 34361  
 Farnsworth, Dana L, 34051  
 Faxon, Henry H, 34341  
 Franseen, Clifford C, 34162, 34471  
 Freiman, David G, 34372  
 Fremont-Smith, Maurice, 34172  
 Gephart, F Thomas, 34071, 34412  
 Giddings, W Philip, 34052, 34271, 34452  
 Gregg, Ward I, 34271  
 Halsted, James A, 34371  
 Hamlin, Edward, Jr, 34172  
 Hanelin, Joseph, 34302, 34332, 34451, 34461  
 Hardy, Irad B, 34252, 34382  
 Harwood, Reed A, 34172, 34342  
 Holmes, Joseph A, 34112  
 Jacobson, Bernard M, 34062, 34331, 34362, 34531  
 Johnson, Charles I, 34482  
 Kelley, Rita M, 34451  
 King, Donald S, 34031, 34142, 34262, 34272, 34342, 34392  
 Kowalski, Henry J, 34131  
 Kranes, Alfred, 34091, 34261, 34312, 34451  
 Kubik, Charles S, 34131, 34182, 34192, 34201  
 Leadbetter, Wyland F, 34262  
 Lerman, Jacob, 34261, 34352, 34412, 34432  
 Linton, Robert R, 34121, 34122  
 Lowe, Charles, 34302  
 Lurie, Moses H, 34352  
 Mabrey, Roy E, 34012, 34492  
 McCort, James J, 34141, 34252, 34262, 34272, 34291, 34371, 34382, 34402, 34412, 34422, 34432, 34442, 34462, 34471, 34482, 34501, 34512  
 McDonald, Francis, 34161  
 McKittick, John B, 34282, 34291  
 Means, James H, 34391  
 Meigs, Joe V, 34042, 34281, 34411  
 Miller, Carroll C, 34021, 34202, 34211, 34401, 34412  
 Myers, Gordon S, 34532  
 Parsons, Langdon, 34411  
 Pittman, Helen S, 34242, 34412  
 Racker, J W, 34102  
 Reid, John A, 34232  
 Reysersbach, Gertrud C, 34351, 34512  
 Richardson, W R, Jr, 34531  
 Richardson, Wyman, 34141, 34251  
 Risley, Thomas S, 34082  
 Robbins, Laurence L, 34401  
 Rogers, Horatio A, 34121  
 Ropes, Marian W, 34092, 34402, 34501, 34531  
 Ross, Ralph A, 34182, 34512  
 Sarris, S Peter, 34102  
 Scannell, John G, 34022, 34061, 34372, 34462  
 Schatzki, Richard, 34181, 34431  
 Schier, W Wilson, 34422  
 Schulz, Milford D, 34032, 34082  
 Short, Charles L, 34072, 34432  
 Simmons, Channing C, 34381  
 Simmons, Fred A, 34471  
 Smith, Judson J, 34042, 34281  
 Sniffen, Ronald C, 34161, 34181, 34182, 34312  
 Sosman, Merrill C, 34152, 34481  
 Soutter, Lamar, 34022, 34481, 34522  
 Sprague, Howard B, 34191, 34442  
 Stanbury, John B, 34521  
 Sturgis, Somers, 34042  
 Swank, Roy L, 34192  
 Swartz, Jacob B, 34272  
 Sweet, Richard H, 34071, 34292, 34452, 34462  
 Talbot, Nathan B, 34302  
 Taylor, Grantley W, 34132, 34322, 34482, 34522  
 Taylor, Isaac M, 34101, 34391  
 Townsend, James H, 34332, 34521  
 Ulfelder, Howard, 34282  
 Welch, Claude E, 34072, 34082, 34121, 34431, 34492  
 Wells, Bertrand, 34101  
 White, Paul D, 34051, 34101  
 Williams, Conger, 34111  
 Wyman, Stanley M, 34011, 34021, 34022, 34031, 34051, 34052, 34071, 34072, 34081, 34091, 34101, 34102, 34111, 34121, 34122, 34132, 34142, 34151, 34161, 34162, 34171, 34172, 34191, 34201, 34202, 34211, 34212, 34222, 34231, 34232, 34241, 34242, 34251, 34261, 34281, 34292, 34301, 34311, 34312, 34321, 34322, 34341, 34342, 34351, 34352, 34361, 34362, 34372, 34381, 34391, 34392, 34421, 34441, 34472, 34491, 34492, 34502, 34521, 34531, 34532  
 Young, Edward L, 34311  
 Zamecnik, Paul C, 34342, 34391

work despite occasional nocturnal seizures. In this patient circumscribed softening in the arm area was also present. A man who required evacuation of a subcortical clot in addition to a large subdural collection suffered mild sensory attacks every four to six months for two years, and has subsequently remained free for four years. Another, who in addition to a small subdural hematoma had a large subcortical clot with considerable contusion to the neighboring area of the brain, developed seizures for the first time six weeks after operation. In this case the chronic epilepsy, which has continued for the past two years, cannot be ascribed to the subdural hemorrhage, since an extensive cerebral cicatrix remains. Although subdural hematomas, if uncomplicated and evacuated early, are not likely to cause residual epilepsy, we have found trapped pockets of yellow fluid in the course of three operations for chronic epilepsy, which were probably residua of former extravasations of blood into the subdural space. One of these patients had had a hematoma evacuated one year previously.

*Cortical compression from depressed fractures*  
Acute compression of the underlying cortex by simple depressed fractures of the cranial vault may lead to rapid onset of focal seizures. This was encountered in 6 of a series of 54 cases of these lesions. In each case there was definite cortical compression by the depressed cranial fragments, and the result of decompression by their elevation or removal was prompt and permanent disappearance of the seizures. This fortunate result is ascribed to the fact that in each of these civilian injuries the dura remained intact and the underlying cortex presumably was not lacerated, so that there was no permanent meningocerebral cicatrix or focal injury of the cortex to lead to late chronic epilepsy. Early removal of the compressing fragments, especially if in the vicinity of the motor cortex, is essential to prevent the formation of a cortical scar and a high incidence of chronic epilepsy. The following case report serves to illustrate this situation.

A 5-year-old girl riding her tricycle fell over an embankment and suffered a left temporoparietal depressed fracture (Fig 1). She was briefly unconscious and then had a lucid interval. An hour later she again became comatose and developed twitching movements of the right side of the face and the right extremities. These soon became continuous, the coma deeper, and the respirations slow and labored. Exploration without anesthesia revealed a subgaleal hematoma and two large angulated fragments of bone, which deeply depressed the intact dura. As soon as these were elevated the convulsive movements ceased. There was no evidence of residual damage to the brain, and the patient left the hospital 10 days later in excellent condition. A recent follow-up letter, 5 years later, states that she is a nervous, maladjusted child at school, but has had no convulsive seizures.

Of the severer wartime injuries reported by Ascroft,<sup>9</sup> even when the dura was not torn, 23 per cent were followed by chronic seizures. This incidence, however, was only half as high as that when the dura was penetrated. When the underlying

dura is torn and the cortex lacerated, especially in the presence of indriven fragments of bone or infection, even though the acute seizures may clear up, there is high incidence of chronic epilepsy. This amounted to 45 per cent in the best military statistics of World War I (Ascroft<sup>9</sup>), although indriven fragments were removed and damaged cortex radically sucked away. Injuries of this type are followed by scar formation and frequently result in recurrent seizures for this reason. It is a matter



FIGURE 1 *Comminuted Depressed Temporoparietal Fracture, Which Caused Acute Status Epilepticus. Continuous seizures ceased as soon as the depressed fragments were elevated.*

of major concern to the United States Veterans Administration that there are listed 15,000 cases of craniocerebral injuries in which the patients have survived the present war, nearly half of whom may develop chronic seizures (Watson<sup>10</sup> and Bailey<sup>11</sup>).

#### *Chronic Epilepsy Following Cerebral Injury*

This series of 28 patients with chronic epilepsy due to cerebral scars, on whom operation was undertaken and adequate follow-up obtained, is subdivided as follows: cortical scars or areas of local atrophy (microgyria) following cranial injuries, 27 cases, and postoperative epilepsy following cortical resection, 1 case.

earlier years of this decade. In some previous reports<sup>3</sup> the surgical epileptic cases have been subdivided on the pathological basis of expanding lesions and focal scars. In such a classification the intracranial hematomas and acute abscesses have been included with the neoplasms. In this review it has seemed best to discuss the actual tumors as a separate group.<sup>1</sup> We are therefore classifying the

TABLE 1 *Classification of Epilepsy after Cerebral Injury and Infection in 62 Patients Selected for Statistical Analysis*

LESION	No. of CASES
Epidural hemorrhage (early or acute epilepsy)	5
Traumatic from bleeding middle meningeal artery	1
Postoperative bleeding	4
Subdural hemorrhage (acute epilepsy)	10
Depressed and compound fractures (acute epilepsy)	6
Cerebral scars (chronic epilepsy)	28
Traumatic	27
Postoperative	1
Brain abscesses	13
Acute seizures	9
Chronic seizures	4
Total	62

hematomas with the post-traumatic group of depressed and compound fractures, meningocerebral cicatrices and focal cortical scars, and separating the abscesses into a third group of postinfectious cases (Table 1).

These two groups of post-traumatic and post-infectious cases, which are the subject of this paper, can be subdivided again on the basis of whether the lesion caused acute or chronic epilepsy. Thus the hematomas, depressed fractures and acute abscesses that may produce early seizures fall into the acute group, whereas healed abscesses and penetrating wounds of the brain that form contracting fibroglial scars may result in late chronic epilepsy.

## EPILEPSY AFTER CEREBRAL TRAUMA

### *Acute Epilepsy from Cerebral Compression*

**Intracranial hematomas.** Intracranial bleeding of all types may bring on convulsive seizures either by acute compression of the brain or by concomitant damage to the cortex.

Gamsu and Kubik,<sup>6</sup> who are making a special study of subarachnoid hemorrhage in this hospital, have found that bleeding of this type was accompanied by acute convulsions in 20 out of 118 cases. Fourteen patients died, with verification of ruptured congenital aneurysms in all 9 on whom post-mortem examination was permitted. It deserves passing comment that only 2 of these brains on sectioning showed direct injury to the cortex and underlying white matter by intracerebral extension of the clot. In this decade these patients were not submitted to arteriography or ventriculography, and none had intracranial explorations. It is diffi-

cult to explain why acute seizures develop when hemorrhage is limited to the subarachnoid space. On the other hand, when blood burrows into the cortex and underlying white matter their occurrence is easy to understand, both in the acute stage and also at later periods if the patient survives and the clot is replaced by a meningocortical scar or deeper cerebral cicatrix. The situation here is identical with that seen after drainage and healing of cerebral abscesses, which are generally recognized as a cause of chronic seizures. At present we have a patient under observation in whom a large subcortical hematoma has been effectively evacuated and the bleeding point in the anterior cerebral artery ligated at another clinic.\* Despite this brilliant diagnosis and life-saving surgical treatment, the delayed appearance of chronic epilepsy may necessitate another surgical intervention.

Focal seizures are a frequent warning signal of the development of a postoperative clot, having been present in 4 out of 12 cases that required secondary re-elevation of the bone flap for postoperative bleeding. These seizures are generally minor ones, producing fine twitching movements of the opposite side of the face, with rare extension to other areas. Prompt surgical exploration, with evacuation of the clot and control of any bleeding that is still present, has invariably resulted in early cessation of the seizures in both the postoperative hematomas and the post-traumatic variety discussed below.

Intracranial hematomas such as clots that occur after tearing of the middle meningeal artery may cause convulsive seizures. During this decade we have encountered this complication in only 1 of 9 cases of typical acute epidural hemorrhage following temporoparietal fractures with injury to the middle meningeal artery.

Subdural hematomas of venous origin, which expand much more slowly than the arterial extradural variety, may also lead to seizures. Kunkel and Dandy<sup>7</sup> reported attacks in 12.7 per cent of 48 cases, but Elvidge<sup>8</sup> concludes that this is a rare complication of subdural bleeding unless there is concomitant cortical injury. Our findings support those of Kunkel and Dandy.<sup>7</sup> Among 120 patients in whom such clots were diagnosed and evacuated, transitory seizures were observed in 10†. In 6 out of 7 cases in which there was no other obvious damage to the brain the seizures stopped and have not recurred. In the single exception there were only two attacks in the next two and a half years. In a case of closed head injury that had occurred eleven years previously, drainage of a large subdural hygroma has resulted in great improvement, so that the patient is able to

\*This patient a relative of one of us was referred to Dr. J. L. Poppen.

†Three other subdural hematomas accompanied by convulsions have been drained during this decade. As it has been possible to keep the patients under observation for only a few months their freedom from epilepsy cannot be regarded as permanent.

visual aura (a small black bird hovering in the right upper visual field) and major Jacksonian convulsions lateralized to the right. X-ray films showed the 22 caliber bullet at the tip of the temporal lobe with the ventricle dilated and drawn toward the scar. The patient had a very slight aphasia and reduction of the right visual field. At the time of exploration (September 5, 1940) the track of the bullet was disclosed wiping out the sylvian fissure (Fig 2). Stimulation at marker No 4 set off a mild facial seizure with twitching of the corner of the mouth, followed for about 5 minutes by partial aphasia. We were therefore forced to content ourselves with resecting the posterior portion of the scar, where the bullet had entered, and a deeper area at the tip of the left temporal lobe. The bullet, embedded in bone, was not removed. With the exception of four major seizures, the last in 1943 after the patient had omitted dilantin, he has had only rare minor spells. In these he has to stop work in a shoe factory for a few minutes on account of a sense

methods of obtaining electrocorticograms by means of the sterile electrode holders and by mapping the spread of the after-discharge following electrical induction of a subclinical seizure (Walker et al <sup>4, 5</sup>), it is possible to excise small active foci of irritable

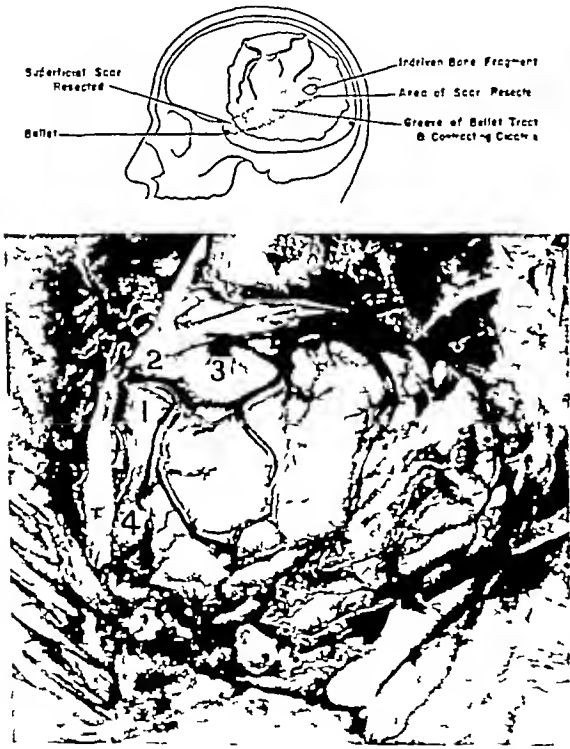


FIGURE 2 Cortical Cicatrix in Dominant Temporal Lobe, Which Caused Major Jacksonian Seizures Starting with a Visual Aura

Electrical stimulation at the markers caused flexion of the fingers of the right hand (No 1), contraction of forearm flexors (No 2), sensation at the right knee (No 3) and a brief convulsion limited to the face starting with movements of the corner of the mouth on the right side (No 4)

of confusion, but can talk with difficulty. At the time of his last visit, 4 1/4 years after operation, he had had no seizures for 6 months.

In this decade, although accurate mapping of the motor strip could be carried out under local anesthesia with the thyratron stimulator, the method of delimiting epileptogenic areas by inducing clinical seizures through electrical stimulation was at best a crude one. At present, with the more refined

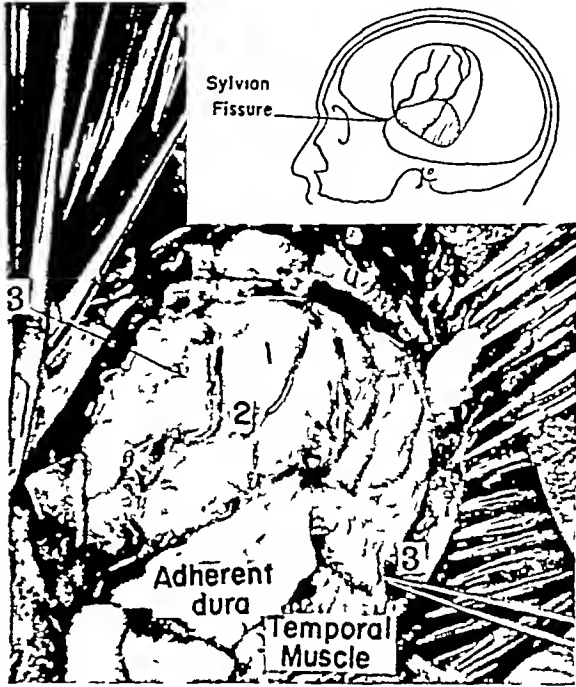


FIGURE 3 Adherent Meningocortical Cicatrix in Dominant Temporal Lobe, Which Gave Rise to Jacksonian Seizures Starting with an Auditory Aura. Difficulty in Speech, Paresthesias in Arm and Leg and Final Loss of Consciousness. Electrical stimulation at Marker No 1 caused supination and flexion of the right wrist. Electrical stimulation at Marker No 2 caused a low prolonged cry, followed by flexion of arm muscles and then a generalized convulsion. Areas of abnormal-appearing cortex and pia arachnoid (Marker No 3).

cortex at the edge of large scars even in the most important areas of the brain. Considering the difficulties of accurate localization of epileptogenic foci during this period, the complete eradication or pronounced amelioration of seizures in 14 out of 28 patients has been most encouraging.

Mere freeing up of adhesions in a meningocortical cicatrix, which was all that could be undertaken when the epileptogenic focus lay in vital speech or motor areas, was at best an unsatisfactory procedure. At present exploration can be carried farther by analysis of the cortical electrogram, whereby small epileptogenic foci can often be localized at the edge of the scar by their emission of abnormal electrical waves and excised without serious loss of function. In addition, dural repair with fibrin film

The circumscribed lesions listed above may be classified further as examples of meningocerebral cicatrices or focal lesions of the cortex with more or less involvement of the underlying brain. Air studies, which frequently revealed pronounced distortion of the underlying ventricle, showed that the pathologic process was usually a deep one, with gliosis and atrophy extending into the white matter.

In all these cases every effort had been made to control the frequency and severity of seizures by

Results following exploratory craniotomy in 28 cases of traumatic epilepsy are summarized in Table 2. In these the trauma was traced back to birth or infancy in 9. In the 19 patients in whom it occurred in later childhood or adult life, 10 had suffered depressed or compound fractures, 7 closed head injuries (2 of whom had complicating subdural hematomas that had been previously evacuated), and 1 a focal scar, the exact cause of which could not be determined. The last is included with

TABLE 2 *Operative Statistics in Chronic Epilepsy of Traumatic Origin*

INJURY	NO OF CASES	PATHOLOGIC LESION	OPERATION	EXCELLENT RESULT NO OF CASES	GOOD RESULT NO OF CASES	IMPROVEMENT NO OF CASES	FAILURE NO OF CASES
Depressed or compound fracture	10	Meningocortical scar	Excision	3		1	
		Cortical cicatrix	Lysis of adhesions				1
			Excision	1	1		
			Partial excision		1		1
Closed head injury	7	Porencephalic cyst	Excision			1	
		Meningocortical scar	Lysis of adhesions	1*	2		
		Cortical cicatrix	Excision	1			
		Diffuse cortical atrophy	Lysis of adhesions	1			1
Previous surgery	1	Cortical cicatrix	Excision only			1	
Focal atrophy of undetermined origin	1		Partial excision				1
Birth injury	9	Meningocortical scar	Excision		1		
		Cortical cicatrix	Excision			1	
		Porencephalic cyst	Excision	1			
			Partial excision		1		
		Diffuse cortical atrophy	Excision only				2
		No visible lesion	Exploration only				2
			Negative exploration				1†
Totals	28			8	6	5	9

\*Adhesions in this case were the residua of a previously drained subdural hematoma — small quantities of yellow fluid trapped in the subdural space with additional lakes in the subarachnoid.

†Re-exploration has recently been carried out with localization of an epileptogenic focus by the electrocorticogram. Excision has been followed by early improvement. Again no definite cortical scar was seen.

anticonvulsant drugs and general medical treatment. Operation was advised only in patients who failed to improve and in whom there was definite evidence of focal scarring shown by the aura and clinical manifestations of the seizure, neurologic examination, electroencephalogram (in the latter part of the series) and air studies.

**Post-traumatic epilepsy.** Exploratory craniotomy was performed in 37 patients after old or recent injury to the brain. Of these, 28 have been under observation for prolonged periods and are suitable for this study. It is important to remember that the source of the epileptic discharge is never within the cicatrix itself, but at some point in the transition zone between the completely scarred area and normal brain. Although the cortex at this point may not appear grossly abnormal, the nerve cells are distorted and compressed by a fine network of fibroglial tissue.<sup>2</sup> It is impossible to locate the epileptogenic focus in the periphery of one of these scars by inspection, and the best method available, prior to the recent development of electrocorticography, was locating the area from which seizures could be induced by the thyratron stimulator with minimal current. In the smaller scars situated in relatively silent areas, the entire area was excised with a small amount of surrounding cortex.

the cases of traumatic origin for want of a better classification. In another the cicatrix was due to a previous cortical resection in the premotor area for Parkinsonian tremor. With a single exception, follow-up studies have been carried over a period of eighteen months to nine years in all cases. The final status of these patients on whom our evaluation of the results is based is presented in Table 3.

Of 11 patients with foci that were small or so favorably situated that the entire visible cortical cicatrix or meningocortical scar could be excised, 6 have never had another seizure, and 2 others have had such a reduction in frequency and severity of attacks that they are able to work and to lead normal lives. The remaining 3 have shown definite, maintained improvement in the severity and frequency of the seizures, so that with the aid of medication all have been able to lead active lives.

In 7 patients with partial excision of the cerebral lesion, 4 failed to obtain any notable improvement. In the remaining 3, however, the results were very definitely encouraging. The following case report is of interest because the site and extent of the scar presented a particularly difficult problem.

A 21-year-old man had had a previous debridement of a gunshot wound of the left temple at this hospital in 1933. Epilepsy began 7 years later, characterized by an elaborate

visual aura (a small black bird hovering in the right upper visual field) and major Jacksonian convulsions lateralized to the right. X-ray films showed the .22 caliber bullet at the tip of the temporal lobe with the ventricle dilated and drawn toward the scar. The patient had a very slight aphasia and reduction of the right visual field. At the time of exploration (September 5, 1940) the track of the bullet was disclosed wiping out the sylvian fissure (Fig 2). Stimulation at marker No 4 set off a mild facial seizure with twitching of the corner of the mouth, followed for about 5 minutes by partial aphasia. We were therefore forced to content ourselves with resecting the posterior portion of the scar, where the bullet had entered, and a deeper area at the tip of the left temporal lobe. The bullet, embedded in bone, was not removed. With the exception of four major seizures, the last in 1943 after the patient had omitted dilantin, he has had only rare minor spells. In these he has to stop work in a shoe factory for a few minutes on account of a sense

methods of obtaining electrocorticograms by means of the sterile electrode holders and by mapping the spread of the after-discharge following electrical induction of a subclinical seizure (Walker et al<sup>4,5</sup>), it is possible to excise small active foci of irritable

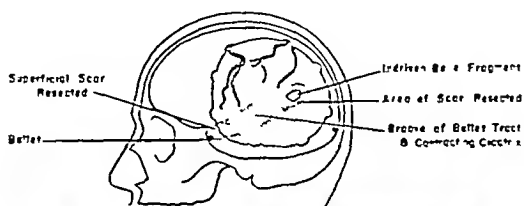


FIGURE 2 Cortical Cicatrix in Dominant Temporal Lobe, Which Caused Major Jacksonian Seizures Starting with a Visual Aura

Electrical stimulation at the markers caused flexion of the fingers of the right hand (No 1), contraction of forearm flexors (No 2), sensation at the right knee (No 3) and a brief convulsion limited to the face starting with movements of the corner of the mouth on the right side (No 4)

of confusion, but can talk with difficulty. At the time of his last visit, 4 1/4 years after operation, he had had no seizures for 6 months.

In this decade, although accurate mapping of the motor strip could be carried out under local anesthesia with the thyratron stimulator, the method of delimiting epileptogenic areas by inducing clinical seizures through electrical stimulation was at best a crude one. At present, with the more refined

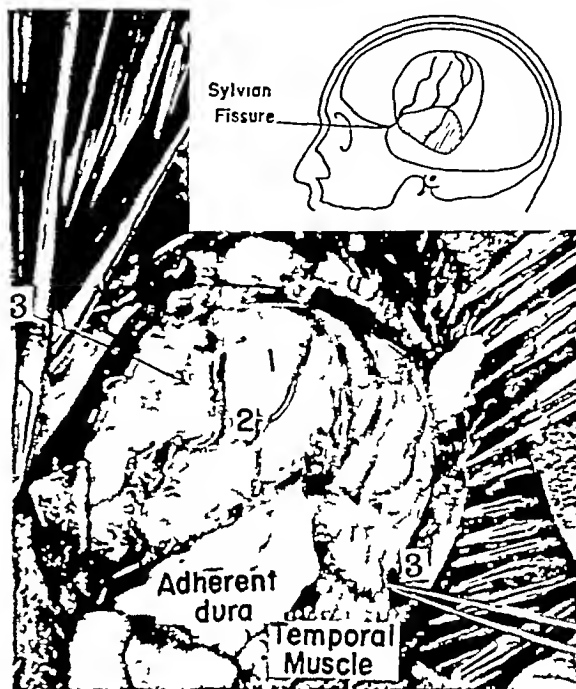


FIGURE 3 Adherent Meningocortical Cicatrix in Dominant Temporal Lobe, Which Gave Rise to Jacksonian Seizures Starting with an Auditory Aura Difficulty in Speech, Parasthesias in Arm and Leg and Final Loss of Consciousness

Electrical stimulation at Marker No 1 caused supination and flexion of the right wrist

Electrical stimulation at Marker No 2 caused a low prolonged cry, followed by flexion of arm muscles and then a generalized convulsion

Areas of abnormal-appearing cortex and pia arachnoid (Marker No 3)

cortex at the edge of large scars even in the most important areas of the brain. Considering the difficulties of accurate localization of epileptogenic foci during this period, the complete eradication or pronounced amelioration of seizures in 14 out of 28 patients has been most encouraging.

Mere freeing up of adhesions in a meningocortical cicatrix, which was all that could be undertaken when the epileptogenic focus lay in vital speech or motor areas, was at best an unsatisfactory procedure. At present exploration can be carried farther by analysis of the cortical electrogram, whereby small epileptogenic foci can often be localized at the edge of the scar by their emission of abnormal electrical waves and excised without serious loss of function. In addition, dural repair with fibrin film

and reconstruction of cranial defects with acrylic resin plates\* can now be used to reduce the reformation of meningeal adhesions that distort the vasogial framework of the adjacent cortex. Penfield and Erickson<sup>3</sup> have stated that mere lysis of adhesions cannot be expected to give any significant improvement, and with this we are in general agreement. However, it is remarkable that a patient whose operation was limited to the release of yellow subdural fluid left from the previous drainage of a

of the high-protein-containing fluid and lysis of adhesions the former had no seizures and was working hard over a four-year period, whereas the latter has been unimproved. The difficulties encountered in the remaining case, in which dense adhesions bound the dura down to the cortex in Broca's area, are illustrated by the following report:

A 28-year-old man, after a compound depressed fracture in the left temple, developed epilepsy within 1 month. He had Jacksonian seizures for 3 years, beginning with an

TABLE 3 Postoperative Follow-up Data on 28 Patients with Chronic Traumatic Epilepsy Selected for Statistical Analysis.

CASE NO.	SEX	AGE yr	POSTOPERATIVE COURSE	ANTICONVULSANT MEDICATION	FOLLOW UP PERIOD
Excision of scar with depressed or compound fracture					
18	M	24	No attacks except immediately after operation	No	12 yr
28	M	12	Patient symptom free and leading normal life	No	2½ yr
21	M	25	Patient working sporadically; no seizures but some character change reported	?	2½ yr
15	M	31	Patient working	No	7½ mo
12	F	9	Patient attending school; seizures only when medication is omitted	Yes	3 yr
16	F	31	Patient engaged in housework; 2 or 3 seizures yearly, but none for last 6 mo	Yes	3½ yr
1	M	26	Patient working hard but has had seizures at rare intervals and one period requiring hospital admission	Yes	2 yr
Partial excision of scar with depressed or compound fracture					
26	M	21	No seizures on dilantin for past 6 mo	Yes	4 yr
13	M	15	No change; patient in corrective institution	Yes	4½ yr
Lysis of adhesions with depressed or compound fracture					
22	M	28	No change in frequency or severity of seizures	Yes	8½ yr
Excision of scar with closed head injury					
20	M	33	No seizures, patient works as athletic coach	?	4 yr
Lysis of adhesions with closed head injury					
4	M	20	No seizures, patient engaged in heavy construction work	?	4 yr
14	M	14	Headache and 2 seizures; patient in school and is ardent athlete	?	2 yr
17	M	19	Patient working and looks well but had one bout of status epilepticus (his statements may not be reliable)	No	11 yr
24	M	26	No change in epileptic status	Yes	6½ yr
27	M	40	No seizures; patient director of a War Production Board during war	?	10½ yr
Exploration only for scar with closed head injury					
6	M	18	Definite reduction in frequency of seizures; patient able to work as farmer but has series of seizures occasionally	Yes	6 yr
Partial excision of scar due to previous surgery					
3	M	25	No change in seizure pattern; recent re-exploration	Yes	6 yr
Excision of scar of undetermined cause					
25	M	38	Patient does regular office work; seizures reduced to less than half their former frequency	Yes	2 yr
Excision after birth injury					
23	M	15	Patient works for General Electric Company; two spells in last 6 mo	Yes	6½ yr
5	M	12	Patient goes to school and leads normal life; no seizures.	No	5½ yr
Partial excision after birth injury					
10	M	11	About 2 seizures per month but less frequent and severe than preoperatively; patient keeps up at school	Yes	1½ yr
19	M	19	Only 1 seizure per year; patient engaged in active work	Yes	7½ yr
9	M	3	Patient in state school and has series of convulsions about once a year; hemiplegia has increased	Yes	9 yr
11	F	20	Seizures continue with progressive mental deterioration	Yes	7 yr
Diffuse atrophy due to birth injury; no focus excised					
8	M	8	No change in seizures	Yes	2 mo.
2	M	19	No change in seizures	Yes	9 yr
Negative exploration after birth injury					
7	M	25	No change in seizures; second exploration recently has localized resectable focus	Yes	8 yr

hematoma, with evacuation of further lakes under the arachnoid, has had complete freedom from seizures over a period of nine years. During the war he became head of the War Production Board in a large industrial city. Two other patients have been operated upon with the finding of trapped lakes of yellow fluid in the subdural space and accompanying atrophy of the underlying cortex following old closed head injury (Tables 2 and 3). After release

auditory aura, difficulty in speech and numbness and tingling of the right arm and leg, followed by loss of consciousness and biting of the tongue. At the time he left the New Haven Hospital, where the cerebral laceration was debrided and a hematoma evacuated by Dr. William J. German, he had difficulty in reading, writing and speaking, but this had improved so that on his second hospital admission here he had difficulty only when excited or at the onset of an attack. Neurologic examination was not remarkable except for slight residual aphasia. An electroencephalogram demonstrated slow waves in the left motor area, and a pneumoencephalogram showed the ventricle on the left to be slightly dilated and drawn to this side. The situation found at operation on October 19, 1948, is shown in Figure 3. The dense adhesions between the dura and cortex were divided and some areas of yellow, softened cortex in the temporal

\*Cranioplasty with plates of acrylic resin is preferable to the standard method with tantalum in epileptic patients since this material permits subsequent pneumograms to be made if continued seizures necessitate further investigation.

lobe sucked away, but at that time it was impossible to proceed farther for fear of producing a profound aphasia. There has been no change in the number or severity of the seizures.

Technical advances developed during the war have made surgical cure of cases of this sort possible. This patient will soon be readmitted, and it is planned again to free up the meningocerebral adhesions. With the cortical electrodes and direct recording of the brain waves it may then be possible to locate and excise a small epileptogenic focus at the periphery of the extensive scar without interfering with the speech areas of the dominant temporal lobe. The dura will be repaired with fibrin film to prevent reformation of a contracting meningocerebral scar, and the defect in the skull closed with an x-ray-transparent plate of acrylic resin.

Of 5 patients submitted to exploratory craniotomy, in whom diffuse areas of cortical atrophy were exposed without any clear-cut local lesion that could be excised, only 1 (Table 3, Case 6) maintained a lasting improvement of minor degree. He is able to work as a farmer, but has occasional recurrences of seizures. In several other cases, however, there was temporary improvement that might have been considered significant if follow-up observations had not been carried over prolonged periods. Brief postoperative observation in the past has often given rise to misleading conclusions, since any nonspecific operation, such as sympathectomy or even resection of the colon, has led to a temporary reduction of seizures.

When the presence of an irritable focus is well established by characteristic Jacksonian seizures and persistent abnormality in the electroencephalogram, the failure to find an epileptogenic lesion should lead to a most careful search for an underlying neoplasm. We have failed to locate such tumors in 3 cases. Pneumoencephalograms in these patients did not suggest an expanding lesion, and 2 of them gave a definite history of previous cranial injury. After the bone flap had been turned down, no very convincing cortical lesion, but only a mild degree of diffuse cortical atrophy, was disclosed in 2 cases. In the third a pinkish area with increased vascularity was observed and excised, since it gave rise to seizures on electrical stimulation. Microscopical examination, however, failed to show either gliosis or tumor. All 3 patients were regarded by the operating surgeon as tumor suspects, and careful exploration was made by palpation and diagnostic puncture. No patient had lasting relief of seizures, and all failed to return for further observation. Subsequent investigation disclosed that the first died three years later after a period of aphasia followed by coma. The other 2 were reoperated upon at other neurosurgical centers, with the discovery of an oligodendroglioma and a fibrillary astrocytoma, respectively. We have had a number of similar experiences with epileptic pa-

tients who had had a previous exploration at other clinics. Since epilepsy is frequently the first symptom of an underlying glioma or meningioma, since the seizures may persist for years without causing any rise in intracranial pressure or neurologic signs and since the pneumogram may at first be perfectly normal,<sup>1</sup> it is most important to bear in mind the possibility of a subcortical tumor even in a

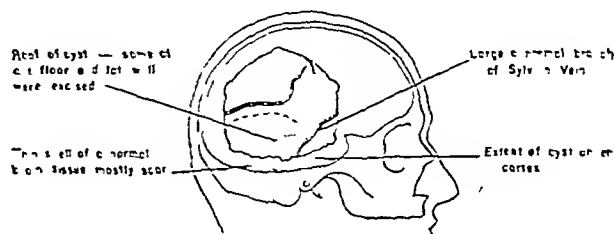


FIGURE 4 Large Porencephalic Cyst in a Young Woman with a Ten-Year History of Epilepsy Accompanied by a Mild Left Hemiparesis and a Homonymous Field Defect (Seizures Began with a Sensory Aura, Followed by Turning of the Eyes and Head to the Left and Contraction of the Left Facial Muscles)

Marker No 6 is on the motor strip. Electrical stimulation at the other markers induced no seizure or other response.

patient whose seizures have followed a definite cranial injury.

The statistics presented above give a good idea of the relative value of complete versus inadequate eradication of epileptogenic foci. After apparently complete excision good results were obtained in over half the patients, whereas failure to locate a circumscribed lesion in cases of diffuse atrophy was invariably followed by a continuation of the convulsive seizures. It is also of interest to break down the statistics in another way to show the results of surgery in seizures resulting from the more fre-

quent pathologic lesions that follow cerebral injury. These are presented in Table 2. From our experience with these cases we have come to the conclusion that surgical intervention can be undertaken with approximately equal chances of success in the various types of epileptogenic scars that follow trauma in the adult brain. In 11 of the 19 patients followed over adequate periods the results of surgical intervention were distinctly worth while. On the other hand, in the 9 cases in which epilepsy followed a history of birth injury or damage to the brain in early infancy, only 4 patients obtained lasting reduction in the frequency and severity of seizures. This is because injury to the rapidly developing brain of an infant is likely to produce diffuse areas of atrophy or large porencephalic cysts of the type illustrated in Figure 4. None of the patients with diffuse atrophy improved, since no focal areas could be excised. Of the 4 cases of porencephalic cysts treated by partial excision of the cyst wall and glial scar at the periphery, the results in 2 are not encouraging. Case 5, a twelve-year-old boy whose spells began at the age of three and averaged a major seizure daily, has had complete freedom for a period of five and three-quarters years. Neurologic examination is negative, and the electroencephalogram has returned to an almost normal pattern. He requires no medication and has been able to catch up with his proper grade in school. The other (Case 19), whose seizures began at the age of twelve, was operated on at the age of nineteen, and a large cystic lesion was found in the postcentral cortex. This led down to the lateral ventricle, and much of its anterior margin could not be excised owing to the proximity of the motor arm area. During the ensuing eight years he has been able to work steadily as a welder, with only occasional seizures, which disappear altogether when he remains on a careful regime with adequate anticonvulsant medication. The other patients received no benefit, and the one whose lesion is shown in Figure 4 has deteriorated mentally to the point where she should soon be committed to an institution. When birth injury results in a small cortical scar or focal atrophy (microgyria) the results of excision can be just as good as those in the adult group. Judging from Penfield and Erickson's<sup>3</sup> much larger series, it seems fair to conclude that in our few cases there was an unduly small proportion of eradicable lesions. Even in this least promising group the results following resection of a local scar or atrophied convulsion should be distinctly worth while, provided there is not coexistent extensive atrophy of the brain.

*Epilepsy after cortical excision.* Epilepsy as a result of cortical excision has rarely been reported. That it may follow operations for brain tumor is a possibility, for seizures sometimes occur for the first time after the apparent total resection of meningiomas and certain circumscribed gliomas.<sup>1</sup>

Under these circumstances, however, the epileptic disturbance has been ascribed to the tumor rather than to the operative scar. Be that as it may, this unfortunate complication does follow cases of cortical resection undertaken for the control of abnormal movements and uncontrollable tremor as seen in Parkinsonism and athetosis. Here, even with the most perfect surgical technic, a cicatrix is produced close to the motor strip, in an area that is known to produce the greatest risk of seizures. In view of the frequent enthusiastic publications of Klemme<sup>12</sup> the risk of such a complication is important to bear in mind. Postoperative epilepsy, which is also a complication of prefrontal leukotomy, has been reported by Freeman and Watts<sup>13</sup> in 4 per cent of their cases. We have encountered 2 cases in which epilepsy developed after cortical resection for tremor and have heard reports of others. In our personal cases there was a history suggestive of minor seizures before operation, the preoperative electroencephalogram was slightly abnormal, and seizures were induced in the course of mapping out the motor area prior to the cortical resection. An experience of this sort should certainly warn the surgeon against resecting the premotor area. In one of these unfortunate cases (Case 3, Table 3) we have twice reoperated and removed the more excitable portion of the scar. There was little improvement after the first operation, but after the second, in which the cortical electrode holder was used, the early results are promising.

#### EPILEPSY AFTER CEREBRAL INFECTION

An expanding cerebral abscess may produce acute epilepsy through cortical compression and added irritation from the zone of thrombosis and encephalitis at its frontier. In a series of 72 cases of supratentorial pyogenic abscess secondary to inflammation in the sinuses, mastoids or lungs, 9 were accompanied by acute convulsive seizures. These had a most serious prognostic import, since only 2 patients survived and these continued to have spells after healing.

In addition to the early seizures seen in the acute inflammatory stage of brain abscess discussed above, the condition has developed chronically in 11 patients with healed lesions, not all of whom were treated initially in this hospital. In only 4 of these was surgical intervention indicated and undertaken. In 1 the parasagittal postcentral scar from which an abscess had been radically enucleated resulted in seizures because of local atrophy and the formation of a porencephalic cyst communicating with the lateral ventricle. Excision of the cyst has given a good seven-year result, marred only by three convulsions at the time of childbirth. Two of the other patients operated upon had large scars binding the frontal lobe to the posterior wall of the diseased sinus. In both the scars were excised with

a narrow margin of normal-appearing brain. One, during a period of nine years, has averaged about one seizure a year, with none in the last three years. The other, whose extensive cicatrix is illustrated in Figure 5, has had no seizures in five years and has been able to work full time as a medical secretary. In a fourth case, in which an epidural abscess developed after a fracture that involved the frontal sinus, radical excision of the underlying cicatrix in the frontal lobe has given a fairly good result. Four and a half years afterward this patient was married and leading a normal life. Although she had rare seizures when off medication, these were controlled effectively by dilantin.

#### SUMMARY AND CONCLUSIONS

Of this series of 80 patients explored for acute or chronic epilepsy following cerebral trauma and infection, 18 have been eliminated from analysis because of inadequate periods of observation or other reasons. Of the remaining 62 in whom prolonged follow-up observations are available, definite lesions were visualized at operation in all but 1. In the acute variety the seizures were associated with intracranial clots in 15, depressed fractures in 6 and abscesses in 9. The results after cortical decompression in the hematomas and depressed fractures were uniformly good, except in cases in which there was a superimposed contusion of the underlying brain. When convulsions accompany a subdural or subcortical abscess the prognosis is extremely poor, both for the life of the patient and for relief of the seizures.

Late chronic epilepsy is caused by fibroglial scars producing meningeocerebral adhesions or cicatrices of the cortex and underlying white matter. When these lesions are small and situated in relatively silent areas of the brain, the results of excision are good. If the cicatrix is a large one, or situated in vital speech and motor areas, total extirpation is out of the question. In such cases it may be possible to find a small focus responsible for the epileptic discharge. This never comes from the scar itself, but from partially damaged cortex at its periphery. In the decade from 1935 to 1944, when the surgeon had to depend on localizing the epileptogenic focus by the crude method of inducing gross seizures by electrical stimulation of the exposed cortex, our follow-up statistics show that in a series of 28 patients explored for chronic epilepsy of traumatic origin, 24 have had focal lesions suitable for surgical attack. Of these, 8 have had complete freedom from seizures for periods up to nine years. Another 6 have had a great reduction in both the frequency and the severity of their attacks, some with only an occasional seizure in the early months followed by long periods of complete freedom. All these patients are able to lead active and relatively normal lives, although they have been urged to

continue taking anticonvulsant drugs. Five others have had sufficient improvement to be able to lead useful lives, whereas the remainder, including those in whom no operable lesion was found, received little or no benefit.

Three patients in whom cortical atrophy was at first held responsible for seizures later developed characteristic signs of brain tumor. Two of these had a definite history of previous cranial injury.

Postoperative results of excision of cortical scars after healing of intracranial abscesses were all that

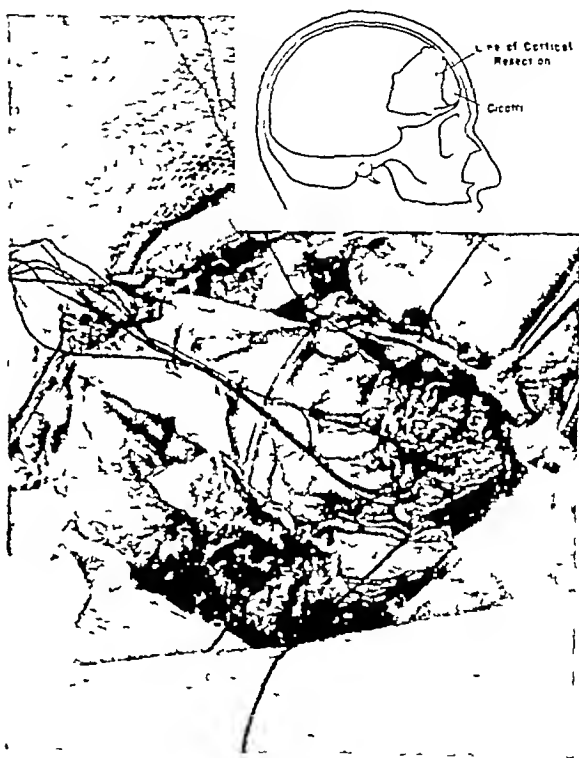


FIGURE 5 Cortical Scar at Tip of Right Frontal Lobe, Resulting from Frontal Sinusitis and Osteomyelitis, Complicated by Brain Abscess Three Years Previously.

*Jacksonian epilepsy, characterized by turning of head and eyes to the left, with clonic movements of the left side, followed by generalized seizures, had been present for a year.*

could be wished for in 1 case and very satisfactory in the other 3.

Recently developed means of delimiting the circumscribed epileptogenic focus with much greater accuracy by the use of direct cortical brain waves at operation and the production and mapping of subclinical seizures promise far better results. This method offers special hope in the extensive scars that are too large for total resection and in those situated in the vital speech and motor areas of the brain. As results obtained by this new technic cannot be evaluated for a period of years, it has

seemed worth while to present this statistical review of end results achieved in the preliminary period of the surgical attack on epilepsy

### REFERENCES

- 1 White, J C, Mixer W J and Liu C T Focal epilepsy, statistical study of its causes and results of surgical treatment. I Epilepsy secondary to intracranial tumors *New Eng J Med* (in press)
- 2 Foerster O, and Penfield W Structural basis of traumatic epilepsy and results of radical operation *Brain* 53 99 119 1930
- 3 Penfield W and Erickson T C *Epilepsy and Cerebral Localization* 623 pp Springfield Illinois Charles C Thomas 1941
- 4 Kaufman I C, Marshall C, and Walker A E Metrolol activated electroencephalography *A Research Nerv & Ment Dis Proc* 26 476-486 1947
- 5 Walker A E, Marshall C, and Beresford E N Electroencephalographic characteristics of cerebrum in post traumatic epilepsy *A Research Nerv & Ment Dis, Proc* 26 502 515 1947
- 6 Gamsu D and Kuhik, C S Unpublished data
- 7 Kunkel P A and Dandy W E Subdural hematoma diagnosis and treatment *Arch Surg* 38 24-54 1939
- 8 Elvidge A R Post traumatic convulsive and allied states. In *Injuries of the Skull Brain and Spinal Cord Neuro-Psychiatric surgical and medico legal aspects* 632 pp Edited by Samuel Brock. Baltimore Williams & Wilkins Co 1940 Pp 233 273
- 9 Ascroft, P B Traumatic epilepsy after gunshot wounds of head. *Brit M J* 1 739 744 1941
- 10 Watson C W Incidence of epilepsy following craniocerebral injury *A Research Nerv & Ment Dis, Proc* 26 516-528 1947
- 11 Bailey P War and epilepsy and Veterans Administration *A Research Nerv & Ment Dis Proc* 26 529 535, 1947
- 12 Klemme R M Surgical treatment of dystonia with report of one hundred cases *A Research Nerv & Ment Dis, Proc* 21 596-601 1942
- 13 Freeman W, and Watts, J W *Psychosurgery Intelligence emotion and social behavior following prefrontal lobotomy for mental disorders* 337 pp Springfield Illinois Charles C Thomas 1942.

## AGGRESSIVE BEHAVIOR — ITS PSYCHIATRIC AND PHYSIOLOGIC ASPECTS, ESPECIALLY IN COMBAT VETERANS\*

LEO ALEXANDER, M D †

BOSTON

**I**MIMPULSIVE aggressive behavior is more frequent among the cases encountered in military psychiatric practice, especially in or near combat zones, than in civilian practice exclusive of cases appearing in combat veterans

While serving with an overseas general hospital as chief of the neuropsychiatric section, I was impressed with the number of cases in which aggressive behavior presented the predominant symptoms and cause for admission or consultation. In the study of these cases from the psychiatric as well as from the neurophysiologic point of view, the courtesy and co-operation of Dr Denis Hill made it possible for the patients to be taken for electroencephalographic examination to the laboratory under his charge at the Sutton Emergency Hospital. In going over the list of these patients and the causes for their admission, I find the following comments

"Irresistible urge to drive and wreck jeeps while intoxicated" "Brutal attack on a woman while intoxicated — had cerebral concussion when enemy shell exploded five feet from him" "Aggressive behavior while intoxicated with beer, covered by retrograde amnesia — knifed a fellow soldier who was his best friend in his organization" "Impulsive aggressiveness under alcohol, pathologic intoxication, with amnesia for entire episode" (The case of this officer, a grounded flier, will be reviewed in

detail later) "Assault and attack on a colonel while intoxicated, one previous episode of assault against a woman while intoxicated, for which he had been punished" (The differential diagnostic question was epileptic equivalent or alcoholic cerebral degeneration) "Attempt to rape 12 women, 8 of them in one afternoon within one hour" "Insults and threats against his hutmates on the part of a staff sergeant who had consumed a not inordinately large amount of alcohol" (This patient was disarmed and put to bed and had no recollection of the episode on the following day)

It was remarkable that with the exception of the last patient, in whom six-per-second low-voltage potentials were found in transverse leads over the parietal areas, such as were found in aggressive personalities of this type by Hill and Watterson,<sup>1</sup> all the patients showed completely normal cerebral electroactivity, a fact that contrasts somewhat with civilian experience. Civilian patients with brutal, impulsive, aggressive outbursts frequently show the type of "psychopathic" abnormality mentioned above, with instability of the cerebral electroactivity to physicochemical stress. It is rather surprising to find that persons with similar outbursts in military life, especially in combat personnel, tended to show these abnormalities only rarely — in only 1 case among my wartime patients. The explanation of this is probably that such outbursts of behavior are, of course, the combined results of biologic abnormality and emotional stress. If the stress is slight, the biologic abnormality has to be great to cause the abnormal behavior

\*From the Division of Psychiatric Research, Boston State Hospital, and the Department of Psychiatry, Tufts College Medical School

†Instructor in psychiatry Tufts College Medical School, associate director of psychiatric research, Boston State Hospital, consulting psychiatrist and neurologist, Washington Hospital, assistant neurologist, Beth Israel Hospital, attending neuropsychiatrist, Veterans Administration Hospital, West Roxbury, Massachusetts.

When the stress is great, little or no biologic abnormality is necessary to produce the same result.

Another important fact was that, without exception, alcohol played a part in bringing out the abnormal behavior. In a few cases, especially in combat personnel under stress, remarkably slight amounts of alcohol sufficed to bring out the aggressive behavior reaction, but ingestion of alcohol precipitated the outburst in all. An exception was a recent case, in which the disturbance of cortical inhibitory centers, essential for bringing out this behavior pattern and usually produced by alcohol, was accomplished by another physiologic interference with cortical activity. This case is discussed below.

The types of aggressive behavior that presented themselves could be divided into the following groups:

Aggressive behavior that is directed against a specific person who incurs the patient's hostility, which is displaced, however, against another, either a similar person or a symbol of that person. An example of this type is that of a sergeant in the Air Force who received a letter from his wife telling him that since his absence overseas she had become interested in another man. He brooded over this for some time and finally wrote to his wife that he would be willing to give her a divorce. On his next day off he went to a pub with friends. After drinking not more than his usual amount of liquor, he went out into the street, walked up to a civilian couple, kicked the man and started choking the girl. Later, he had no recollection of this episode at all. His electroencephalograms were normal. He spoke of the marked resentment he felt against his wife and it was quite obvious that in that setting he committed an act symbolic of what he wanted to do to his wife. He had had a fine military record before this incident, the only predisposing factor in his background was that his father was an alcoholic who had finally lost his home and his financial and social standing because of his drinking.

Aggressive behavior in terms of projection occurred particularly in combat personnel who had had some anxiety regarding combat and who had been temporarily or permanently released from combat duty. A rather common example of this was the flier grounded after a number of combat missions because of his increasing emotional tension. Such a man, after drinking for a while at the club, sometimes accosted another man grounded for similar reasons, abusing him verbally, pulled his gun and tried to shoot him. Here, his aggression, generated against himself, was projected and directed against another person in a similar position — especially in a setting that included drinking.

During aggressive behavior resulting when a large amount of aggressive hostility is directed indiscriminately against any and all people, the patient's consciousness is usually clouded. He is often described as having been rather subdued and not in as good spirits as usual prior to the outburst. An example is afforded by the following case:

A flier (second lieutenant), who had been under considerable combat-flying stress, was grounded because of tension and became self-critical, self-reproachful and anxious. In this state, he went to a neighboring town one evening and bought a quart of whisky to share with friends at a private club. He did not drink more than usual, he was a man who could usually handle his liquor well. He had in a somewhat subdued and tense mood consumed his usual amount of alcohol when he suddenly rose, called bystanders "Yellow, dirty Germans" and then literally tore the club apart. He was in a state of wild excitation. It took several men to restrain him, and even then he tore the buttons off the uniform of a flight surgeon who had been called to the scene. The next day he was quite subdued, tense and anxious — not on account of the incident, but just in general.

The British police have a very thorough way of taking down statements practically verbatim, as they did in this case. When I read the record of the exclamations and statements that this officer had made during the fracas, I found them to be strikingly similar to the expressions that another officer had poured forth under therapeutic abreaction by sodium pentothal, the latter officer was likewise a combat aviator, who had had two crash landings as well as other combat stress and who had become very tense. During an abreaction treatment with sodium pentothal he had suddenly given vent to a violent, aggressive emotional reaction, using almost exactly the same violent expressions as the lieutenant had used on the dance floor of the club. A comparison of the practically identical stenographic statements led to the conclusion that this lieutenant had inadvertently abreacted himself with the alcohol, which had acted on the cortex, or the outer cortical layers, in such a manner as to allow the tension and reactive aggression that had accumulated in the lower cerebral mechanisms to express themselves. The military court accepted my interpretation of the incident.

Regardless of what causes the cortical dysfunction — alcohol, sodium pentothal or any other cortical sedative or disorganizing agent — the accumulated excessive emotional pressures in the deeper centers of the brain frequently express themselves in that aggressive manner. Aggression is the natural consequence of anxiety. And in men who go through their daily combat routine, with its inevitable anxieties, there is an accumulation of aggressiveness that is bound to explode under conditions of depression of the higher cortical functions. The higher levels of the cortex, the inhibitory

ing organ, restrain the lower cortical spheres and the basal ganglions, which are the main outlets for aggression on a primitive physiologic level and probably also on a higher psychologic plane. Anything that disturbs the higher discriminating functions of the cortex will cause a release in the more primitive mechanisms, including those of the sub-cortex, this release in no way depends on what incapacitates the cortex. In epilepsy, for example, a great deal of abnormal cortical electroactivity is present, which may indicate a degree of cortical disturbance sufficient to interfere permanently or temporarily with the higher discriminating functions of the cortex. In patients with focal brain lesions there is usually only focal abnormal cortical electroactivity. The ingestion of alcohol may cause the abnormality to spread from its focal point to envelop the entire cortex, normally a source of controlling influence, and the entire cortex may become temporarily worthless. In the presence of emotional disturbance, especially anxiety and tension, the disorganization of cortical discriminating functions by alcohol alone is sometimes sufficient to release aggressive outbursts. In both of the two latter instances, one speaks of "pathologic intoxication." In "normal intoxication," there is a proportionate inhibition of cortical discriminating functions and of activity, including aggressive activity.<sup>2</sup>

I have encountered interesting cases of eruption of aggression in veterans after their return to civilian life. One of the surprising features in these cases is the understanding sympathy and tolerance of the patient's relatives. An example is provided by the following case of a husband who cut his wife's throat with a razor, for which act he is now serving a sentence at the state prison colony. His wife holds no grudge against him but considers the assault a symptom of his emotional illness—certainly a most enlightened view on the part of the victim. This view was not shared by the court.

The patient had been an ammunition loader in the Pacific Theater and had performed his duties well until the time when he was unloading an ammunition ship in the Aleutian Islands and had to get off the ship in a hurry because of an approaching storm. He slipped and fell 25 feet to a barge below. He was unconscious for 10 minutes, bled from the nose and injured his left hand. Shortly after this episode he developed nervous excitability and headaches, which soon became disabling, he was sent home and discharged for neurosis.

One evening when he dined out with his wife he consumed three mugs of beer and a "shot" of whisky. His manner was calm, and they had no arguments. On returning home his wife lay down for a nap, and he covered her with a blanket. About ½ hour later she was suddenly awakened by a sharp pain. Blood was flowing from a long, deep cut on the right side of her neck (a 4-inch scar remained as evidence when I saw her 8 months after the incident). Her husband was standing over her, staring at her, a razor blade in his hand. When she asked him what he had done he did not answer but went to the closet, got a clean towel and wrapped it around her neck to check the bleeding. Then he ran out and gave himself up at the police station. All the patient remembered about the incident, however, was covering his wife with a blanket when she first lay down, and the next thing he knew "she was lying there bleeding, and I ran out of the

house for help." He was observed at the metropolitan state hospital and was considered legally sane but suffering from "psychoneurosis." He was tried and convicted for assault.

When I examined him at the state prison colony I found a man of small stature, extraordinarily tense, anxious and jittery, as well as definitely depressed. His sleep was still haunted by nightmares, he frequently dreamed of loading an ammunition ship, of somebody yelling, "Get off quick!" and then of awakening from the explosion, which usually turned out to be a slammed door or a similar noise. However, he was free of guilt feelings about his deed "because I did not know what I was doing at the time—I just pleaded guilty because the lawyer told me to." He did think that he had made other mistakes. He felt he should have stayed in the Army, and had a stronger guilt feeling about that than about attacking his wife.

Neurologic examination revealed normal findings—especially, normal Achilles reflexes and vibration sense. My diagnosis was "psychoneurosis, anxiety-tension state, severe." The recent history suggested that marked unconscious, repressed aggressiveness had erupted under cortical sedation by a small amount of alcoholic beverages, producing a state of pathologic intoxication.

In the cases discussed above, cortical dysfunction was always affected by alcohol. Hill<sup>3,4</sup> found that in cases in which there was a focal abnormal cortical electroactivity, ingestion of alcohol—especially beer—made this abnormal electroactivity spread all over the cortex. Hill<sup>3,4</sup> has likewise shown that with ingestion of a similar amount of water, especially in cold weather, which facilitates hydration of tissues, the same result could be obtained. In a case of matricide described by Hill and Sargent<sup>6</sup> aggressive behavior associated with abnormal cerebral electroactivity resulted from the combined effects of low blood sugar and hyperventilation incidental to a violent argument.

I was recently asked to examine a combat veteran who had committed an unreasonable aggressive act that was not in keeping with his personality or his situational needs. He had been under tension incidental to frustrating experiences after his return to civilian life—he had not succeeded in getting into the college of his choice, he had not obtained the job he wanted, and his girl had jilted him while he was overseas. About his state of mind after his return in January, 1946, he said, "I was unsettled. I wanted so much, but nothing was panning out. It wasn't what it was cracked up to be. A lot of things I didn't want to happen did happen." This case is reported in detail, as follows.

In March, 1946, this 21-year-old man started working 9 or 10 hours daily in a cold-storage plant at -10 to -15°F. When he left the plant after work, at first he was chilly for ½ hour and then became uncomfortably warm, and if he engaged in any exercise he "perspired to beat the band while my friends would be dry as a bone." This feeling usually subsided during the night.

One evening after coming home from work, he changed to his dungarees and field jacket, stuck an unloaded German Luger pistol into his belt (for which action he had no explanation) and then drove around for several hours and vaguely headed toward the home of the girl who had jilted him, but on the outskirts of the town he turned and drove back toward Ft. Devens and then to Littleton, where he stopped at a store for a package of cigarettes.

In reaching for his wallet in his back trouser pocket, he exposed the gun in his belt, and when he noticed that the storekeeper became frightened and panicky, he was surprised, for he had forgotten that the gun was there. "I did

not know exactly what to do, so right off I hacked away, pulled out the gun, and said, 'Give me the folding money'." The storekeeper gave him about \$20, which he put in his wallet, where he had \$47 of his own. Then he ran out and got away in his car, but a police car that was parked across the street chased and caught him. He surrendered, was very co-operative, helped the police look for the gun, which he had thrown from his car window, and in every way acted his usual polite self.

The robbery occurred at 10 00 p.m., after he had been driving around seemingly aimlessly for about 3 hours, he had left the cold-storage plant at about 5 30 p.m. He could give no motive for his crime. He had sufficient money of his own — about \$1000 in accumulated pay. His family, with whom he lived and with whom he was very congenial, were of good middle-class circumstances, owned their own home and car and were capable of supplying a college education for their children. The patient himself was a clean-cut, tall, personable young man who had been outstanding in high-school athletics and who on the basis of his intelligence, ability and personality assets, as well as on his own and his family's standing in the community, was entitled to look forward to a happy and successful development. He had never committed any criminal acts before, had been a good student in high school and had shown no signs of psychopathic instability in the past. There was no record of truancy or disorderliness. His war record was excellent, he had been a sergeant in the combat engineers attached to the Fourth

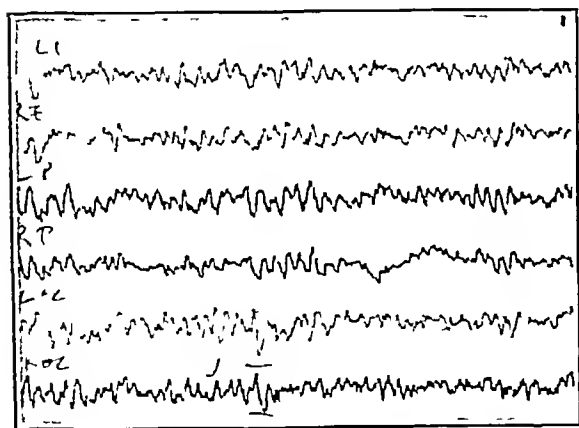


FIGURE 1 *Electroencephalogram Taken before Exposure to Cold*

The six leads are shown in the following order: left frontal, right frontal, left parietal, right parietal, left occipital and right occipital.

Armored Division, holding the rating of platoon sergeant from August, 1944, to January, 1946.

The history of his combat experience disclosed an incident of concussion with unconsciousness followed by a state of probable postconcussional confusion lasting 3 hours on February 4, 1945. This occurred during the battle of the crossing of the Saar River when an enemy shell struck a rocky ledge near his head. This instance of confusion was probably organic since it was not followed by any disturbance during subsequent combat activity (he afterwards participated in the Battle of the Rhine), as would inevitably have occurred had the incident been a neurotic fugue state.

Physical and neurologic examination revealed weakness of the right lower facial muscles, disturbance of abdominal reflexes on the right (the right upper being frequently absent), and the right middle and lower showing early exhaustibility), the right plantar reflex was abnormal, showing dorsiflexion of the great toe associated with outward rotation of the thigh and leg, and contraction of the fascia lata without fanning of the small toes.

Psychiatric examination demonstrated excellent general intelligence, and nonverbal testing by the Kohs block test revealed a mental age of 18½ years. However, his vocabulary level was reduced to one of 15½ years. A reading test revealed the presence of a moderate amount of dyslexia. There was some deterioration of the fund of knowledge, especially of history. All this contrasted with his high-school record of A's and B's in English and history. His blood pressure was elevated to 160/90.

Emotionally, the patient presented a superficially calm appearance, with a good deal of tension and resentment coming to the fore on psychiatric exploration.

Electroencephalographic examination, which was performed at Dr. Lennox's laboratory, revealed a focus of abnormal

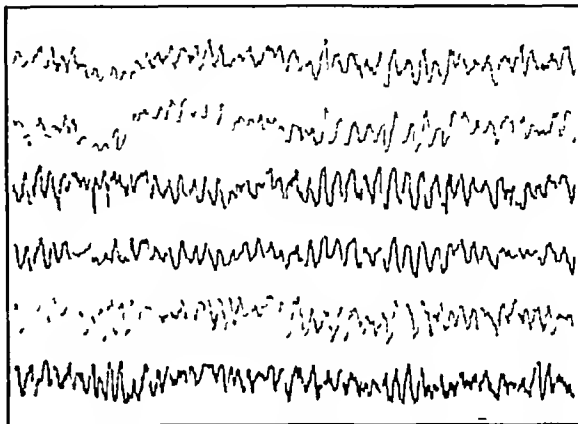


FIGURE 2 *Electroencephalogram Taken Four and a Half Hours after Exposure to Cold through Seven Hours with Alternating Periods of Twenty to Thirty Minutes Spent In and Outside a Cold-Storage Room with a Temperature between -10 and -15°F*

The six leads are shown in the same order as in Figure 1.

cerebral electroactivity with high-voltage, slow discharges at the rate of 5 or 6 per second, some of them square-topped, and diphasic slow spike discharges involving both occipital and parietal regions, more marked on the left (Fig. 1).

The aggressive outburst had occurred along the line of least resistance — namely, after the storekeeper had shown fear. In other words, the accumulated aggression, which was directed against those responsible for his frustrations and which the patient had held within him, had erupted toward the one man who had shown any fear of him.

From a study of the total personality it was believed that some organic factor was responsible for the patient's obtaining so much cortical release — that is, so much relaxation from his usually upheld behavioral standards in life, which are a function of his cortex. He was thoroughly questioned regarding whether or not he had been taking alcohol prior to the aggressive outburst. It was explained to him that whether he had been drinking or not would not make much difference from the medicolegal point of view, and the concept of pathologic intoxication was explained to him, but he steadfastly maintained he had had no liquor that day or even that week, that although he was not a teetotaler, he drank only on rare social occasions, that he did not derive particular pleasure from alcohol, and that he had throughout his military life abstained except on occasional passes and leaves because he felt that his position as platoon sergeant necessitated such abstinence.

The patient's actions on that day and his daily routine were reviewed. I then believed that it would be worth while investigating whether his occupational exposure to cold had any effect on his abnormal cerebral electroactivity. There is evidence<sup>6</sup> that the action of cold on cerebral electroactivity is similar to that of metrazol or eserine<sup>7</sup> and that in man shock from exposure to cold may be associated with tonic-clonic convulsions. These findings prompted Noell<sup>7</sup>

and others to advise against the use of analeptic stimulants such as metrazol and camphor for the treatment of shock from exposure to cold

It was arranged for the patient to return to the cold-storage plant, to spend a day there under conditions of observation with recording of his temperature, and to follow it by another electroencephalographic examination. It was found that the patient's temperature, which was 98°F at the start, fell to 97.2°F after 1 hour and to 97 after 3 hours' sojourn in the cold-storage room (in spite of 30-minute interruptions as usual in his work), it remained 97°F until he emerged at the end of the day, whereupon it began to rise gradually to 97.6°F 1 hour after emerging, to 98°F 2 hours after emerging, and then continued till it reached 99°F 4 hours after he emerged, staying at that level for an additional 5th hour and then gradually falling back to normal, his normal temperature of 98°F being reached 8 hours after emergence from the cold room.

The electroencephalogram was taken during the 5th hour after emergence—which was the approximate time at which he had committed the crime. It was found that the abnormal high-voltage activity had spread to all leads, in a way similar to what might have been expected from the effects of metrazol, eserine, alcohol or hydration (Fig. 2).

It was concluded that in this case heightened subcortical emotional aggressiveness was released because the cortical inhibitory centers had been disorganized, not by the effects of alcohol but by the effects of exposure to cold, which had permitted the abnormal electroactivity of a circumscribed traumatic focus to spread over the entire brain. No attempt was made to determine whether this

spread was actually the direct consequence of the cold or the consequence of the hyperthermic response elicited by the exposure to cold.

On the basis of these facts, which were presented to the Court, the patient was given a suspended sentence with a probationary period of two years.

### CONCLUSION

The study of aggressive behavior is a field of neuropsychiatry characterized by a remarkable degree of interplay of psychiatric and physiologic forces, the unraveling of which demands an understanding of the psychiatric as well as of the physiologic aspects of behavior.

433 Marlborough Street

### REFERENCES

- 1 Hill D and Watterson D. Electro-encephalographic studies of psychopathic personalities. *J Neurol & Psychiat* 5:47-65 1942.
- 2 Alexander L. Alcoholism and mental disease. In *Mental Health*. (Publication of the American Association for the Advancement of Science) 470 pp. Edited by F R Moulton and P O Komora. New York: Science Press 1939. Pp 83-93.
- 3 Hill D. Cerebral dysrhythmia: its significance in aggressive behaviour. *Proc Roy Soc Med* 37:317-320 1944.
- 4 *Idem*. Personal communication.
- 5 Hill D and Sargent W. Case of matricide. *Lancet* 1:526 1943.
- 6 Alexander L. Treatment of shock from prolonged exposure to cold, especially in water. Combined Intelligence Objectives Subcommittee Item No 24. (File No XXVI-37) Pp 1-228 July 1942.
- 7 Neell W. Personal communication.

## PRIMARY TERATOMATOUS CHORIONEPITHELIOMA OF THE OVARY\*

### Report of a Case

HOWARD M OLIVER, M D,† AND ELWOOD O HORNE, M D‡

WORCESTER, MASSACHUSETTS

**C**HORIONEPITHELIOMA of the ovary may arise from two fundamental sources—a pregnancy, uterine or ectopic, and a teratoma. It is our purpose to discuss only the latter, and to add a case to the literature.

Pick,<sup>1</sup> in 1904, described a nine-year-old girl whose abdomen revealed a teratoma of the ovary with mesodermal, entodermal and ectodermal components, and pure chorionepithelioma. Since then 12 other proved cases have been reported,<sup>2-13</sup> only 3 of which are reviewed in the American literature<sup>3, 12, 13</sup>. A few other cases must be eliminated because they followed pregnancies and may have represented metastases from uterine chorionepitheliomas that regressed spontaneously, were expelled with the placenta<sup>14-27</sup> or were removed by the curette.<sup>28</sup> A primary ovarian chorionepithelioma can be assumed with certainty only in a child.<sup>7</sup> Nine of the cases reported, including the one pre-

sented below, occurred in children before the age of puberty. Four of these (Table 1) presented evidence of precocious sexual development, and a fifth had uterine bleeding. In such cases a diagnosis can be made clinically since a positive pregnancy test (Aschheim-Zondek or Friedman)<sup>13</sup> diagnostic of teratomatous chorionepithelioma,<sup>13</sup> especially with dilute urine and spinal fluid. Other cases presented no typical symptoms, and 2 cases were diagnosed as appendicitis.<sup>4, 6</sup> Because of the age and the positive pregnancy test, the cases of Fasold,<sup>5</sup> Bettinger,<sup>6</sup> and Tscherne and Schäffer<sup>9</sup> are accepted as chorionepithelioma of teratomatous origin even though histologically no teratomatous elements were found. In adults the picture is that of ectopic pregnancy with irregular vaginal bleeding and the finding of an abdominal mass.

Treatment in such cases is unsatisfactory, and the longest recorded survival after operation is eight months.<sup>13</sup> Since the diagnosis is usually made postoperatively, the proper course is controversial. The consensus is that complete operation with removal of the uterus and other ovary is indicated

\*From the Departments of Surgery and Pathology Worcester City Hospital.

†Resident in pathology, Mary Hitchcock Hospital, Hanover, New Hampshire formerly, resident in pathology Worcester City Hospital.

‡Senior surgeon, Outpatient Department, and assistant in surgery East Surgical Service Worcester City Hospital.

if there is no x-ray or hormonal evidence of metastasis<sup>29-31</sup> Crossen<sup>32</sup> prefers surgery to radiation, which is of little value in this type of tumor

The following case of teratomatous chorion-epithelioma of the ovary is considered worthy of report because of the rare occurrence of this type

to be densely adherent to the right posterior peritoneum, and extended deep into the pelvis. The entire mass, including the right tube, was dissected free and removed without difficulty. No gross evidence of metastasis was noted. The uterus, left tube and left ovary appeared normal. The immediate postoperative course was uneventful. On the 3rd postoperative day the patient began to menstruate for the first time, and although bleeding was not excessive,

TABLE 1 *Proved Cases of Primary Chorionepithelioma of the Ovary according to Year of Publication*

AUTHOR	YEAR	AGE OF PATIENT	SYMPTOM	SURVIVAL AFTER OPERATION
Pick <sup>1</sup>	1904	9	Abdominal swelling	Few weeks
Albrecht <sup>2</sup>	1915	15	Abdominal mass	5 months
Read <sup>3</sup>	1928	11	Abdominal pain	1 month
Freund <sup>4</sup>	1929	7	Abdominal pain	"
Fasold <sup>5</sup>	1931	8	Precocious sexual development and vaginal bleeding	"
Betinger <sup>6</sup>	1932	7	Pain in pelvis, precocious sexual development and vaginal bleeding	"
Siegmund <sup>7</sup>	1932	6	Precocious sexual development and vaginal bleeding	5 weeks
Fikentscher <sup>8</sup>	1937	14	Vaginal bleeding	"
Tscherne and Schäffer <sup>9</sup>	1939	8	Vaginal bleeding and precocious sexual development	2 months
Sbarcea <sup>10</sup>	1939	27	Vaginal bleeding	10 weeks
Oda et al. <sup>11</sup>	1940	11	Abdominal mass	"
Backus and Griffin <sup>12</sup>	1941	13	Right lower-quadrant pain	6 months
Stanley <sup>13</sup>	1942	19	Vaginal bleeding	8 months
Oliver and Horne	1947	11	Abdominal pain	4 months

of neoplasm, with a scarcity of reports in the literature, and because of the hopeless prognosis offered, irrespective of the type of treatment administered

CASE REPORT

S F, an 11-year-old Italian girl, was first seen in the accident ward of the hospital on December 12, 1946, complaining of low abdominal pain. She was observed for 24 hours and discharged, improved, with a diagnosis of mesenteric adenitis. She returned to the hospital on January 19, 1947, again complaining of low abdominal pain, which had suddenly occurred 5 hours before admission and was limited to the hypogastrium. The pain was constant, dull and not accompanied by nausea, vomiting or bowel change. There were no urinary complaints, vaginal discharge or bleeding. Neither chills nor fever had been noted, and the patient had never menstruated.

Other than the usual childhood diseases, no serious illnesses had been contracted and the family and social histories were irrelevant.

Physical examination revealed a thin, but well developed girl, who was in no acute distress. The heart was within normal limits, and no murmurs were present. The lungs were resonant throughout, with no rales or abnormal breath sounds. Palpation of the abdomen revealed an ill defined, lemon-sized mass in the right lower quadrant, which extended 5 cm. above the symphysis to the right of the midline. It was freely movable, hard and nontender. No muscle spasm or fluid wave was present. The vaginal orifice was infantile, but rectal examination disclosed a rather firm mass bulging into the rectum, it did not appear to be attached to the uterus. In view of the fact that the patient had had a similar attack 6 weeks previously it was believed that she had appendicitis, with rupture and abscess formation, although the white-cell count was only 6400, with 61 per cent neutrophils, and the sedimentation rate 35 mm in 1 hour.

The temperature was 98.6°F, the pulse 100, and the respirations 20. The blood pressure was 85/55.

On January 21 a laparotomy was performed under nitrous oxide, oxygen and ether anesthesia through a low-midline incision. The appendix was easily located and found to be normal. On further exploration, a large hemorrhagic necrotic tumor of the right ovary was clearly visualized. It proved

the hemoglobin gradually fell to 49 per cent and multiple transfusions of whole blood were given. Except for continued weakness, she was apparently in good condition. Further surgery was considered to be inadvisable until a positive pathological report of a malignant lesion could be verified, and radiation therapy was considered only as a

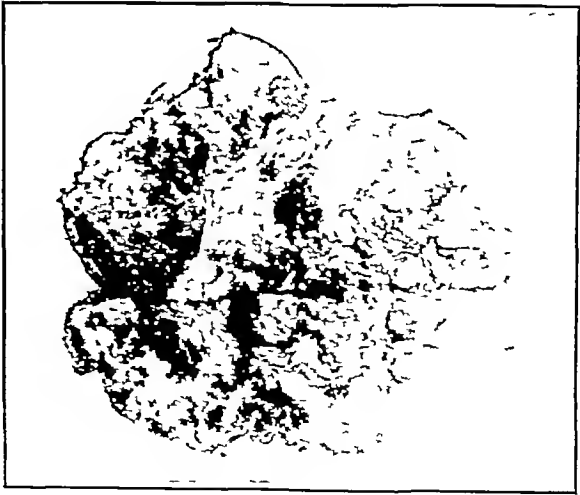


FIGURE 1 *Photograph of the Tumor of the Ovary*

last resort. A Friedman test was negative on February 1, but strongly positive on February 10 and positive with spinal fluid on February 17. No evidence of metastases was found by x-ray examination on January 29 and February 15 and 22. X-ray therapy was started on February 26, and continued through March 25. The patient received twenty-one treatments for a total of 4000 r given in four different fields. The hemoglobin continued to remain between 50 and 60 per cent,

despite repeated small transfusions until March 23, when she had improved clinically to the extent that she was afebrile and asymptomatic with a rise in hemoglobin to 75 per cent. She was discharged on the 65th hospital day. The Friedman test remained strongly positive with dilutions of urine, uninfluenced by the radiation therapy. By April 15 she was losing weight and was unable to return to the tumor clinic for follow-up examination. Her family physician stated that a nontender mass had developed in the lower abdomen and gradually enlarged, reaching to the xiphoid process before

four years, only 3 other proved cases have been found in the American literature. The diagnosis was not made preoperatively, and the gross disease was difficult to recognize. Evidence of precocious sexual development was not noted.

The prognosis is poor as illustrated in the case reported, death occurring in all cases in less than a year. Removal of the uterus and other ovary at the time of the original operation might have prolonged this patient's life, although this point is controversial even among leading gynecologists. Treatment at its best is unsatisfactory. More case reports should be forthcoming if this interesting tumor, which presents an unfavorable outcome, is to be recognized.



FIGURE 2. Photomicrograph of the Ovarian Tumor, Showing the Islands of Langhans and Syncytial Cells Imbedded in Hemorrhagic Tissue.

death. The patient expired suddenly 4 months after operation. Permission for autopsy was not granted.

Macroscopic examination was as follows (Fig. 1).

The surgical specimen consists of an ovary and tube. The ovary measures 7.5 by 7 by 7 cm. The surface is smooth and shiny with a mottled blue and red sheen except for a small shaggy area. On section, some areas are yellow and caseous, and others are dark brown and firm. Between these areas the surface is hemorrhagic. There are numerous cysts scattered throughout the ovary, the largest measuring 2 cm in diameter. They have a smooth shiny lining. The tube measures 5.5 by 0.5 cm. The serosa is smooth and glistening, the lumen patent throughout, and the mucosa normal. The mesosalpinx is normal.

Microscopical examination was as follows (Fig. 2).

The capsule consists of partially hyalinized connective tissue, which contains foci of lymphocytes. Beneath the capsule are scattered areas of normal ovarian stroma with a few follicles lined by a single layer of columnar and cuboidal epithelium. The macroscopic cysts have a definite wall of stratified squamous epithelium. The greater part of the cortex and medulla, however, is markedly hemorrhagic, with large areas of necrosis. Adjacent to the hemorrhagic areas are several masses of round to cuboidal cells varying greatly in size. They have a distinct cell outline and a clear cytoplasm with a round, dark nucleus, and represent Langhans cells. These cells are separated into small clusters by large cells, which have an indefinite cell wall. They are deeper staining and contain irregularly shaped, dark nuclei, some of the cytoplasmic masses being multinucleated. These represent syncytial cells. Mitoses are not seen.

#### SUMMARY

A case of primary teratomatous chorionepithelioma of the ovary in a young girl is reported. This appears to be the fourteenth authenticated case report, none having been reported in the past

#### REFERENCES

1. Pick, L. Das epithelioma chorioectodermale. *Berl klin Wochschr.* 41:158-162, 1904.
2. Albrecht, L. Discussion of Klein, G. Über maligne Ovarialtumoren mit chorionähnlichen Funktion des Epithels. *Zentralbl. f. Gynäk.* 37:622, 1913.
3. Read, C. D. Chorion-carcinoma of ovary with torsion of pedicle in child aged 11. *Proc Roy Soc Med* 21:1331-1333, 1928.
4. Freund, E. Ein Fall von teratogenen Chorionepitheliom des Ovariums beim Kinde. *Frankfurt Ztschr f. Path* 38:313-318, 1929.
5. Fasold, H. Ein Teratom des Ovars mit chorionepitheliomähnlichen Metastasen als Ursache einer Pubertas praecox mit positiver Schwangerschaftsreaktion. *Ztschr f. Kinderh* 51:519, 1931.
6. Bettinger, H. Beiträge zur Lehre vom Chorionepitheliom. *Zentralbl. f. Gynäk* 56:1451-1456, 1932.
7. Siegmund, H. Pubertas praecox als Folge chorionepitheliomstör. Wucherungen. *Arch f. Gynäk* 149:498-514, 1932.
8. Fikentscher, R. Zur Kenntnis metastasierender Chorionepitheliomteratome des Eierstocks und der vermehrten Bildung gonadotropen Hormons. *Med Klin* 33:509-513, 1937.
9. Tieberne, E. and Schaffer, W. P. Pubertas praecox durch ein Chorionepitheliom des Ovarium. *Zentralbl. f. Gynäk* 63:241-242, 1939.
10. Sbarcea, J. Ein Teratom des Ovars mit positiver AZR. (Teratogenes Chorionepitheliom). *Zentralbl. f. Gynäk* 63:936-946, 1939.
11. Oda, T., Matsushita, S. and Kurosu, F. Über einen Fall von Ovarialteratom in Begleitung von Chorionepitheliom malignum und Karzinom. *Gann* 34:319-324, 1940.
12. Backus, G. R. and Griffin, E. P., Jr. Primary chorionepithelioma of ovary. *Am. J. Clin. Path.* 11:252-256, 1941.
13. Sturley, R. F. Teratomatous chorionepithelioma of ovary: critical review of literature with report of new case. *Minnesota Med* 25:629-637, 1942.
14. Kleinbans, F. Case report. *Zentralbl. f. Gynäk* 26:1148, 1902.
15. Fairbairn, J. Primary chorionepithelioma of ovary. *J. Obst. & Gynaec. Brit Emp* 16:1-8, 1909.
16. Kynoch, J. Primary chorionepithelioma of ovary. *Edinburgh M. J.* 22:226-229, 1919.
17. Frank, R. T. Adenocarcinoma of corpus uteri, nearly complete removal by curet. ectopic chorio-epithelioma of pelvis. *Am. J. Obst.* 74:369-376, 1916.
18. Chisholm, J. Chorionepithelioma of ovary. *Brit M. J.* 2:938, 1920.
19. Lubarsch, O. and Henle, F. *Handbuch der speziellen pathologischen Anatomie und Histologie*. Vol. 7, Part 3, 1047 pp. Berlin: Julius Springer, 1937.
20. Simard, L. C. Production of decidinal cells in ovary about primary chorio-epithelioma. *Canad. M. A. J.* 24:496, 1931.
21. Idem. Primary chorionepithelioma of ovary: report of two cases. *Am. J. Cancer* 30:298-307, 1937.
22. de Zalka, E. Concerning ectopic chorionepithelioma: report of two cases. *Am. J. Path.* 4:59-73, 1928.
23. Rohdenburg, G. L. Analysis of 500 tumors of ovary. *J. Lab. & Clin. Med.* 12:211-225, 1926.
24. Phillips, M. Case of chorionepithelioma of ovary in woman aged 25. *Brit M. J.* 2:938, 1920.
25. Preston, W. F. and Gay, D. M. Primary chorioma of ovary. *Am. J. Obst. & Gynec.* 33:651-656, 1937.
26. Ries, E. Primary syncytioma of ovary. *Am. J. Obst.* 72:46-56, 1915.
27. Seitz, A. Über das primäre Chorionepitheliom des Ovariums. *Ztschr f. Geburtsh. u. Gynäk* 78:244-259, 1915.
28. Dougal, D. Primary chorionepithelioma of ovary. *J. Obst. & Gynaec. Brit Emp* 31:387-397, 1924.
29. Meigs, J. V. Personal communication.
30. Novak, E. Personal communication.
31. Papanicolaou, L. E. Personal communication.
32. Crossen, J. S. Personal communication.

## YAWS IN MASSACHUSETTS\*

JOHN G. DOWNING, MD †

BOSTON

**Y**AWS can occur in Massachusetts. Several physicians refused to believe this possibility and doubted the history given on several occasions by the mother of the patients in the cases reported below. The return of overseas veterans and the rapidity of transportation increase the likelihood of sporadic cases of tropical diseases. A carefully taken history, including recent change of abode, is important. The diagnosis in both these cases was promptly made by the original observers in Jamaica.

Ease of transmission, owing to abundance of the etiologic agent on the exposed skin, makes yaws a serious disease in crowded neighborhoods. It must be considered in the differential diagnosis of persistent granulomas. History, dark-field examination and serology of a patient presenting echthymatous lesions will readily establish the diagnosis, especially in children, because it is a nonvenereal disease.

## CASE REPORTS

**CASE 1** E. R., an 8-year-old Negress, was seen in the Boston City Hospital Out-Patient Department on September

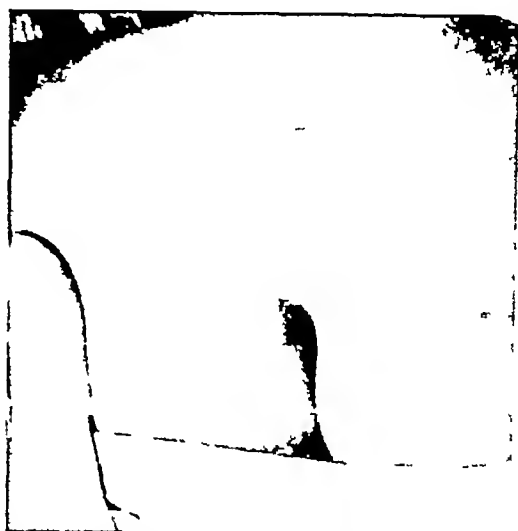


**FIGURE 1** Photograph of the Right Heel in Case 1, Showing an Inverted Saucer-like Granuloma.

Dark-field examination of the serum showed *Treponema pertenue*.

ber 24, 1947, complaining of sores on the right heel and left buttock. The history revealed that her family had lived on the island of Jamaica, British West Indies, from 1945 until August, 1947. On April, 1946, she had stepped on a tack, and a crusted area had subsequently appeared. It per-

sisted for months until the patient was seen by a district nurse, who diagnosed the lesion as yaws. The diagnosis was confirmed by laboratory studies at the hospital, and treatment consisting of a few doses of bismuth and salvarsan was given. After the first treatment, the patient suffered a generalized "measle-like" eruption, which with the initial lesion disappeared after treatment. In July a blister appeared on the right heel and became crusted. It was present



**FIGURE 2** Photograph of the Left Buttock in Case 1, Showing the Frambesiform Lesion of Yaws.

on her return to the United States in August, and assumed the appearance seen on September 15. The lesion was circular, 5 cm in diameter, elevated, crusted and indurated, with a surrounding ring of satellite vesicles (Fig 1). Dark-field examination showed *treponemas*. Further examination revealed a similar lesion on the left side of the intergluteal fold (Fig 2). The blood Hinton test was positive. The patient was given 4,000,000 units of penicillin.

**CASE 2** D. R., the 5-year-old brother of the patient in Case 1, was seen on October 10, 1947, when examination showed a sore on the left heel and left buccal mucous membrane. The history revealed that 6 months previously, while living in Jamaica, he had injured his leg, and a lump that crusted had appeared. It was diagnosed as yaws, and he received three injections of bismuth and seven injections of salvarsan. The lesion had healed when he returned to the United States in August. On October 1 the left heel had broken down, and his mouth became sore. Examination showed a small superficial ulceration on the left buccal mucous membrane and an indurated, crusted ulcer, 1.5 cm in diameter, on the left heel. Many enlarged nontender nodules were present in the post-cervical area. Dark-field examination showed many *treponemas*. The blood Hinton test was doubtful on October 10 and strongly positive on October 15. This patient was also given 4,000,000 units of penicillin.

## DISCUSSION

In the differential diagnosis of persistent granulomatous lesions in addition to reactions to drugs

\*From the Department of Dermatology, Boston City Hospital.

†Professor of Dermatology, Tufts College Medical School and Boston University School of Medicine.

including bromides, syphilis, tuberculosis and deep-seated mycotic infections, yaws must be considered. Although it is endemic in the East and West Indies and equatorial areas, sporadic cases may be seen in the United States.

The primary lesion is almost invariably extragenital, occurring most often on the lower extremities, usually at the site of recent injury. *Treponema pertenue* is the etiologic agent that invades the blood stream. The primary lesion is found, after three or four weeks' incubation. It is usually an elevated ulceration with constant crusting. The secondary lesions start as macules, becoming papules and later typical frambesiform lesions. These are elevated nodules, from 1 to 2 cm in diameter, often covered by dried serum. When this dried serum

is washed off, a round, pink, lobulated surface resembling a raspberry is seen. Such a lesion was present on the patient's heel in Case 1. Washing the surface of a crusted ulceration with soap and water is often very revealing. It may show a carcinoma, syphilis, yaws or blastomycosis, all of which have characteristic clinical pictures. Penicillin apparently successfully arrests this disease and perhaps cures it.

#### SUMMARY

The possible occurrence of yaws in Massachusetts, as well as the points to be considered in diagnosis and treatment, is briefly discussed.

Two cases that occurred in residents of Massachusetts who had lived in Jamaica are reported.

520 Commonwealth Avenue

## MEDICAL PROGRESS

### MALARIA\*

QUENTIN M. GEIMAN, PH.D.†

BOSTON

IN 1943 an article was written to review the significant concepts and facts about malaria among human beings.<sup>1</sup> In that account, a brief allusion was made to the comprehensive program placed in operation by the armed forces to control malaria. Nothing could be said at that time about the extensive mobilization of clinicians, chemists, parasitologists and entomologists and the training of skilled personnel to attack unsolved malarial problems, which were of extreme strategic importance to the Allies.

Sufficient time has elapsed since the close of World War II to evaluate the foremost advances made in the knowledge of malaria in human patients during and since the conflict. The majority of advances arose out of laboratory and field solutions to problems of diagnosis, prophylaxis, treatment and control that confronted the armed forces fighting in tropical areas. Fortunately, many of the advances, particularly in chemotherapy, were made and applied in time to aid in tipping the balance in favor of the Allies during operations in malarious areas. In the words of Russell<sup>2</sup> "Military experience taught once more that the prevention of malaria is neither automatic nor simple but is compounded of law and persuasion, organiza-

tion and training, supplies and technical applications."

The necessity of war forced the expenditure of large sums of money, which speeded the production, organization and application of newer insecticides to the drastic control of malaria in heavy malarious areas. The results have been so satisfactory that malarialogists are predicting the complete eradication of malaria from this<sup>3</sup> and other countries<sup>4</sup> if the new weapons for control are used wisely. A discussion of the development of insecticides and methods for their use against malarial vectors and other arthropods that transmit tropical diseases is not within the scope of this paper. It is sufficient to say that the continued intelligent and skilled uses of the newer methods of mosquito control and the proper use of new antimalarial drugs will go far in reducing the menace of malaria to that of a minor tropical disease. Unfortunately, the existence of lethal insecticides and effective antimalarial drugs does not guarantee their proper use in hyperendemic malarious areas where the problem equals that which existed prior to World War II.

The purpose of this article is not to give a comprehensive account of progress in malariology or to argue in favor of new methods for the treatment of malaria and the control of anopheline mosquitoes. The contributions considered add to the basic knowledge of the parasites, to clinical knowledge of the course and sequelae of the disease so that a prompt diagnosis can be made and to methods of treatment.

\*From the Department of Comparative Pathology and Tropical Medicine, Harvard Medical School.

The material reviewed in this paper was compiled in connection with a malaria-research project supported by a grant in aid to Harvard Medical School from the Division of Research Grants and Fellowships of the National Institute of Health, United States Public Health Service.

†Assistant professor of tropical diseases, Harvard Medical School.

## THE PARASITES

Pertinent information about the mechanism of disease production by malarial parasites was reviewed previously.<sup>1</sup> The precise biochemical basis for the interpretations is just beginning to unfold. Growth and multiplication of mammalian plasmodia in vitro have been obtained,<sup>2, 6</sup> and the methods developed for the studies have provided tools to determine the physical and chemical requirements for growth and nutrition of the parasites.<sup>7, 8</sup> The medium developed for these studies is the result of attempts to devise a synthetic plasma, containing inorganic salts, sources of calories such as glucose, glycerol and sodium acetate, amino acids for protein synthesis, vitamins, para-aminobenzoic acid, purines and pyrimidines. Of these substances, glucose, para-aminobenzoic acid<sup>8</sup> and methionine<sup>9</sup> have been established as essential nutrients for *Plasmodium knowlesi*, and the other ingredients appear to be accessory growth-promoting compounds. These studies also showed that the malarial organism cannot survive on the available hemoglobin and cytoplasm of the red cell. The plasma must supply other nutrients for diffusion through the cell membrane if the parasite is to grow and metabolize normally and produce progeny or merozoites for reinvasion of other erythrocytes. Thus, there are plasma or host factors that control levels of parasitemia and perhaps pathogenesis of malarial parasites.<sup>10</sup>

In 1943 and 1947 Trager<sup>11, 12</sup> reported on the effect of biotin and a biotin-like substance upon susceptibility to avian malaria. This work was confirmed and extended by Seeler and his collaborators<sup>13-16</sup> to experiments with riboflavin, thiamin, folic acid and protein deficiencies. Rigdon<sup>17</sup> failed to detect any effect of vitamin A deficiency on *P. lophurae* in ducks.

The cultural studies with mammalian parasites in vitro have pointed the way to a further extension of studies in vivo. Monkeys (*Macaca mulatta*) deficient in ascorbic acid<sup>18</sup> will control spontaneously an infection with *P. knowlesi*. The absence of methionine from the diet of monkeys and monkeys on fast will also control this highly pathogenic organism.<sup>19</sup> This work is of fundamental importance and the results of more experiments will be followed with interest.

Direct biochemical studies of suspensions of avian and mammalian plasmodia show that the parasitized erythrocytes consume twenty-five to seventy-five times more glucose than the normal red cells.<sup>20, 21</sup> *P. knowlesi* and *P. gallinaceum* contain proteolytic enzymes, which are capable of splitting, degrading<sup>17</sup> and synthesizing protein.<sup>21, 22</sup> The finding that *P. gallinaceum* produces amino nitrogen and ammonia as by-products of protein and glucose under certain conditions<sup>22</sup> might lead

the way to studies that will prove or disprove the production of "toxins" by malarial parasites.

The sequence of events in avian malaria between the bite of an infected mosquito and the blood stages of the parasites has been worked out in detail by Huff and Coulston.<sup>23, 24</sup> These studies are outstanding contributions to malariology. Infective mosquito stages of the malarial parasite, *P. gallinaceum*, were inoculated into young chicks. The chicks were killed at given time intervals and examined histologically. In this way the precise development of the sporozoites (infective stages) through stages called cryptozoites and metacryptozoites within fibroblasts and other lymphoid cells was discovered. The stages resulting from this tissue development emerged later into the blood stream to reinvade the erythrocytes. Although similar stages have not been found in any of the malarias occurring in human beings, they have been found<sup>25, 26</sup> in the parenchymal cells of the liver in monkey infections with *P. cynomolgi* and verified by Hawking.<sup>27\*</sup>

It is believed that such tissue stages exist at least in benign tertian malaria (*P. vivax*) of man and that they are the basis for the serious relapsing nature of this type of malaria. The exact reasons for the relapsing nature of *P. vivax* have not been determined satisfactorily. The explanations that are accepted at present are based by inference on experiments in vivo conducted before the war and later during the war by Fairley and his collaborators<sup>28</sup> in Australia and by the discovery of the so-called "tissue stages" in avian malaria mentioned above. The infective stages, or sporozoites, injected by female anopheline mosquitoes, do not enter the circulating erythrocytes immediately. Patients inoculated experimentally by infected mosquitoes did not have circulating blood parasites from about thirty-six hours to times ranging from two hundred and six to two hundred and fifty-four hours after the infective bite. This was proved by transfusions of large quantities of blood (200 to 500 cc) from infected patients to normal persons. Parasites could be found on an average of twelve days (range, ten to seventeen days) after exposure. These results indicated that tissue stages of *P. vivax* must exist and that the time required for their appearance differs with species and perhaps strains of parasites.

Similar experiments with *P. falciparum*<sup>28</sup> gave negative blood tests up to one hundred and forty-four to one hundred and sixty hours after the infective bite, and parasites could be demonstrated seven to twelve days after the bite.

It is also believed that the inability to obtain radical cures of relapsing tertian malaria with anti-malarial drugs is due to the failure of these drugs to penetrate and exert a lethal action on tissue

\*Since this paper was received for publication the tissue stages of *P. vivax* have been discovered and described by Professor Shortt at the Fourth International Congresses on Tropical Medicine and Malaria.

stages of the plasmodia. The ease by which it is possible to cure benign tertian malaria in paretics who receive their infection by the passage of infected blood gives credence to the theory. These patients receiving malaria induced by blood passage have no tissue stages, and therefore radical cures can be effected with antimalarial drugs. It remains to be determined experimentally whether or not the ability to obtain radical cures of naturally acquired malignant tertian (*P. falciparum*) infections with drugs (a point discussed below) means that the hypothetical tissue stages do not exist or that they are more susceptible to drugs if they do exist.

### DIAGNOSIS

The laboratory detection of malarial parasites in blood films still remains the most reliable method for the diagnosis of malaria. Advances in staining technic of thin and thick films have been directed toward obtaining a more speedy and satisfactory stain.

The basic technics, discussed previously,<sup>1</sup> continue to be used and relied upon. However the requirement of ten to forty-five minutes to obtain stains with various modified Giemsa technics was supplanted during the war by the more rapid Field stain.<sup>29</sup> More recently, another procedure, the J S B stain, appears promising.<sup>29, 30</sup> The handicap to these methods lies in the fact that the stains are not available commercially. The stains for the solutions must be compounded in the laboratory by a combination of standardized stains, methylene blue and eosin. The Field stain, furthermore, is not so permanent as Giemsa's stain. The J S B stain appears to be permanent, but insufficient time has elapsed since its development to be certain about its permanency.

An interesting colorimetric test for malaria has been devised that deserves further investigation and trials. Since serologic and other known tests for malaria fail too frequently during intervals between relapses and in latent malaria, Carlson, Mueller and Bissell<sup>31</sup> sought a new test. In recognition of the changed nature of the host's blood plasma during malaria and the known combining qualities of colloidal dyes with proteins, a test using dyes as indicators to detect the changes in plasma was devised. The test developed by these authors makes use of Congo red, quinine hydrochloride and the serum to be tested. The test gave positive results when tested against *P. knowlesi*, *P. allinaceum* and *P. vivax* infections.

### IMMUNITY

During World War II, the seriousness of white people contracting malaria when going into malarious areas was greatly increased by the necessity of operations in the tropics. Immunity can be acquired to the disease by natives but only by constant infection or reinfection with local strains of

parasites throughout life. The mechanism of acquiring immunity involving both antibody production and cellular defenses was reviewed previously, and the poor antigenicity of the parasites and the low protection of immune serum were discussed.<sup>1</sup> Few contributions have been made to alter the theories and interpretations expressed at that time. The advances, by necessity, have been concerned with practical serologic tests that could be used to detect quiescent malarial infections and characterize the strains of parasites encountered in diverse areas.

Relapsing tertian malaria contracted in the Mediterranean and Pacific theaters of World War II became a diagnostic problem of great importance. Since parasites cannot always be detected by laboratory methods during intervals between relapses, serologic tests, particularly the complement-fixation test, offered a possible solution to the difficulties.

In 1938 Coggeshall and Eaton<sup>32</sup> demonstrated the complement-fixation reaction for malaria. They showed that the reaction was group specific and that the simian and avian species of parasites could be used as antigens. The test subsequently was applied in the field to malaria in human beings by Dulaney and Stratman-Thomas<sup>33</sup> and Kligler and Yoeli.<sup>34</sup> This work was limited in extent, and during the war it became worth while to determine the value of the test in detecting *P. vivax* infections.

Extensive laboratory experimentation and field trials with the reaction produced a refined test that could be used with greater precision<sup>35, 36-37</sup> than originally. This new procedure failed to give the desired results in detecting the existence of relapsing malaria. The conclusion was reached that the test was still a supplementary rather than a dependable single diagnostic procedure. The work of Mayer and Heidelberger<sup>38</sup> showed that a single test with serum from a patient with suspected malaria was of value only if positive, but if negative, malaria could not be excluded. Furthermore, these authors make the following statement:

The reaction diminished 1-6 weeks after relapses only to increase again shortly before or during or immediately after a subsequent relapse. Similar fluctuations may occur, however, without a clinical relapse rendering predictions hazardous.

These fluctuations occurred with a crude vivax antigen, or with normal red-cell stromata antigen.<sup>39</sup> The "soluble," more purified vivax antigen that Mayer and Heidelberger developed gave no such fluctuations, and it aided these workers in discovering for the first time a species specificity with complement-fixation methods. By the use of this "soluble" vivax antigen it was discovered that a positive complement-fixation test did not indicate the existence of protective immunity, since patients were observed who relapsed despite the detection of antibody in serum drawn shortly

before an attack. The results of Dulaney and Watson,<sup>36</sup> who used a "crude" antigen further illustrate this point.

Heidelberger et al.<sup>40, 41</sup> also attempted to protect patients with relapsing vivax malaria by treatment with a homologous vaccine. These experiments were well controlled, and the relapse rate in the vaccinated groups was the same as that in the controlled groups. A further attempt was made by Heidelberger and his co-workers<sup>42, 43</sup> to vaccinate patients against subsequent blood-borne infections and mosquito-borne infections with *P. vivax*. The patients, when infected with malaria three weeks after the last injection of vaccine, came down as usual with malaria, thus, no protection was obtained by vaccination. These very thorough studies verify previous results with animal malarial infections. For reasons unknown, the asexual stages of parasites appear to be very poor antigens. Freund et al.<sup>44-46</sup> were able to protect monkeys and ducks against malaria by using a vaccine containing asexual parasites, an adjuvant, emulsifying agent, and killed tubercle bacilli, but this method of vaccination has not been tried against malaria in human beings. Freund<sup>47</sup> reviews the theory and facts about this type of active immunization in a recent paper.

The development of false-positive tests for syphilis in patients with naturally acquired or artificially induced malaria has been the subject of extensive study. The need for clarifying the basic phenomena that cause positive syphilitic tests in patients having only malaria and for publicizing the occurrence among physicians became necessary to avoid placing under treatment for syphilis persons who do not have the disease. One book<sup>48</sup> and two review papers<sup>49, 50</sup> present the subject thoroughly. The results of a detailed study by Rein and Kent<sup>51</sup> of 7493 serums obtained at suitable intervals from 90 nonsyphilitic volunteers with naturally induced malaria are important. Some of the patients were studied as long as eighteen months. Each serum was subjected to a battery of 7 serodiagnostic tests for syphilis, and 44,958 tests were performed. Of the 90 infected subjects 57 (63.3 per cent) developed false-positive reactions with one or more tests during the course of the disease. The Hinton flocculation and micro-flocculation test employing a cardiolipin antigen yielded results of high specificity and the highest percentage of false-positive tests was obtained with the Kahn standard test. The results showed that false-positive tests for syphilis were highest in early primary malaria, lower in delayed primary attacks and lowest in relapses. Thus, any patient with a recent history of malaria or with a history of living in an endemic malarious area and a positive blood test for syphilis should have the existence of malarial infection ruled out before syphilitic treatment is instituted.

## PHYSIOLOGIC PATHOLOGY

During World War II, malaria was an acute problem to the armed forces and personnel stationed in endemic areas. The problem involved not only the diagnosis and treatment of the clinical disease but also returning a man to full-time or limited duty or back to the United States from overseas. Later, after discharge from the services, the amount of disability to which a previous malarial patient was entitled had to be determined. Thus, criteria of radical cure and an investigation of physical and functional effects of the disease on the host had to be established. Too often misapprehension on the part of the patient was aided and abetted by the unfamiliarity of the physicians with the course and results of the infection.

As a result of experimental and field trials, quinacrine (synonyms, atabrine and mepacrine) was found to be a true causal prophylactic and a radical cure for infection with the malignant tertian parasite *P. falciparum*. The majority of the problems resulting from malarial infection had to do, then, with relapsing tertian malaria. Several investigations were conducted by the Army and Navy to discover the organic and the psychologic causes for morbidity produced by *P. vivax*. These investigations were very thorough, they were conducted independently of each other, and the results add greatly to knowledge of the course of this infection and the sequelae from the disease. These results are of distinct value in determining procedures concerned with the disability granted by the Veteran's Administration to persons who previously had an infection with malaria.

In the first study of Tumulty et al.,<sup>52</sup> 50 soldiers who had suffered recurrent attacks of benign tertian malaria were selected. These soldiers were subjected to a long period of functional, metabolic and psychiatric tests. The evaluation of each soldier and his physical and mental condition was extended over a period of seven days. The procedures are not mentioned in detail, but they included a complete history and physical examination, basal metabolic rate, liver-function test, neurologic test, clinical pathologic test, hematologic test, stool examinations for ova and parasites and serologic test for syphilis.

It is impossible to give in detail the methods of testing used in this study and the very careful evaluation and interpretation of the results. The 50 patients revealed no evidence of damage or dysfunction of the organic systems measurable by the technics employed. The authors believed that the absence of such organic changes was the result of the fact that these patients were treated adequately and early in their attack. However, weight loss, weakness and debility in varying degrees were present in all but a very few of the pa-

tients The chronic symptomatology found in these soldiers was believed to be caused primarily by malaria However, the way the patient adjusted himself to the disease and the environmental factors present at the time of illness were believed to contribute greatly to the development of the symptoms

A second series of studies by Bianco et al<sup>53</sup> differs from those of Tumulty in the fact that they extended over a period of twenty-six months During this time 1500 attacks of malaria were observed, and the persons studied were tested in ways that coincided in some cases with the tests used by Tumulty and his associates but differed in other respects

All the men examined in this study were either Marine or Navy personnel One third of the men had recently returned from overseas duty, and two thirds had been back in this country two to eighteen months without having had intervening quinacrine therapy It is important to note that these authors refused to admit a patient to their study without first having found definite malarial parasites to establish the diagnosis of malaria It was found that the information given by the patient and the available history were unreliable in many cases, and thus competent technicians were used to arrive at the diagnosis of malaria in the presence of fever and with or without an enlarged spleen The technicians never failed to find parasites in the peripheral blood within seventy-two hours when thick smears were examined at eight-hour intervals It should be noted further that parasitemia was commonly of low density, revealing itself, however, during the first few days of clinical malaria The blood-smear technic was of no value if the patient had taken antimalarial drugs several days previously or if a clinician had prescribed sulfonamides to the patient, thinking that fever was due to another infectious agent

Some of the findings that these authors report include the absence of the chronically enlarged spleen, although the spleen in a number of cases was palpable during an attack of acute malaria Leukopenia was fairly common The erythrocyte sedimentation rate was increased in 68.9 per cent of the cases during the acute attack, and in 16.3 per cent during the remission stage of the disease The icteric index was also increased during an acute attack Some of the complement-fixation tests failed to show any relation between parasitemia and the development of subsequent relapse The results with the serologic tests for syphilis were as follows: a variety of tests or methods of testing were used, and the authors found that in a more or less random sample of serum from patients taken during clinical malaria and between attacks, about 90 per cent of the results were negative Positive reactions increased during the second and third weeks after the onset of

clinical malaria, but the serum became negative in most cases within four weeks and in all cases within ten weeks after onset The importance of these tests is included in the statement that 20 to 30 per cent of the cases gave positive reactions by one or more of the tests used two to three weeks after the onset of clinical malaria Positive tests, however, were almost never found later than four to six weeks after onset

The attempt on the part of Bianco and his collaborators to pin down the exact mechanism underlying malaria relapses is worth commenting upon Their purpose, in part, was to allay the fears of many medical and lay personnel that "South Pacific" malaria meant a long if not permanent disability Studies on the relapses and associated symptoms, length of time between relapses, precipitating causes and reactions to treatment led to the following conclusions "With the passage of time away from highly endemic areas, the frequency and severity of relapses shows an unmistakable trend toward the eradication of the malaria within 3 years by development of immunity in the host" Furthermore, they state that "many of the alleged postmalarial sequelae bear no relation to malaria *per se*, but are rather directly related to the personality of the individual"

(To be concluded)

## REFERENCES

- 1 Geiman Q M Advances in malaria research. *New Eng J Med* 229:283-290 and 324-332 1943
- 2 Russell, P F Lessons in malariology from World War II. *Am J Trop Med* 26:5-13 1946
- 3 Freeborn, S B Problems created by returning malaria carriers. *Pub Health Rep* 59:357-363 1944
- 4 Soper F L and Wilson D B Species eradication: practical goal of species reduction in control of mosquito borne disease. *J Am Malaria Soc* 1:5-24 1942
- 5 Ball E G, Anfinsen C B, Geiman Q M, McKee R W, and Ormsbee R A In vitro growth and multiplication of malarial parasite. *Plasmodium knowlesi*. *Science* 101:542-544 1945
- 6 Geiman, Q M, Anfinsen, C B, McKee, R W, Ormsbee, R A, and Ball E G Studies on malarial parasites. VII. Methods and techniques for cultivation. *J Exper Med* 84:583-606 1946
- 7 McKee R W, Ormsbee, R A, Anfinsen, C B, Geiman Q M, and Ball E G Studies on malarial parasites. VI. Chemistry and metabolism of normal and parasitized (*P. knowlesi*) monkey blood. *J Exper Med* 84:569-582 1946
- 8 Anfinsen C B, Geiman, Q M, McKee R W, Ormsbee, R A, and Ball E G Studies on malarial parasites. VIII. Factors affecting growth of *Plasmodium knowlesi* in vitro. *J Exper Med* 84:607-621 1946
- 9 McKee R W, Geiman Q M, and Cobbey T S Jr Amino acids in nutrition and metabolism of malarial parasites. *Federation Proc* 6:276 1947
- 10 Geiman Q M Cultivation and metabolism of malarial parasites. *Proc 4th Internat Congr on Trop Med & Malaria* (in press)
- 11 Trager, W Influence of biotin upon susceptibility to malaria. *J Exper Med* 77:557-582 1943
- 12 *Idem* Relation to course of avian malaria of biotin and fat soluble material having biological activities of biotin. *J Exper Med* 85:663-683 1947
- 13 Seeler A O, Ott W H, and Gundel, M E Effect of biotin deficiency on course of *Plasmodium lophurae* infection in chicks. *Proc Soc Exper Biol & Med* 55:107-109 1944
- 14 Seeler A O and Ott W H Effect of riboflavin deficiency in course of *Plasmodium lophurae* infection in chicks. *J Infect Dis* 75:175-178 1944
- 15 *Idem* Studies on nutrition and avian malaria. III. Deficiency of folic acid and other unidentified factors. *J Infect Dis* 77:82-84 1945
- 16 *Idem* Effect of deficiencies in vitamins and in protein in avian malaria. *J Nat Malaria Soc* 5:123-126 1946
- 17 Rigdon R H Effect of vitamin A deficiency on *Plasmodium lophurae* infection in chicks. *J Infect Dis* 79:272-277 1946
- 18 McKee, R W, and Geiman Q M Studies on malarial parasites. V. Effects of ascorbic acid on malaria (*Plasmodium knowlesi*) in monkeys. *Proc Soc Exper Biol & Med* 63:313-315 1946

- 9 McKee R. W. and Geiman Q. M. Methionine in growth of malarial parasite *Plasmodium knowlesi* *Federation Proc* 7:172 1948
- 10 Silverman M. Ceithaml J. Taliaferro L. G. and Evans E. A. Jr. *In vitro* metabolism of *Plasmodium gallinaceum* *J Infect Dis* 75:212-230 1944
- 21 Ball E. G. McKee R. W. Anfinsen C. B. Oswald Cruz, W. and Geiman Q. M. Studies on malarial parasites. IX. Chemical and metabolic changes during growth and multiplication *in vivo* and *in vitro* *J Biol Chem* (in press)
- 22 Moulder J. W. and Evans E. A. Jr. Biochemistry of malaria parasite. VI. Studies on nitrogen metabolism of malaria parasite *J Biol Chem* 164:145-157 1946
- 23 Huff C. G. and Coulston F. Development of *Plasmodium gallinaceum* from sporozoite to erythrocytic trophozoite *J Infect Dis* 75:231-249 1944
- 24 Conlston F. Cantrell W. and Huff C. G. Distribution and localization of sporozoites and pre-erythrocytic stages in infections with *Plasmodium gallinaceum* *J Infect Dis* 76:226-238 1945
- 25 Shortt H. E. and Garnham P. C. C. Pre-erythrocytic stage in mammalian malaria parasites *Nature* London 161:126 1948
- 26 Shortt, H. E. Garnham P. C. C. and Malambo B. Pre-erythrocytic stage of mammalian malaria *Brit J* 1:192-194 1948
- 27 Hawking F. Pre-erythrocytic stage in mammalian malaria parasites *Nature* London 161:175 1948
- 28 Fairley N. H. et al. Sidelights on malaria in man obtained by subinoculation experiments *Tr Roy Soc Trop Med & Hyg* 40:621-676 1947
- 29 Russell P. F. West, L. S. and Maxwell, R. D. *Practical Malariology* 684 pp Philadelphia W. B. Saunders Co. 1946
- 30 Maxwell R. D. J. S. B. stain for blood parasites *J Lab & Clin Med* 30:1078-1082 1945
- 31 Carlson H. J., Mueller M. G. and Bissell H. D. Colorimetric diagnostic test for malaria *J Lab & Clin Med* 31:677-686, 1946.
- 32 Coggeshall L. T. and Eaton M. D. Complement fixation reaction in monkey malaria *J Exper Med* 67:871-882 1938
- 33 Dolanay A. D., and Stratman-Thomas W. K. Complement fixation in human malaria. I. Results obtained with various antigens. II. Diagnostic application *J Immunol* 39:247-264 1940
- 34 Kligler I. J., and Yoeli M. Diagnostic and epidemiologic significance of complement fixation test in human malaria *Am J Trop Med* 21:531-543 1941
- 35 Lippincott, S. W., Gordon H. H., Hesselbrunck W. B. and Marhle, A. Complement fixation in human malaria using antigen prepared from chicken parasite *Plasmodium gallinaceum*. *J Clin Investigation* 24:362-371 1945
- 36 Dolanay, A. D. and Watson R. B. Complement fixation in relapsing *Plasmodium vivax* malaria *Am J Trop Med* 25:473-480 1945
- 37 Rein, C. R. Bulantiz, S. and Kent, J. Cited by Russell et al.
- 38 Mayer M. M. and Heidelberger M. Studies in human malaria. V. Complement-fixation reactions *J Immunol* 54:89-102 1946
- 39 Heidelberger M. and Mayer M. M. Normal human stromata as antigens for complement fixation in sera of patients with relapsing vivax malaria. *Science* 100:359 1944
- 40 Heidelberger M. Mayer M. M. and Demarest C. R. Studies in human malaria. I. Preparation of vaccines and suspensions containing plasmodia *J Immunol* 52:325-330 1946
- 41 Heidelberger M. Coates W. A. and Mayer M. M. Studies in human malaria. II. Attempts to influence relapsing vivax malaria by treatment of patients with vaccine (*Pl. vivax*) *J Immunol* 53:101-107 1946
- 42 Heidelberger M. Prout, C. Hindle J. A., and Rose A. S. Studies in human malaria. III. Attempts at vaccination of patients against blood borne infection with *P. vivax* *J Immunol* 53:103-112 1946.
- 43 Heidelberger M. et al. Studies in human malaria. IV. Attempt at vaccination of volunteers against mosquito-borne infection with *Pl. vivax* *J Immunol* 53:113-118 1946
- 44 Freund J. Thomson K. J. Sommer H. E. Walter A. W. and Schenkman E. L. Immunization of rhesus monkeys against malarial infection (*P. knowlesi*) with killed parasites and adjuvants *Science* 102:202-204 1945
- 45 Thomson K. J., Freund J., Sommer H. E., and Walter A. W. Immunization of ducks against malaria by means of killed parasites with or without adjuvants *Am J Trop Med* 27:79-105 1947
- 46 Freund J., Thomson K. J., Sommer H. E., Walter A. W. and Pisani, T. Immunization of monkeys against malaria by means of killed parasites with adjuvants *Am J Trop Med* 28:1-22 1948
- 47 Freund J. Some aspects of active immunization *Ann Rev Microbiol* 1:291-306 1947
- 48 Dattner B. Thomas E. W. and Wexler G. *The Management of Neurosyphilis* 398 pp New York Grune & Stratton 1944
- 49 Davis B. D. Biologic false positive serologic tests for syphilis *Medicine* 23:359-414 1944
- 50 Beerman H. Biologic false positive reactions in tests for syphilis. *Am J M Sc* 209:525-542 1945
- 51 Rein, C. R. and Kent, J. F. False positive tests for syphilis study of their incidence in sporozoite induced vivax malaria *J A M A* 133:1001-1003 1947
- 52 Tumulty P. A. Nichols E. Singewald M. L. and Lidz, T. Investigation of effects of recurrent malaria, organic and psychological analysis of fifty soldiers *Medicine* 25:17-75 1946
- 53 Bianco A. A. Saunders G. A. Levine A. S. and Cohn R. Long-term observation of *Plasmodium vivax* malaria in returned servicemen *U S Ar M Bull* 47:352-367 550 567 and 753 765 1947

## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

EDITH E. PARRIS, *Assistant Editor*

### CASE 34271

#### PRESENTATION OF CASE

A fifty-eight-year-old unmarried woman, a floral designer, entered the hospital complaining of abnormal vaginal bleeding.

The patient underwent a normal menopause ten years before entry. Her periods prior to that time had always been regular. Since the menopause she had had no vaginal bleeding until six weeks before entry. At that time she noted enough bloody staining to require the wearing of a pad. This bleeding recurred every three or four days until three weeks before entry, when the bleeding occurred almost every day. It was never profuse, was not accompanied by pain and was otherwise asymptomatic.

She had lost no weight. Two weeks before entry a vaginal smear was reported negative.

The family history and past history and a review of the systems were noncontributory.

Physical examination showed a well developed, well hydrated, obese woman. The heart was slightly enlarged, the border of cardiac dullness extending to the left. The blood pressure was 150 systolic, 95 diastolic. In the abdomen was a movable, nontender mass arising from the pelvis and extending to the level of the umbilicus. Vaginal examination revealed the presence of old blood. The cervix itself was clear. Rectovaginal examination disclosed a large mass filling the pelvis, rising nearly to the navel. It was more prominent on the left and could be moved somewhat. Movement of the mass produced motion of the cervix, and the two seemed to be connected.

The urine was normal, and the hemoglobin was 13.6 gm.

On the day after entry an operation was performed.

#### DIFFERENTIAL DIAGNOSIS

DR. WARD I. GREGG. In this fifty-eight-year-old unmarried woman, whose periods were always regular and who had lost no weight, bleeding had been active for three weeks but present off and on for six weeks.

The causes of postmenopausal bleeding ten years after the menopause I will name and discuss as we go along. The most common cause occurring in 50 per cent of postmenopausal bleeders is adenocarcinoma of the fundal portion of the uterus. Today the next most frequently observed cause—but perhaps in this case not quite so important—is the use or misuse of various estrogens for menopausal symptoms. Proliferation or even hyperplastic endometrium can be produced by continued ingestion of estrin at any age. In this case, however, ten years with no mention of menopausal symptoms is rather late for symptoms to develop. We can forget about that.

To proceed to the findings on physical examination, the patient had a large pelvic mass, which extended up above the pelvic brim almost to the umbilicus and was consistently felt as one mass. We have all examined women and found that one mass may actually consist of a number of adherent masses over the uterus. For the purpose of this discussion we should consider this one mass connected with the cervix and assume that it was the uterus. It was a large uterus, and the next possible diagnosis is therefore a degenerated fibroid. This is apparently rare unless it was a submucous fibroid in which ulceration had occurred. Another possibility that we see from time to time is a polyp, either endocervical or endometrial. Polyps sometimes ulcerate, bleed and produce symptoms similar to those in the case under discussion. Ten years after the menopause is a short period for atrophic vaginitis. Also, the bleeding of atrophic vaginitis rarely becomes constant like that which occurred during the first three weeks of this woman's illness. Carcinoma of the ovary, with bleeding as the primary symptom, is rare unless it has invaded the endometrium. The same statement is true of carcinoma of the Fallopian tube, in which bleeding occurs very rarely until the carcinoma has penetrated the endometrium by way of the tube. It is a possibility but not likely. A year ago a patient was presented to me with an almost identical history, and she had a carcinoma of the Fallopian tube.

I think probably the point of greatest significance here is the fact that two weeks before entry a vaginal smear was reported negative. One vaginal smear, if positive, may mean that the patient has an endometrial carcinoma. However, in the experience of the Vincent Laboratory 23 per cent of proved adenocarcinomas of the endometrium have had negative smears. Scheffey et al.<sup>1</sup> in Philadelphia, have found 40 to 50 per cent of proved adenocarcinomas with negative smears. A negative smear does not rule out completely the possibility of adenocarcinoma. The frequency with which fibroids appear along with carcinoma of the fundus runs in the neighborhood of 33 per cent. The rather scanty bleeding in this particular case may

point toward a small, early lesion. But an advanced carcinoma may break down late. The other thing of importance is that this patient was an unmarried woman, and it has been shown in various series that adenocarcinoma is more likely to develop in nulliparous women who have been exposed to long, uninterrupted estrogen levels. The same group of people usually have dysfunctional bleeding with anovulatory cycles at the climacteric. Randall<sup>2</sup> pointed out in his series that about 45 per cent of postmenopausal adenocarcinomas occurred in women who had dysfunctional bleeding at the time of the climacteric, although the carcinoma was not evident until years afterward. I therefore have a strong feeling that this patient had a uterine fibroid and adenocarcinoma of the endometrium.

#### CLINICAL DIAGNOSIS

Ovarian cyst?  
Degenerating fibroid uterus?

#### DR GREGG'S DIAGNOSIS

Adenocarcinoma of the uterus, with uterine fibroid

#### ANATOMICAL DIAGNOSES

*Adenoacanthoma of fundus of uterus*  
Follicle cyst of ovary  
Uterine leiomyomas

#### PATHOLOGICAL DISCUSSION

DR W. PHILIP GIDDINGS: Dr. Arthur W. Allen thought that the mass, of which, as I recall it, the patient was not aware, represented ovarian disease of some type. She was operated on with a diagnosis of ovarian cyst. Prior to laparotomy a curettage was performed, and grossly carcinomatous material was obtained. At laparotomy a slightly enlarged uterus and a large cyst of the ovary, arising on the left side, were removed.

DR BENJAMIN CASTLEMAN: Although the large mass that was felt was an ovarian cyst, there was, in addition, a uterine fibroid 2 cm in diameter. I do not believe that it had much to do with the adenocarcinoma that was located in the fundus. In a few areas the cancer showed some squamous cell metaplasia, making it an adenoacanthoma. The ovarian cyst was smooth, both inside and out, and perfectly benign.

DR HOWARD ULFELDER: It would be interesting to know if the vaginal smear showed estrogen effect. In a woman of this age estrogen effect in a vaginal smear is found much more frequently in women with adenocarcinoma of the fundus.

DR GREGG: Along with that there is another point that comes up. An estrogen effect in a vaginal smear can occur with granulosa-cell tumor of the ovary. A granulosa-cell carcinoma of the ovary

and an adenocarcinoma of the endometrium are frequently found together and could be caused by the constant estrogen stimulation. I do not believe that the amount of bleeding or the duration indicate such an effect in the case under discussion.

DR CASTLEMAN: The endometrium away from the carcinoma was of the atrophic senile cystic type, which some people believe is a precursor of adenocarcinoma.

#### REFERENCES

- 1 Scheffey, L. C., Rakoff, A. E. and Hoffman, J. Evaluation of vaginal smear method for diagnosis of uterine cancer. *Am J Obst & Gynec* 55:453-460, 1948.
- 2 Randall, C. L. Adenocarcinoma of uterus. In *Progress in Gynecology*, Edited by J. V. Meigs and S. H. Sturgis. 552 pp. New York: Grune & Stratton, 1946. P. 334.

#### CASE 34272

##### PRESENTATION OF CASE

A twenty-seven-year-old housewife entered the hospital complaining of an itching rash.

Two years before entry, about three months after the birth of her first and only child, the patient developed itching lesions on the left ankle. These gradually spread until a pruritic dermatitis involved the legs, arms and trunk, and even spread to the face and scalp. A slight remission of the dermatitis was noted on two occasions, lasting for several weeks, but each time the dermatitis returned as before. She had been seen by many physicians and had had a variety of treatments, including allergy tests, antihistamines, local applications and x-ray therapy to localized skin areas, all with little or no effect. Four months prior to admission the patient was given penicillin tablets by mouth for the appearance of some enlarged cervical lymph nodes. One week after the penicillin was discontinued she developed a generalized urticaria, and she had repeated attacks of urticaria up until the time of admission.

Physical examination revealed a moderately well developed and well nourished young woman, who was nervous and emotionally upset because of fatigue, itching and worry. Several small firm non-tender lymph nodes were palpable along the anterior border of the sternocleidomastoid muscle and above the clavicle, measuring up to 2 cm in diameter. The skin findings were those of an urticaria with multiple excoriations on the flexor surfaces of the arms and over the scapulas, lower back and buttocks. Similar but less marked lesions were present on all other parts of the body. The rest of the examination was negative.

The temperature, pulse and respirations were normal.

Examination of the blood showed a hemoglobin of 13.2 gm and a white-cell count of 7700, with 49 per cent neutrophils, 24 per cent lymphocytes, 5 per cent monocytes, 19 per cent eosinophils and 2 per cent basophils. A blood smear showed only a slight increase in the number of platelets. The urine

was normal. A stool was guaiac negative, and no parasites or ova were found. The total serum protein was 6.90 gm per 100 cc, with 4.83 gm of albumin and 2.07 gm of globulin. The nonprotein nitrogen was 25 mg, the blood cholesterol 125 mg, the serum calcium 9.9 mg, and the phosphorus 5.4 mg per 100 cc. The alkaline phosphatase was 1.9 units per 100 cc.

A basal metabolic rate was +20 per cent. A chest film showed a rounded mass of increased density measuring approximately 6 by 7 by 9 cm in size, occupying the upper anterior mediastinum. The trachea was deviated to the left and somewhat posteriorly. The mass was smooth in outline. It did not appear to have caused any embarrassment to the aeration of the lungs. The lung fields were clear, the heart was normal in contour, the diaphragm was normal in position, and the chest cage was not remarkable. Tuberculin skin tests in dilutions of 1:10,000, 1:1,000 and 1:100 were negative. A repeat basal metabolic rate was +17 per cent. A cervical lymph node was biopsied and showed chronic inflammation. X-ray studies of the bones of the hands and feet showed no osteoporosis or osteolytic lesions. During the first two weeks in the hospital the dermatitis subsided until only a few lesions persisted on the forearms. During this period the temperature, pulse and respirations had always been normal.

On the seventeenth hospital day an operation was performed.

#### DIFFERENTIAL DIAGNOSIS

DR LOWREY F. DAVENPORT: The only complaint in this case was the persistent itching for a period of two years, with few or no constitutional symptoms. The objective findings are the changes in the differential count, the eosinophil count going as high as 19 per cent, the enlarged lymph nodes and the mass in the chest. In trying to arrive at a diagnosis it might be well at this point to review the x-ray films.

DR JAMES J. McCORT: These films were taken at the time of admission—a posteroanterior chest film, a grid film and a film of the hands. The large mass is present in the anterosuperior mediastinum, extending mostly to the right, but one can see a portion of it on the left. On the lateral film it is seen to be anterior to the trachea and has displaced this structure slightly posteriorly and to the left. There are no enlarged lymph nodes in the perihilar region. Both lungs are clear. The heart and vessels are normal. The mass is quite smooth and shows no calcification.

DR DAVENPORT: We have to decide immediately whether or not the symptom of pruritus over two years was a manifestation of a general systemic disease, or whether it was an incidental complaint and entirely unrelated to the mass in the chest. I

gather from the history that during this two-year period the patient had no symptoms referable to the chest, and her chief complaint was from the itching lesion in the skin. The abstract speaks of pruritic lesions. Pruritus, as I understand it, is a symptom — itching of the skin — without any visible change in the skin itself. It would make some difference whether there actually was a skin lesion present, or whether it was pruritus with secondary changes due to scratching.

DR JACOB H SWARTZ: When I first saw this patient she complained of generalized itching. The predominating lesions were not urticarial as stated in the record but rather excoriations, lichenification and pigmentation, with few urticarial wheals. Most of the cutaneous manifestations were secondary to scratching, although some of the lesions may have been primary and produced itching in this particular case.

DR DAVENPORT: We have to consider for the purposes of discussion the possibility that the itching was not connected with the general picture. I do not need to discuss some of the remote possibilities in the differential diagnosis. If, however, these skin lesions and the primary complaint of itching had nothing to do with the general picture as found, we must consider what could cause a symptomless mass in the anterior mediastinum. We can only go on a percentage basis in the differential diagnosis of such a mass. We have found in the past in young people that in the anterior mediastinum teratoma and dermoid cyst were more common, and neurofibromas were much more common in the posterior portion of the chest. If we assume that the fundamental difficulty was a skin lesion, we should consider such primary skin disturbances as mycosis fungoides, in which, in an occasional case, general changes throughout the body are described. It can affect various internal organs but would not explain satisfactorily this entire picture with a mass such as that seen in the x-ray film, the blood findings, the pruritus and the skin lesions.

For the purpose of differential diagnosis I believe we need discuss only two conditions. Hodgkin's disease and sarcoidosis. Hodgkin's disease is a disease of young age groups. It can cause masses of varying sizes in any of the lymph structures. It quite commonly affects the cervical lymph nodes. It can cause marked enlargement of the nodes in the mediastinum and of the hilar nodes. It can be accompanied by pruritus. As I understand it, the itching that accompanies Hodgkin's disease is in a true sense pruritus, and rarely are definite lesions in the skin associated with this condition. Hodgkin's disease, as I have said, is more common in younger age groups, and this woman was in the third decade. However, on a percentage basis, it affects males more than females. The fact that she was a woman is of no real diagnostic significance. Although a

patient with Hodgkin's disease may have a perfectly normal blood picture, quite commonly there is a slight increase in the leukocytes, and in many cases there is an eosinophilia. The pruritus in Hodgkin's disease may be a premonitory symptom and has been described as going on for months or even years before the development of signs of disease elsewhere. Hodgkin's disease, therefore, could explain everything that has been found in this patient.

Another condition that we see more and more frequently that can produce these changes is sarcoid disease. Sarcoidosis can attack at any age but is more common in young people. It is occasionally a disease with pruritic manifestations. It can and frequently does occur without any symptoms at all. Skin lesions do occur in sarcoid and they are described as elevated, dusky, indurated lesions that, I assume, are at times quite easily confused with urticaria. Itching of such lesions has been described as a distressing and continued symptom throughout the early course of the disease. Sarcoid involvement of the lymph nodes is quite common, and it can involve any organ of the body. Involvement of the hilar nodes is not uncommon. Most cases of sarcoid show a more diffuse involvement of the hilar structures than was present in the case under discussion. The involvement is usually symmetrical in distribution, and the process is apt to spread into the lung itself through a peribronchial pattern. Occasionally, it produces lasting fibrosis with permanent changes in the lung, but many cases have cleared up completely without any visible changes remaining in the x-ray films of the chest.

This scrapbasket of sarcoid is puzzling, and differential diagnosis is difficult. In the absence of histologic evidence we have to reason from negative data. Here is a patient who for two years had a generalized disease, and yet when she came to the hospital the only real complaint was itching. I know of no other situation that could cause such diffuse changes throughout the entire body and cause so few constitutional symptoms as sarcoid. Also, although I do not believe the decision is difficult in this case, we often must distinguish between tuberculosis and sarcoid. We frequently rely on the observation that the tuberculin test in probably 90 per cent of cases of sarcoid is negative. It is recognized, however, that perhaps 10 per cent of cases of proved sarcoid have a positive tuberculin test.

In trying to evaluate the significance of a positive or negative tuberculin test in a twenty-seven-year-old housewife, it would be of some interest to know whether the patient was born with a family background of tuberculosis or where she had lived. A negative tuberculin test through all its dilutions in a twenty-seven-year-old city dweller would be of definite diagnostic significance.

**A PHYSICIAN** The patient was born and brought up in New York City.

**DR DAVENPORT** Unfortunately, the tuberculin test is becoming less and less of a diagnostic aid because the incidence of tuberculosis throughout the country is dropping. In the Midwest there are several counties where no children in the schools show a positive tuberculin test. Here in Massachusetts the figures vary from 40 to 45 per cent in urban high schools to 15 per cent in suburbs such as Newton. This finding of a negative tuberculin test in a woman of twenty-seven, born and brought up in New York City, may be of definite diagnostic importance. We have, in sarcoidosis, a granulomatous disease that can cause skin lesions, severe and continued pruritus, enlargement of the lymph nodes and bizarre changes in the chest. It is a disease that is frequently accompanied by mild leukopenia with occasionally a definite eosinophilia such as that reported in this case.

I believe that the final diagnosis comes down to two granulomatous diseases, Hodgkin's disease and sarcoid. I cannot believe that this person had extensive Hodgkin's disease involving so much of the body with so few constitutional symptoms. A negative biopsy in sarcoid would be less surprising than a negative biopsy in a case of Hodgkin's disease. I should then make as my diagnosis Boeck's sarcoid disease, involving the skin, with a rather unusual involvement of the mediastinal lymph nodes.

**DR DONALD S KING** I saw this patient in consultation. I got off on the wrong track and was inclined to say that the skin lesions and enlarged lymph nodes were a separate condition from the asymmetrical chest lesion. Not having seen an itching sarcoid case, somehow sarcoid did not make much impression on my mind and I tried to bring in a benign tumor of the chest in this locality as an entirely separate condition from the skin and lymph nodes. I was influenced a great deal by the negative biopsy of the nodes. My preoperative guess was bronchiogenic cyst and then dermoid or teratoma.

**DR SWARTZ** I thought this case served as a good example to emphasize the close relation between dermatology and internal medicine. When the patient was first seen a provisional diagnosis of lymphoma was made because of a nonspecific eruption with severe pruritus accompanied by enlarged and hard lymph nodes in the supraclavicular areas, axillas and groins. This woman had the type of eruption seen in Hodgkin's disease: urticarial, morbilliform, scarlatiniform and zosteriform. Goldman,\* in 1940, reported 212 proved cases of Hodgkin's disease with cutaneous manifestations in 38 per cent. The predominant manifestations were urticaria, pigmentation and excoriations with severe itching. This patient had

these symptoms in addition to the presence of adenopathy. The chest film further confirmed the possibility of lymphoma, although the other diagnoses mentioned by Drs Davenport and King could not be ruled out without surgery.

In the presence of a nonspecific eruption I was taught to consider the following possibilities: drug eruption, blood dyscrasia, the lymphoma group, subclinical jaundice or some other systemic disease. The psychogenic factor should be considered only when the above-mentioned conditions had been ruled out. This is well exemplified in this case. This patient was treated for two years for pruritus of psychogenic origin. We recently had a case of generalized pruritus that showed only excoriations and icteric discoloration of the scleras. The diagnosis to date is carcinoma of the head of the pancreas. Systemic disease as a cause of pruritus without specific lesions should always be considered.

Sarcoid lesions of the skin look much different from those that this patient presented and are usually nonpruritic. They are infiltrated. Excoriations are absent as a rule. Dr Davenport did not have the benefit of seeing the lesions that this patient presented. I am certain that he would have excluded sarcoid if he had had the opportunity to examine the patient's skin.

**DR BERNARD M JACOBSON** On a medical consultation I considered all the possibilities mentioned so far. I also got off on the wrong track because of the two-year duration of symptoms of itching in a healthy-looking girl.

#### CLINICAL DIAGNOSIS

Bronchiogenic cyst?  
Lymphoma?

#### DR DAVENPORT'S DIAGNOSIS

Sarcoidosis

#### ANATOMICAL DIAGNOSIS

*Malignant lymphoma, Hodgkin's type*

#### PATHOLOGICAL DISCUSSION

**DR TRACY B MALLORY** An attempt was made to establish the diagnosis by biopsy of a cervical lymph node. That proved fruitless. A group of three small nodes was removed, and they showed only nonspecific, mild lymphoid hyperplasia. Therefore, it was decided that it was justifiable to explore the mediastinal mass, hoping that it might be a tumor that was resectable. The patient was operated on by Dr Richard H Sweet, who found a large tumor lying mostly between the trachea and the superior vena cava. It partially encircled the latter, and although he was able to remove most of the tumor, he could not get all of it. Histologic examination showed a characteristic Hodgkin's disease full of large Reed-Sternberg cells, the largest I have ever seen. There was considerable fibrosis and some tissue infiltration with eosinophils.

\*Goldman, L. B. Hodgkin's disease: analysis of 212 cases. *J A M A* 114:1611-1616, 1940.

# The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established 1828

Official Organ of

THE MASSACHUSETTS MEDICAL SOCIETY

and

THE NEW HAMPSHIRE MEDICAL SOCIETY

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND

PUBLISHED WEEKLY UNDER THE JURISDICTION OF THE

COMMITTEE ON PUBLICATIONS

James P. O'Hare, M.D. Richard M. Smith, M.D. *Chairman*  
Oliver Cope, M.D. Conrad Wesselhoef, M.D.  
John Fallon, M.D.

Joseph Garland, M.D. *EDITOR*

*ASSOCIATE EDITORS*

Thomas H. Lanman, M.D. Donald Munro, M.D.  
Henry Jackson, Jr., M.D.

Clara D. Davies, *EXECUTIVE EDITOR*

Robert O. Leary, *ASSISTANT EDITOR*

*EDITORIAL BOARD*

C. Guy Lane, M.D.	Maxwell Finland, M.D.
Henry R. Viets, M.D.	James M. Faulkner, M.D.
Robert M. Green, M.D.	Carroll B. Larson, M.D.
Dwight O'Hara, M.D.	Francis D. Moore, M.D.
Fletcher H. Colby, M.D.	C. Stuart Weleb, M.D.
Robert L. Goodale, M.D.	Vernon P. Williams, M.D.
Chester M. Jones, M.D.	Benjamin Castleman, M.D.
Harvey R. Morrison, M.D.	Hugh R. Leavell, M.D.

**SUBSCRIPTION TERMS** \$7.00 per year in advance, postage paid for the United States (medical students, \$4.00 per year) Canada, \$8.00 per year (Boston funds) \$9.50 per year for all foreign countries belonging to the Postal Union

**MATERIAL** should be received not later than noon on Thursday three weeks before date of publication

**THE JOURNAL** does not hold itself responsible for statements made by any contributor

**COMMUNICATIONS** should be addressed to the *New England Journal of Medicine* 8 Fenway Boston 15 Massachusetts Telephone KE 6-2094

**NEW ENGLAND ADVERTISING REPRESENTATIVE** Edwin B. Tyler 89 State Street, Boston, Massachusetts Telephone LA 3-5516

## ECONOMIC PROBLEMS OF THE VOLUNTARY HOSPITAL

FIFTEEN years ago, during the height of the depression, voluntary hospitals were confronted with a most critical situation. Private and semiprivate beds were unoccupied, public wards were overcrowded. Philanthropic support was materially affected by general economic conditions, and the voluntary hospitals found themselves in dire straits indeed. As conditions improved, private and semiprivate facilities became increasingly occupied, a fact that demonstrated a willingness on the part of the American public to pay its way in accordance with its financial means.

Today, the voluntary hospital is confronted with an even more critical situation, despite the fact that

hospitals in general are overcrowded as never before, and beds of all types, including private, semiprivate and ward, are in great demand. Hospital income has increased to its highest peak, and yet these institutions are confronted with the largest deficits in their history.

The most important factor in the development of this situation is that operating costs have practically doubled within five years, salaries and wages representing the most substantial factor in the tremendous increase in the per diem cost, with the cost of supplies a close second.

The solution of this problem will be difficult, but it will be found. If the advantages of hospital care are to continue to be available and if the scientific measures that play a part in these increased costs are to continue to be applied, little can be done to reduce expenditures. The answer, therefore, must be found in opportunities for increasing hospital operating income, particularly for the care of patients in need of financial assistance for the payment of the hospital bill.

This brings into focus the importance of reimbursement on the basis of costs from all who are able to pay. It emphasizes the wisdom of insurance protection to meet the expenditures of frequently unpredictable illness. It emphasizes the need for the recognition on the part of governmental agencies of their obligation to reimburse the voluntary hospital on the basis of costs, particularly for those who are considered a public responsibility.

It should be agreed that the voluntary hospital, which concerns itself not only with the care of the sick but also with the training of personnel, the conduct of research and the prevention of disease, is worthy of the increasing and continuing support of everyone in the community who is in a position to give financial assistance.

From the point of view of the patient served, the medical profession should exercise good judgment in limiting admission to patients who are actually in need of "in-bed" care. To hospitalize a person because he is a member of Blue Cross, or even because he can afford to pay for service, is uneconomic, unsound and particularly unwise in that it deprives someone in more urgent need of the opportunity for medical or surgical treatment.

Equally important is the employment of only those diagnostic procedures and therapeutic measures that are essential for diagnosis and treatment. This will save time and money and will play a part in the more regular utilization of a hospital bed.

## TROPICAL DISEASES IN NEW ENGLAND

TROPICAL diseases occasionally invade temperate zones, and the possibility of their occurrence in New England deserves greater emphasis. The report of 2 cases of yaws in this issue of the *Journal* and the recent report of 2 cases of creeping eruption (*Larva migrans*)\* lend added weight to the possibility. Another very recent case of *Larva migrans* infection in a person returning from East Africa, as yet unpublished, further confirms the responsibility of the physician in the matter of tropical disease in New England. These particular diseases are infections that have skin manifestations, they usually occur in warm climates, but the return of military personnel and others from war duty and the rapidity of modern air transportation have increased the risk of transferring to the population of this country certain of the cutaneous diseases, as well as other general diseases ordinarily found in the tropics. The greater volume of travel since the war in the countries to the south of the United States provides additional opportunities for contracting diseases that are endemic in those countries. Tropical and semitropical diseases have been observed with increased frequency along the southern borders, although in the northern third of the country such diseases are still relatively infrequent.

Parasitic diseases of the tropics due to both animal and vegetable parasites and the diseases of bacterial origin, with their complications, will need to be considered in differential diagnosis for some time to come by physicians throughout this area. A carefully taken history, including data about any change of abode or travel, in cases of unusual skin eruptions may be of considerable importance in furnishing a clue to the interpretation of any such manifestation. In the differential diagnosis

of granulomatous lesions and of some of the curious eruptions thought must be given to the possibility of a tropical factor as a causative agent. Moreover, the occasional appearance in this general area of such infections as actinomycosis, blastomycosis, sporotrichosis and tularemia renders it advisable for physicians to be alert to the possibility of these unusual diseases as well.

## RAW MILK AND Q FEVER

SEVERAL times in the past few years attention has been called in these columns to the disease Q fever. At first, this was considered to be an influenza-like disease indigenous to some parts of Australia, where it affected mostly dairy workers and foresters. Interest in the disease in this country was first aroused by the isolation of a rickettsial agent that was identical with *Rickettsia burneti*, the causative agent of Q fever from ticks in many parts of western and southwestern United States, and by the occurrence of occasional cases of infections produced by this agent in Montana.

The first significant infections in this country, however, were observed during an outbreak of laboratory infections at the National Institute of Health in which a rather severe type of atypical pneumonia simulating the viral pneumonias constituted an important part of the clinical picture of the disease. Since that time strains of Q fever have been recognized as the cause of Balkan grippé, of several explosive outbreaks of infections among British and American troops in Italy and the Balkans, and also of additional laboratory outbreaks. In this country circumscribed epidemics of Q fever have been recognized among stockyard and packinghouse workers in Amarillo, Texas, and in Chicago, and serologic evidence of previous infection with this disease among packinghouse workers has recently been uncovered in Fort Worth, Texas.<sup>1</sup>

The most recent findings of interest in this disease have been the occurrence of a number of proved cases of Q fever in the region of Los Angeles, California, and, what is more important, the isolation of the causative rickettsial agent from raw milk in at least four dairies in this region.<sup>2</sup> The isolations of these rickettsias were made from samples of milk studied

\*Lowe, C. U. and Augustine, D. L. Creeping eruption in New England report of two cases. *New Eng J Med* 236 658-661 1947

in three separate laboratories — the Q Fever Laboratory in Los Angeles, the National Institute of Health in Bethesda, Maryland, and the Rocky Mountain Laboratory in Hamilton, Montana

Although the rickettsias were recovered from raw milk, the available epidemiologic evidence did not indicate that the drinking of milk was the cause of the majority of the cases that have been studied thus far. However, it was believed by Huebner and his co-workers<sup>2</sup> that infected milk may serve as a source of infection by some mode as yet undetermined. Proximity to dairies by reason of occupation or residency was a common factor in the histories of more than 50 per cent of the cases in the Los Angeles area. Except for the dairy workers, however, the infected persons rarely used milk from the nearby dairies. Fairly extensive surveys, on the other hand, have revealed that from 10 to 20 per cent of the dairy cows in the Los Angeles area possessed serum antibodies for Q fever, which is strong presumptive evidence of recent infection of these animals with the rickettsia.

The relative ease with which *R. burnetii* was recovered from milk in the Los Angeles dairies suggests a high degree of availability of this pathogenic agent to the human and animal population of that area, since nearly all that milk is transported about the county before processing and much of it is sold raw. The facts that Q-fever infection has been demonstrated in the human population and that a source of the rickettsias of this disease was found to be widely disseminated in the same area suggest a causal relation.

The data, however, do not prove definitely whether or not milk represents an effective source of infection to man. In the outbreaks among packinghouse and stockyard workers and also in some of the laboratory infections a pulmonary route of infection was considered most likely. The same fact may also have been true in outbreaks among troops in the Balkans.

Of additional interest are the studies of a limited number of cows that were shedding *R. burnetii* in their milk. These studies failed to yield the rickettsial agent from whole blood, blood clots, urine or feces. Such findings and the absence of a demonstrable illness in the infected animals suggested that

a local infection of the udder occurs in the absence of concurrent infection in the cow. Furthermore, the presence of these rickettsias was not associated with any observable disease in the udder or with diminution in either the quality or the quantity of the milk. There seems to be no way other than isolation of the rickettsia for recognizing the animals that shed the rickettsia in their milk.

Preliminary studies of the methods of pasteurization of the milk, as practiced in at least two of the large milk plants in the Los Angeles area, indicated that these procedures rendered the naturally infected milk apparently noninfectious, at least for guinea pigs. The residents of Los Angeles will therefore have another potent argument for insisting on pasteurization of their milk.

#### REFERENCES

1. Strauss E., and Salkin S.E. Studies on Q fever complement fixing antibodies in meat packers at Fort Worth Texas. *Proc Soc Exper Biol & Med* 67:139-141, 1948.
2. Huebner R. J. Jellison, W. L. Beck, M. D. Parker R. R. and Shepard C. C. Q fever studies in southern California. I. Recovery of *Rickettsia burnetii* from raw milk. *Pub Health Rep* 63:214-222, 1948.

#### ON SECOND THOUGHT

CONGRESS, on second thought, has reversed its decision to consign the World Health Organization to limbo. The terms on which Uncle Sam is willing to play with the other boys are even being softened. Thus, the House provision that the United States member of the Organization's executive board must have had at least ten years in "active practice" has been reduced to three years' experience in the treatment of patients.

The House has also discarded its insistence that every employee and attaché of this country's delegation must be approved by the Secretary of State. The Senate, not to be outdone in graciousness, has allowed withdrawal notice to be lengthened to a year, instead of the ninety days originally insisted upon by that august body.

#### MASSACHUSETTS MEDICAL SOCIETY

##### DEATH

CROTTY — Martin F. Crotty, M.D., of Cambridge, died on June 5. He was in his fifty-sixth year.

Dr. Crotty received his degree from Boston University School of Medicine in 1924. He was a member of the New England Obstetrical and Gynecological Society and a fellow of the American Medical Association.

His widow survives.

## MEDICOLEGAL ABSTRACT

**Hospitals — Dismissal of nurse at request of physician** In a recent Massachusetts case a registered nurse complained that a doctor had improperly induced a hospital to suspend her right to work at the hospital. There was testimony that it was a valuable business relation for the nurse to have her name on the hospital's call list of nurses and to have the privilege of nursing at the hospital and that the relation afforded her fairly reliable means of access to employment in her profession. The court held that unless the doctor was privileged for some reason he would be liable to a nurse under these circumstances for the harm caused her if he was responsible for her suspension from the hospital. Obviously, a doctor may not obtain a nurse's dismissal solely out of malice or for capricious reasons and without justification.

In this case, however, there was testimony, which the jury may have disbelieved, that a patient of the defendant had told him that the plaintiff had made derogatory remarks about him. These remarks were that he thought he and his patients were the only ones that counted and that he was "a two-cent doctor" and did not know how to take care of his patients. There was also testimony that the defendant had been told that the plaintiff had attempted to take for her patient some bed linen and a blanket intended for the defendant's patient.

Other than the words of the Nightingale Pledge, "With loyalty I will endeavor to aid the physician in his work and devote myself to the welfare of those committed to my care," it appeared that there were no regulations concerning the conduct of the nurses. Their supervision was part of the general administrative duty of the board of management. It was substantially agreed, however, that for a nurse to criticize a doctor to his patient would be a breach of ethics.

The plaintiff testified in effect that she had not made the derogatory remarks about the doctor, that on a prior occasion he had threatened to have her taken off the registry and that the superintendent of the hospital had told her that her name had been taken off the list since he was a very important person in the hospital. The defendant himself contradicted this and testified that he had simply reported to the hospital superintendent what his patient had told him about the conduct and language of the plaintiff, which in his opinion was a breach of ethics, and that he did not request the superintendent to omit the plaintiff or to take her name off the list, but that the superintendent had acted on her own initiative. Both the defendant and the superintendent admitted that the plaintiff was otherwise competent as a nurse and that she would not have been restored to the list until she had seen the defendant.

These conflicts of testimony were for the jury, which found for the plaintiff, to resolve, but in the course of its opinion the court made some interesting remarks about the type of case in which a doctor might be privileged in causing a nurse's dismissal. The court said:

We assume that if the plaintiff did disparage the defendant to his own patient a privileged occasion would arise which would justify the defendant in doing something in relation to the matter for the purpose of maintaining the necessary discipline in the hospital and efficient working relations between nurses and physicians. A privileged occasion of some sort might perhaps arise if the defendant had been credibly informed and believed that the plaintiff had made the statements attributed to her, even if in fact she had not made them. We do not decide these questions.

In any question of privilege the issue is not only whether the doctor was privileged to do what he did but also whether he was privileged to do it as he did. Even assuming that a nurse actually made derogatory statements, the caution of the court's opinion intimates that the doctor's action must be taken "for the purpose of maintaining discipline in the hospital and efficient working relations," and not for the purpose merely of injuring the nurse in her profession, which the jury apparently found was his purpose here, or for other purposes unrelated to the privilege. However, the court thought it unnecessary to consider whether, if the defendant had a privilege of some kind, he exceeded its limits in what he did, or whether the jury could find that he lost any privilege by resort to improper means or that he was so far actuated by express malice that all privilege ceased (*O — v H —*, 1948 *Mass Adv Sheets* 193).

MASSACHUSETTS DEPARTMENT  
OF PUBLIC HEALTHSTUDY OF HEART DISEASE IN  
MASSACHUSETTS

A public-health heart-disease program sponsored jointly by the local boards of health, the Massachusetts Department of Public Health and the United States Public Health Service was endorsed by the Council of the Massachusetts Medical Society at its last meeting. This study is being conducted in an effort to reduce the morbidity and mortality from heart disease in adults, particularly in the productive years. Funds and personnel will be provided by the United States Public Health Service.

The projects have also been endorsed in principle by the New England Heart Association. A technical advisory committee appointed by Dr Vlado A. Getting, commissioner of Public Health, includes Dr Howard B. Sprague, chairman, Dr Edward F. Bland, Dr Laurence B. Ellis, Dr James M. Faulkner, Dr Burton E. Hamilton, Dr Hugh R. Leavell, Dr Samuel A. Levine, Dr Benedict F. Massell, Dr Loren D. Moore, Dr Samuel H.

Proger and Dr David D Rutstein The epidemiologic study of heart disease will be conducted in Framingham in co-operation with the Department of Preventive Medicine of the Harvard Medical School and the Framingham Board of Health with the following objectives to devise and evaluate a method for mass survey of a population for heart disease, to examine a suitable sample of the population to determine the prevalence ratios of various forms of heart disease in the adult groups between twenty and seventy years of age in this area, to carry out a follow-up study to determine the rate at which new cases occur in the population as it ages — that is, the risk of attack — and to observe the natural course of certain forms of cardiovascular disorders, to determine if possible through analysis of data collected the relation of factors such as those of race, heredity, occupation, body build, use of stimulants and diet to the development of heart disease, and to collect records for evaluation of instruments, such as the electrokymograph and photo-fluorograph as case-finding tools

A local professional advisory committee, consisting of T J Carnicelli, M D, Hugh Folsom, M D, H M Levenson, M D, E J DeNicolais, M D, J H McCann, M D, C M Bonzey, Jr, M D, H G Murray, M D, M B Strauss, M D, P B LeBaron, D M D and Mervin Weitz, D M D, will assist in guiding the Framingham program

The heart-demonstration program will be conducted in Newton as a co-operative project with the Newton Health Department, under the immediate supervision of Dr Ernest M Morris, director of public health, with the following objectives to plan and develop in co-operation with the local medical profession and other agencies concerned a public-health program to help meet the increasing problem of heart-disease morbidity and mortality, especially in the productive ages, to prepare a basic manual with information for workers in a public health heart program (the writing of the manual will be supervised and edited by the Technical Advisory Committee)

The local medical advisory committee will participate in the development of the heart-demonstration program, and will consist of members of the public-health committee of the Newton Medical Club These are Drs George Bowers, Theodore Clark and Egon Kattwinkel, with Dr Herbert G Dunphy, president of the club, as *ex-officio* member A committee from the Newton Dental Club is to be appointed

## MISCELLANY

### SAFETY CONFERENCE

One session of the annual Safety Conference, held in April at the Statler Hotel, Boston, was sponsored by the Massachusetts Department of Public Health, Dr Vlado A Getting, commissioner, presiding

Prevention of accidents was the keynote of the afternoon discussion, six speakers emphasizing safety points in their

particular fields Dr Erich Lindemann, of the Massachusetts General Hospital, told of the "accident-proneness" of persons under emotional stress, Miss Frances Frazier, of the Harvard School of Public Health, urged assistance to the aged to prevent falls, and Dr John F Conlin spoke on "The Doctor — Preventive Medicine" Stephen Mahoney, of the Cambridge Recreation Department, stressed the necessity of regular inspection of playground equipment, Mrs Frances Blair, president of the Massachusetts Parent-Teacher Association, spoke on the safety of children, and the concluding speaker, John Chandler, commissioner of agriculture, described the many accidents occurring on the farm.

### BLUE SHIELD FINANCIAL REPORT

The Blue Shield plans of the country, according to a release from the national office in Chicago, recorded a total income of \$48,445,245 during 1947 Of the sum so collected approximately 78 per cent was paid to physicians, 15 per cent went toward operating expenses, and the remainder was added to reserve accounts

### RESEARCH IN SKIN DISEASES

A new and intensive program of research in diseases of the skin was recently announced by Harvard Medical School and the Massachusetts General Hospital The program, financed in part by the Rockefeller Foundation, will bring recent advances in physiology and biochemistry to bear in a search for new knowledge of skin diseases It will be based on close co-operation between dermatologists and experts in general medicine

To develop this new program, Dr Chester North Frazier, head of the Department of Dermatology at the University of Texas, has been appointed Edward Wigglesworth Professor of Dermatology at Harvard University and chief of the Dermatology Service at the Massachusetts General Hospital He will organize a new department of dermatology at the medical school and will lead the research and clinical program at the hospital

## CORRESPONDENCE

### SUGGESTION FOR BETTER PHARMACEUTICAL METHODS

To the Editor A serious problem confronts the medical profession It is becoming more and more apparent that it is the policy of the drug manufacturers to release new drugs as tablets, capsules and ampoules These are all high priced dosage forms The low-cost dosage forms like the powder, which can be used to fill prescriptions that need compounding, and the hypodermic tablet are not available

A drug in point is methadon, which was taken from the Germans in World War II A doctor attending a patient with a gall-bladder attack at night could give an injection of methadon from a hypodermic tablet and then dispense a few such tablets of methadon to be taken by mouth during the night A hypodermic tablet would not cost more than three or four cents However, since the tablet is not obtainable, an ampoule must be used for the injection, at a cost of sixteen cents Then the doctor must have oral tablets of methadon to dispense The hypodermic tablet can be used in two ways and — to make it more pleasant — is much cheaper One must not forget that morphine sulfate has been used in the form of hypodermic tablets for many years, and certainly any of the new drugs can be used likewise

The failure of the drug manufacturers to provide the powder form of drugs is even more serious In the USP (13th edition) I have found that at least twenty of the newer drugs cannot be obtained in the powder form Despite the publicity carried on by drughouses concerning the anti-histaminics, the rank and file of physicians know of many failures with these drugs and would like to combine them in a prescription with ephedrine and aminophylline If the antihistaminic failed, at least the ephedrine and the aminophylline would work in a case of asthma

All physicians should write to the Council on Pharmacy and Chemistry of the American Medical Association urging that steps be taken to make all medicines available in powder form

Brawley, California

BENJAMIN L YELLEN, M D

## BOOK REVIEWS

*A History of Scientific English The story of its evolution based on a study of biomedical terminology* By Edmund Andrews, M.D. 8°, cloth, 342 pp., with 18 illustrations New York: Richard R. Smith, 1947 \$7.50

Dr. Andrews, successful surgeon and erudite philologist, in this outstanding work has produced a history of the origin and transition of scientific language from its beginnings in historic times down to the present. Like some other philologists he believes that all language stems from an unknown ancestor of the prehistoric period. In successive chapters he considers Indo-European philology, semantics and the history of medical terminology. The following chapters discuss various historical aspects, including pre-Hellenic influences, the Aryan heritage, Greek, Latin (including dead or classical Latin), Arabic, French, German and English, divided into Anglo-Saxon, middle and modern. The final chapter deals with the future and advocates Basic English as a common scientific language. A good index concludes the text.

Although Dr. Andrews' book will appeal to comparatively few readers, it should be in all collections of medical and scientific history.

*Emotional Maturity The development and dynamics of personality* By Leon J. Saul, M.A., M.D. 8°, cloth, 358 pp. Philadelphia: J. B. Lippincott Company, 1947 \$5.00

The task of presenting psychodynamic understanding of human motivation that will reach a large and varied group is always a difficult one. In this book, the author presents his material in an extremely readable form. Although his orientation is psychoanalytic, he maintains a conscious oversimplification of the problem, sacrificing completeness and depth for clarity and schematization. He concerns himself with the main motive forces of behavior and personality, accentuating early training and environment but not entirely losing sight of the fundamental biologic drives. He gives considerable attention to the problem of neurosis, illustrating it with numerous well chosen cases.

This book is an excellent primer to the dynamics and development of personality couched in language designed for the layman. It also contains much of interest for those farther advanced in the field of psychiatry.

*Medicine* By A. E. Clark-Kennedy, M.D., F.R.C.P. Volume 1 *The patient and his disease* 8°, cloth, 383 pp. Baltimore: Williams and Wilkins Company, 1947 \$5.00

The author of this work, physician to the London Hospital and dean of its Medical School, rebels against the present-day textbook of medicine, rating it either as a compilation of second-hand facts or as a symposium of disconnected subjects by a panel of writers. This is a harsh and surely contestable evaluation. His own object is to give an account, based on his personal experience as practitioner and teacher, of the nature of the patient and to explain the meaning of his disease, correlating facts rather than enumerating them, and emphasizing the general principles underlying medicine as a whole. As a science medicine deals with the physical aspects of disease as an art it handles all the complexities of the human mind and the many shades of human personality.

Some of the chapter headings in this volume suggest its scope and method: "Body and Mind", "Symptoms and Signs", "Heredit and Environment", "Reactions of the Body and the Mind", and "Nature of Disease". Each chapter has a comprehensive summary.

The following paragraph in the chapter on "The Nature of Disease" exemplifies the author's style and thinking:

The body of man and his mind, at least to some extent, are the product of organic evolution, the result of natural selection of variation in the struggle for existence. Every individual struggles for existence. His genetic endowment may handicap him from the start. Throughout his life he is exposed to all the dangers inherent in the physical world and to competition with other forms of life. There is never-ending competition between man and man. Danger lies in the power of man's will. Adverse factors in heredity and environment act on his body and disturb his mind. All tend to lessen his physical and mental efficiency, and produce pain and suffering. Many shorten his existence and may abruptly terminate his life. Without the power of

adaptation the individual would not survive long and the human race would soon cease to maintain the dominant position which it occupies in the animal world.

It is a work well worth leisurely reading and study.

*Radium Dosage The Manchester System* Edited by W. J. Meredith, M.Sc., F.Inst.P. 8°, cloth, 124 pp., with 38 illustrations, 4 plates and 27 tables. Baltimore: Williams and Wilkins Company, 1947 \$4.50

This publication is an extremely valuable compilation of papers that have appeared in recent years by members of the Holt Radium Institute at Manchester. A method of dosage measurement, correlated with a scheme of distribution giving homogeneity for planar and irregular moulds, cylinders and interstitial radium application, is described simply and lucidly. None of these methods, however, are applicable to the treatment of cancer of the cervix because of the great variation in size, shape and type of the parts and the tissues to be treated. A special chapter is devoted to this subject in which the types of radium applicators advised and the principles underlying their use are described.

Radium has had a much wider use in England than in this country, where, apparently, this therapy has been stymied by the ease with which x-ray dosage may be approximated and phased by the calculations necessary for accurate dosage when radium is employed. Very few clinicians have the type of mentality or the interest to wrestle with the theoretical physics involved in dosage measurement, but welcome data in readily applicable form.

Paterson and Parker, in England, and Quimby, in the United States, have done just that for radium dosage. They have reduced involved formulas to such simple terms that anyone with knowledge of arithmetic can apply them.

The first part of this monograph consists of the clinical aspects of the constituent papers rewritten to form a continuous whole. The purely physical aspects of the work are considered in the second part.

This book should be in the library of every radiologist and radiologic department.

## BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

*Atlas of Bacteriology* By R. Cranston Low, M.D., F.R.C.P.E., F.R.S., member, Bacteriology Department, University of Edinburgh, and consulting physician, Skin Department, Royal Infirmary, Edinburgh, and T. C. Dodds, F.I.M.L.T., F.I.B.P., F.R.P.S., laboratory supervisor, Department of Pathology, University of Edinburgh and lecturer to the Society of Radiographers (Fellowship Course), Scottish Branch. 8°, cloth, 168 pp., with 168 illustrations. Baltimore: Williams and Wilkins Company, 1947 \$5.50

The authors have produced an atlas primarily intended for undergraduate students to supplement class work and standard texts. All the plates except one are in color, and were made from actual color photographs and water-color drawings when it was found impossible to use photographs. Great care was taken to reproduce exact color tones, but unfortunately eight illustrations were reprinted too light in color and because of the shortage of paper could not be reprinted. Each figure shows the magnification, stain and source of culture and notes any other pertinent facts. The color work is good, and the volume well published. The book should prove useful as a ready reference source.

*Applied Medical Bacteriology* By Max S. Marshall, Ph.D. With the collaboration of Janet B. Gunnison, M.A., Alfred S. Lazarus, Ph.D., Elizabeth L. Morrison, M.A., and Marian C. Shevlin, A.B., division of bacteriology, Medical Center of the University of California, San Francisco. 8°, cloth, 340 pp., with 10 illustrations and 12 tables. Philadelphia: Lea and Febiger, 1947 \$4.50

This practical manual has been written for the student, clinician and public-health worker interested in bacteriology.

as applied to his problems. The early chapters have to do with the various technics. These are followed by chapters on viruses, yeasts and molds, biologic products and sanitation. The final chapter, consisting of over half the book, discusses the various diseases due to micro-organisms. These are arranged in alphabetical order, and describe the organism, specimens, microscopical examination, laboratory procedures and reports. The material is well arranged, the text well written, and the volume well published. A good index concludes the volume. An up-to-date list of biologic products and their makers is included.

*Pharmacology and Experimental Therapeutics. A survey for 1941-1946.* By Hamilton H. Anderson, Fumiko Murayama and Benedict E. Abreu. 8°, cloth, 368 pp. Berkeley and Los Angeles: University of California Press, 1947. \$6.50.

In this survey the authors have arranged their material in an alphabetical form obviating the need for an index. The effects of drugs and therapeutic agents are briefly considered, and the references, on which the text is based, are made part of the text. The volume is well published and should prove useful as a reference source in medical libraries and valuable to all persons interested in pharmacology.

*American Medical Research, Past and Present.* By Richard H. Shryock, Ph.D., professor of history and lecturer in medical history, University of Pennsylvania, and acting director, American Council of Learned Societies. 8°, cloth, 350 pp. New York: The Commonwealth Fund, 1947. \$2.50.

Dr. Shryock has written a history of American medical research from its beginning in the middle of the eighteenth century to the present time. The work is divided into twelve chapters, considering in order the formative period of British influence, 1750-1820, early support of research, 1860-1895, the era of private support by foundations and institutions, 1895-1940, research trends, research fields, public relations and public support. The last chapter analyzes the part Government agencies, federal, state and local, have taken in this field since 1940. The text is interesting and well written. Each chapter is documented with references to original sources. There is a good index, and the volume is well published. It should be in all medical, university and general libraries and in historical collections.

*Teaching Psychotherapeutic Medicine. An experimental course for general physicians.* By Walter Bauer, M.D., Douglas D. Bond, M.D., Henry W. Brosin, M.D., Donald W. Hastings, M.D., M. Ralph Kaufman, M.D., John M. Murray, M.D., Thomas A. C. Rennie, M.D., John Romano, M.D., and Harold G. Wolff, M.D. Edited by Helen L. Witmer, Ph.D. With an introductory chapter by Geddes Smith. 8°, cloth, 464 pp. New York: The Commonwealth Fund, 1947. \$3.75.

This book is based on lectures and discussions of the pilot course in psychotherapy in general practice given at the University of Minnesota in 1946, covering a period of two weeks. Nine specialists took part in the presentation of papers and discussions, with illustrative case reports on backache and headache, psychoneuroses, anxiety neuroses, the care of veterans and life situation, emotions and disease. The early chapters deal with general orientation, history-taking, patient-physician relation and normal personality development. Twenty-five physicians took the course, and in addition to the lectures they treated by psychotherapy patients in the outpatient service who suffered from headache, backache, indigestion, vague and persistent pains, fatigue and nervousness. This teaching course was successful from a practical point of view. The volume is well published in every way and is recommended for all medical libraries and should prove valuable to the general practitioner.

*140 Million Patients.* By Carl Malmberg. 12°, paper, 242 pp. New York: Reynal and Hitchcock, 1947. \$2.75.

Mr. Malmberg was formerly information specialist for the United States Public Health Service and chief investigator for the United States Senate Subcommittee on Health and Education. In this volume he advocates the establishment of socialized medicine and the passage of the revised

Wagner-Murray-Dingell Bill, introduced in Congress in May, 1947, as S. 1320 and H.R. 3548. He discusses the subject in five pertinent sections: health inventory of the United States; the cost of sickness; the quality of American medical care; prescription for better health; and voluntary plans—"too little and too late." He concludes with a short chapter entitled, "140 Million Patients Can't Be Wrong."

The author believes that voluntary plans have reached their peak of service and that the Blue Cross has reached the saturation point although the increase in 1947 was 22 per cent over 1946, an increase of over five and a half million new enrollments.

He states that the Taft Bill (S. 545, 80th Cong. First Session) is not constructive but is a delaying action to offset the Wagner-Murray-Dingell Bill.

In the statistical tables of infant and maternal mortality, general mortality and morbidity rates, only countries with a better showing than the United States are listed, those with poorer rates being ignored.

The paper-covered volume is well printed with a good type, on good paper. It should be in all public-health collections.

## NOTICES

### NEW YORK STATE SOCIETY OF ANESTHESIOLOGISTS

The third postgraduate assembly of the New York State Society of Anesthesiologists will be held at the Hotel New Yorker, New York City, on December 9 and 10.

### AMERICAN COLLEGE OF SURGEONS

The thirty-fourth Clinical Congress of the American College of Surgeons will be held in Los Angeles, with headquarters at the Biltmore Hotel, from October 18 to 22. The program of scientific sessions on subjects in the fields of general surgery, eye, ear, nose, and throat surgery, gynecology and obstetrics, urology, and orthopedic, thoracic, plastic and neurologic surgery will be supplemented by operative clinics in hospitals in Los Angeles and vicinity by showings of operations by television and motion pictures, and by a four-day hospital-standardization conference for hospital personnel. There will also be extensive technical and scientific exhibits.

## SOCIETY MEETINGS AND CONFERENCES

### CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, JULY 8

**FRIDAY, JULY 9**  
 \*10:00 a.m.-12:00 p.m. Medical Staff Rounds. Peter Bent Brigham Hospital.  
 12:00 p.m.-1:00 p.m. Clinicopathological Conference (Boston Floating Hospital). Joseph H. Pratt Diagnostic Hospital.  
**TUESDAY, JULY 13**  
 \*12:15-1:15 p.m. Clinicorontogenological Conference. Peter Bent Brigham Hospital.  
 \*1:30-2:30 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.  
**WEDNESDAY, JULY 14**  
 \*12:00 p.m.-1:00 p.m. Clinical Conference (Children's Hospital). Amphitheater, Peter Bent Brigham Hospital.

\*Open to the medical profession.

**JUNE 28-JULY 23** Harvard Seminar on Health Education. Page 856 issue of June 10.  
**JULY 6-24** Students' International Clinical Congress. Page 455, issue of March 25.  
**JULY 12-17** First International Poliomyelitis Conference. Page 36 issue of January 1.  
**AUGUST 11-21** International Congress on Mental Health. Page 344 issue of March 4.  
**AUGUST 23-26** International Society of Hematology. Page 419, issue of March 18.  
**AUGUST 26-28** American Association of Blood Banks. Page 420 issue of March 18.  
**SEPTEMBER 7-11** American Congress of Physical Medicine. Page 582, issue of April 15.  
**SEPTEMBER 13-15** American Academy of Pediatrics. Olympic Hotel, Seattle, Washington.  
**SEPTEMBER 16-18** Vermont State Medical Society. Annual Meeting, Burlington.  
**SEPTEMBER 20-23** American Hospital Association. Page 310 issue of February 26.

(Notices concluded on page xiii)

## NOTICES (Concluded from page 34)

- SEPTEMBER 29 Mississippi Valley Medical Editors' Association  
Page 170 issue of January 29
- OCTOBER 6-9 American Board of Ophthalmology Page 170, issue of  
January 29
- OCTOBER 18-22 American College of Surgeons Page 34
- OCTOBER 27 New England Obstetrical and Gynecological Society  
Annual Meeting Hotel Somerset, Boston
- NOVEMBER 1-3 American Clinical and Climatological Association  
Page 582 issue of April 15
- NOVEMBER 8-12 American Public Health Association Page 420 issue  
of March 18
- NOVEMBER 10-13 Association of Military Surgeons of the United  
States Page 722 issue of May 13
- NOVEMBER 20-23 American Academy of Pediatrics Annual Meeting  
Chalfonte Haddon Hall Hotel, Atlantic City, New Jersey
- DECEMBER 7-9 Southern Surgical Association Annual Meeting  
Page 543 issue of April 8
- DECEMBER 9 and 10 New York State Society of Anesthesiologists  
Page 34

**Tablets Ferglate-B with C**

High in vitamin B complex content to quicken hemo-  
globin response to iron therapy

**EACH TABLET CONTAINS**

Ferrous Gluconate (5 grains)	0.375 gm	Pyridoxine HCl	0.15 mg
Thiamin HCl	3 mg	Calcium Pantothenate	0.5 mg
Riboflavin	2 mg	Ascorbic Acid	30 mg
Niacinamide	20 mg	Yeast-Liver Base	q.s.

**INDICATIONS**

Iron deficiency and nutritional anemias as a source of iron and  
B complex factors

Write Department A12 for Professional  
Sample and Literature

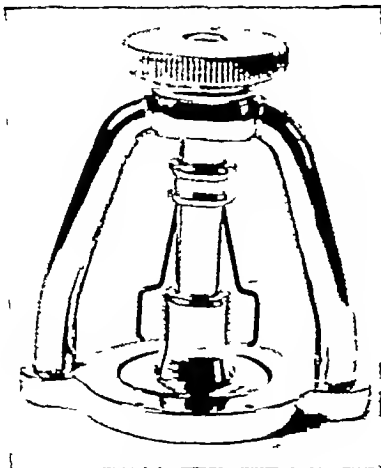
**KENMORE PHARMACAL CO.**

500 COMMONWEALTH AVENUE  
BOSTON 15, MASS

**NEW INSTRUMENT !!**

Actual size

- Bloodless
- Simple in construction and assembly
- Light in weight
- Easy and efficient to use
- Small-Compact
- Interchangeable in sizes
- Comes in two interchangeable sizes — NEW BORN and CHILD with complete instructions in black leather snap cover case



The LEM-BLAY

**CIRCUMCISION CLAMP**

Through your regular Supply House

*The Elbe Company*

165 PARKER STREET, LAWRENCE, MASSACHUSETTS  
Telephone Lawrence 24672

Advertisement



From where I sit  
*by Joe Marsh*

**How to Live  
Longer**

*Someone asked Pappy Miller last week how he stayed so spry at ninety Pappy told him*

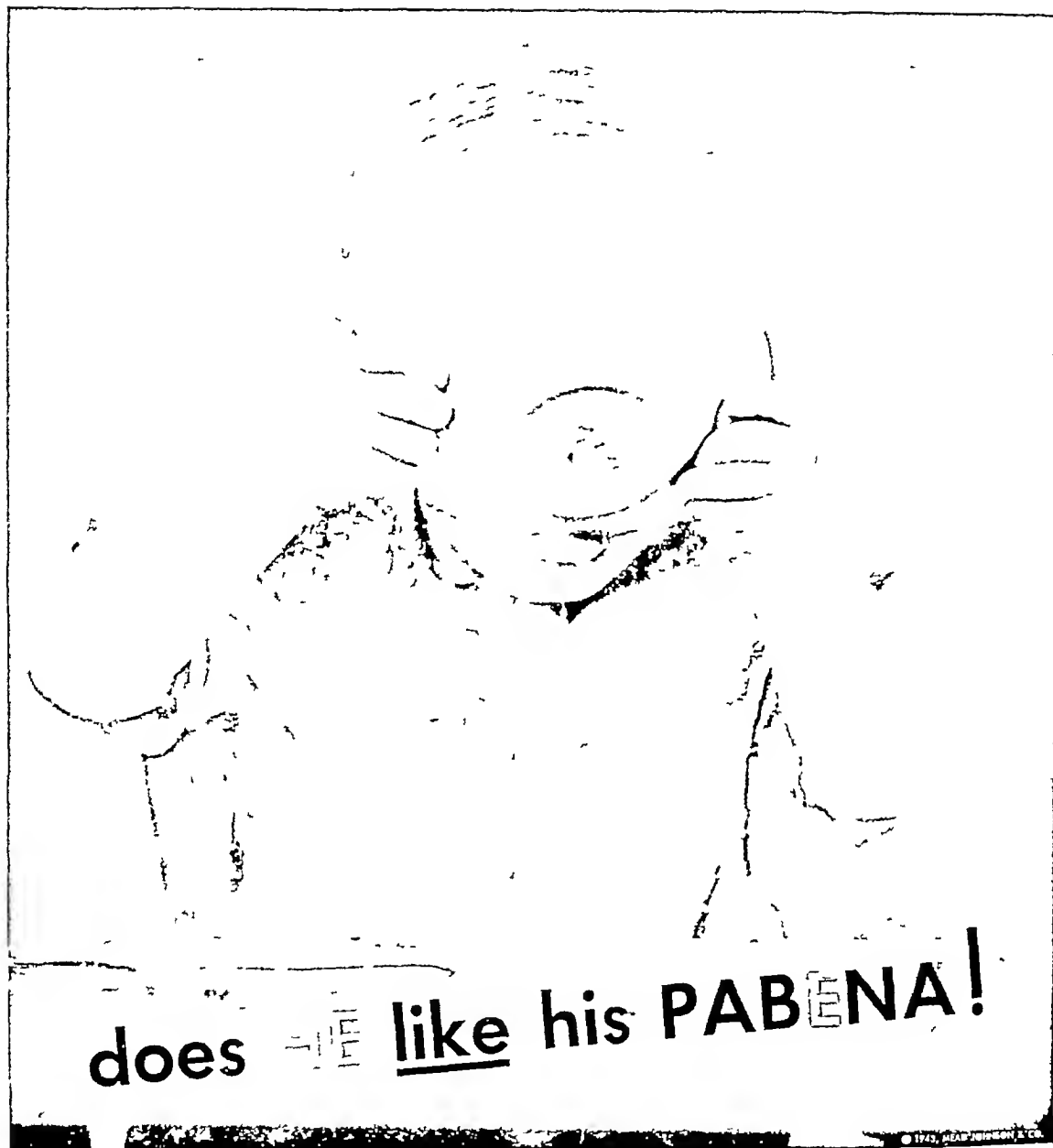
*"Well, sir—when I work, I work hard When I set, I set loose When I think, I go to sleep"*

*According to Doctor Hollister, that formula isn't far amiss "Hard work," he says, "never wore out anyone before his time, providing he knew how and when to relax"*

Hollister himself works overtime, with his daytime patients at the office, and his evening calls And when he gets home he takes it easy with a mellow glass of beer and chats with the missus until it's time to go to bed.

*From where I sit, relaxing is certainly a fine art—especially in these tense, fast-moving times And there's nothing just quite like a temperate glass of beer—enjoyed with pleasant company—to restore that easy frame of mind that one really needs after a hard day's work.*

*Joe Marsh*



does HE like his PABENA!

**W**HEN interviewed between platefuls, this 11-months-old young man emphatically stated: "I have been brought up on Pablum and still like it, but some days when I'm in the mood for oatmeal, nothing satisfies me like Pabena!"

*Nutritious, quick and easy to prepare,  
both products are for sale at drug stores.*

**MEAD JOHNSON & COMPANY, EVANSVILLE, IND., U.S.A.**

# The New England Journal of Medicine

Copyright 1948 by the Massachusetts Medical Society

Volume 239

JULY 8, 1948

Number 2

## RETROPUBIC PROSTATECTOMY\*

GEORGE AUSTEN, JR., M.D.,† AND WILLIAM C. QUINBY, M.D.‡

BOSTON

UNTIL recently, time and experience had accepted as satisfactory three principal operative approaches to the prostate: perineal prostatectomy, suprapubic transvesical prostatectomy and transurethral prostatectomy. No single one of these procedures alone is applicable for the treatment of every type of prostatic obstruction. In spite of the contention of surgeons who are strong proponents of one method to the exclusion of the others, it seems fair to say that each of these procedures has certain indications and contraindications, as well as certain limitations and disadvantages, and that each is attended by various technical difficulties that may render the results of operation unsatisfactory. Therefore, when a new and logical method of treatment is proposed, which apparently produces good results in intelligent hands, the progressive surgeon must examine it carefully.

In 1945 Millin,<sup>1</sup> of London, presented his initial report of "a new extravesical technique" of prostatectomy—a suprapubic operation for non-malignant lesions of the prostate to which he applied the name "retropubic prostatectomy." Although Millin considered his operation original, he noted that a somewhat similar suprapubic extravesical approach to the prostate had been made and reported by others. He referred to the reports of van Stockum<sup>2</sup> in 1909 and of Jacobs and Casper<sup>3</sup> in 1933. In both communications there were certain variations in the technic of actual enucleation of the obstructing lobes and closure of the capsule that differed distinctly from the operation described by Millin. He also added that in 1924 Maier<sup>4</sup> reported 4 cases in which the gland was removed by an inguinal extravesical route. However, a review of the literature demonstrates that Millin's report is the first record of any appreciable series of cases treated consistently in this fashion, and it is fair to allow his claim to the

originality and development of the technic that he described.

In his initial publication Millin reported the results obtained in 20 patients with benign prostatic disease who were operated upon by this method, 13 patients had generalized hypertrophy, 2 had fibrous glands with sclerotic bladder neck, 1 had calculous disease, 2 had pure lateral-lobe hypertrophy, 1 had generalized hypertrophy associated with a prostatic abscess, and 1 had post-prostatectomy scarring of the prostatic urethra. There were no postoperative deaths, and complications were few. There were 2 cases of minor delayed bleeding, both in patients who had had grossly infected bladders before operation which was easily controlled by the use of an indwelling catheter for forty-eight hours. No cases of immediate hemorrhage, gross infection, pyelonephritis or renal failure were encountered. A femoral-vein thrombosis developed in 1 case, and an abscess of the testis in another. In only 3 cases was there suprapubic leakage of urine after removal of the urethral catheter on the sixth or seventh postoperative day, and in these cases it was felt that this occurrence was the result of initial faulty adjustment of the catheter. Concerning the long-term follow-up results, Millin believed that it was too early to pass a verdict on the incidence of post-prostatectomy obstruction, but subsequent reports from his clinic<sup>5-7</sup> have shown that postoperative contracture of the vesical neck occurs occasionally. For that reason he has made a modification in his original technic which is described below. However, in summarizing the results in his first 20 cases, Millin stated that "The post-operative comfort has to be seen to be believed." There was apparently very little bleeding into the bladder, catheter irrigations were rarely necessary, and "bladder spasms, so common after the classical prostatectomy," were "absent or minimal."

During the year and a half since the publication of his first report of this new operation, Millin has presented the results obtained by this technic in increasingly larger series of 85 cases<sup>6</sup> and 184 cases<sup>6</sup>. Of his 85 cases, 75 were done in a one-stage and

\*Presented at the annual meeting of the New England Surgical Society, Providence, Rhode Island, October 3, 1947.

†From the Urological Clinic, Peter Bent Brigham Hospital.

‡Instructor in urology, Harvard Medical School; associate in urology, Peter Bent Brigham Hospital; urologist, Free Hospital for Women, Brookline.

§Clinical professor of genitourinary surgery, emeritus, Harvard Medical School.

10 in a two-stage procedure. In the series of 184 cases, approximately 4 per cent had been two-stage procedures. Millin believed that in the future these might form a larger proportion — perhaps 10 per cent. He found no particular difficulty in carrying out a second-stage retropubic prostatectomy when a previous cystostomy had been performed. Although the morbidity and mortality rate for the total series of 184 cases was not recorded, he noted that among his first 85 cases he had had 4 cases of minor hemorrhage and 5 of bladder-neck obstruction due to postoperative stricture or contracture of the vesical outlet. There had been 4 deaths — 2 from pyelonephritis, and 2 from cardiac failure. Since these reports Millin has performed retropubic prostatectomy in more than 400 cases, with a mortality rate of approximately 4 per cent. His experiences with the procedure in this larger group of cases were discussed at the 1947 meeting of the American Urological Association. The operation has been described in the book that he published recently.<sup>7</sup> As a result of his experience to date, he considered retropubic prostatectomy to be "the procedure of choice in every case affording a reasonable operative risk, except for those cases which presented fibrosis and which should have endoscopic resection."

Since Millin's original communication, reports of the results obtained by this operation have been published by other authors in the British medical literature. Although no specific mention has been made of the type of obstruction for which the operation was performed, in the majority of recorded cases the patients apparently had simple benign hypertrophy of the prostate. Series numbering from 3<sup>8</sup> to 63 cases<sup>9</sup> are mentioned. With one exception,<sup>10</sup> all authorities seemed to believe that the procedure had great merit, primarily because of its direct approach to the prostate, avoidance of trauma to the bladder, easy postoperative course with absence of persistent suprapubic leakage of urine, and good functional results. Although the number of patients operated upon by Millin's technic is still relatively small, the death rate and frequency of occurrence of complications in the published cases seem to confirm the optimism of the authors. Jacobs,<sup>9</sup> in a series of 63 cases, had 5 deaths (a mortality of 7.9 per cent), only 2 of which could be attributed to complications directly attendant upon the operation itself. Complications were few and of minor importance. Riches,<sup>12</sup> in commenting upon his results in a series of 40 cases, recorded no deaths. He had 4 postoperative strictures at the vesical neck and 1 case of osteitis pubis. Galbraith<sup>13</sup> noted in his series of 23 cases only 2 minor complications, and Ward<sup>14, 15</sup> reported good results in 7 cases. The principal technical difficulties of the operation mentioned were inability to control bleeding from the periprostatic veins and the possible difficulty of enucleation where

there was much prevesical fat, a deep pelvis and a small prostate. Although no cases of carcinoma of the prostate operated upon by this technic have been noted in the literature, it is reported that Millin himself has performed total prostatectomy through a suprapubic prevesical approach and that the complete removal of the gland was as readily accomplished as simple removal of hypertrophied lobes and fibrosed nodules.

After reviewing the published reports of Millin and others, and as a result of our own experience in attacking the prostate by this approach, we believe that the operation of retropubic prostatectomy, in comparison with the three standard methods of prostatectomy, has the following definite features to recommend it.

The anatomy of the approach is simple and direct, and it presents no important structures that need be sacrificed or organs whose function need be endangered. The dangers of the perineal approach — namely, injury to the external sphincter and rectum — are avoided, and since the procedure is an extravesical one, neither the bladder nor the vesical neck is exposed to the trauma attendant upon the suprapubic transvesical approach.

The exposure of the prostate is excellent, and the entire gland, except for its posterior surface, may be clearly visualized and palpated from the level of the apex below to the level of the bladder neck above.

After enucleation of the hypertrophied lobes, the entire prostatic cavity and vesical outlet may be exposed and examined far more completely than in either of the other standard types of open prostatectomy. Particularly advantageous is the easy control of bleeding, especially that which is prone to occur beneath the posterior vesical lip, and the accessibility of the bladder neck to inspection and any corrective plastic procedures that are found to be necessary. Since the latter structure is not unduly torn or traumatized, as inevitably occurs in the transvesical operation, the intact outlet with its sphincteric action may act immediately after operation as a barrier to the retrograde ooze of blood from the closed prostatic cavity into the bladder and thus prevent to a certain degree much of the postoperative vesical spasm and discomfort often associated with the other types of prostatectomy. Although the exposure is unusually satisfactory, we believe that the Millin operation affords no particular advantage over transurethral resection for the treatment of patients with contracture or sclerosis of the bladder neck except when a plastic procedure is also required.

Reconstruction and repair of the prostatic urethra, with watertight closure of the prostatic

capsule, is easier by this approach than by the other types of prostatectomy. Provided closure of the capsule and fascia is accurately performed in layers and the indwelling catheter is properly adjusted, leakage of urine, which is not infrequent after either perineal or suprapubic transvesical prostatectomy, should rarely occur.

If hemostasis and closure are complete, and urinary leakage avoided, pelvic sepsis is greatly minimized.

In our experience, as in that of others, the most striking feature of the operation is the easy postoperative course for the patient and hospital staff alike. There is very little bleeding into the bladder, and in the majority of cases the urine is clear within twenty-four to thirty-six hours. As a result, frequent irrigations are rarely necessary for more than a few hours after operation and may generally be discontinued except for several cleansing washings daily within twelve to twenty-four hours. There is a variable amount of serosanguineous drainage from the lower angle of the abdominal wound, which may require a change of dressing every eight to ten hours for the first twenty-four to forty-eight hours postoperatively, but thereafter drainage is slight or absent and the incision is usually completely healed in seven to ten days. With no accumulation of blood clots in the bladder and with a dry suprapubic wound after the first few days, the patient has a remarkably comfortable convalescence with little local pain and generally no bladder spasm whatsoever. The use of a small No 20 to 22 Fr Foley balloon catheter minimizes the occurrence of urethritis and any resulting local discomfort. As a rule, the patient is urged to be out of bed on the first day after operation and is ambulatory on the second day.

After removal of the urethral catheter on the fifth to the seventh postoperative day, the patient voids easily and freely, rarely complains of any dysuria and has excellent control of urination. In only 1 case in our series has there been any incontinence, and this was of short duration.

Postoperative urinary sepsis is minimal, and, in contrast to the findings in patients who have undergone transurethral or suprapubic transvesical prostatectomy, a good proportion of cases show a grossly clear urine with little microscopical evidence of infection in the sediment.

In the majority of cases, discharge from the hospital may be accomplished in ten to fourteen days.

In spite of the advantages offered by Millin's operation, the procedure has the following disadvantages, which, at this stage of its development, may be more apparent than real.

The approach may require some time and effort in the adipose patient or in one with an unusually deep and narrow pelvis where the prostate is situated deep at the bottom of a funnel.

In cases in which a previous open cystostomy had been performed, the retropubic approach would probably entail more dissection and trauma than the transvesical method and would thus be less desirable than the latter for a second-stage prostatectomy. We have had no experience with this type of case.

The control of bleeding from the larger vessels in the endopelvic fascia is not always readily accomplished. However, this difficulty is a minor one and should be overcome as the surgeon becomes better acquainted with the operation and the anatomic variations that occur in this region. Hemostasis at this point is greatly facilitated by the use of proper instruments, such as a long-handled needle holder or the boomerang needle, as well as by knowledge of exactly where and how deep to place the transfixing ligatures.

Since the large central vein running longitudinally across the anterior surface of the prostate is in direct communication with the deep dorsal vein of the penis, it has been suggested that ligation and division of this vessel might be followed by edema of the penis. Mild and temporary edema of the penis, which subsided in two or three days, occurred in only 1 case in our series. A similar occurrence of temporary duration has been reported in a few cases by other authors. In view of the extensive anastomotic communications between the veins of the penis and the pudendal plexus, it is difficult to believe that any serious permanent vascular complications of this sort would occur.

When enlargement of the lateral lobes is slight, or when hypertrophy is confined to a subtrigonal or intravesical median lobe, it may be difficult to reach the obstructing tissue with ease. In such cases the outline of the presenting portion of the prostate is hard to define clearly by palpation, and the gland is so mobile that it tends to fall away from the dissecting finger or instrument. This is a disadvantage when one is dealing with the small sclerotic gland or fibrosed vesical neck unless one resorts to the use of a finger in the rectum or a rectal balloon to elevate the gland.

In cases with hypertrophy of the median lobe only, particularly when the enlargement is chiefly intravesical or subtrigonal and is accompanied by excessive fibrosis, enucleation is likely to traumatize and tear the bladder neck. As a result, one of the purposes of the operation — that is, preservation of an intact vesical outlet — is defeated. However, in our experience, this complication has not interfered with a good func-

tional result. When the bladder neck has been torn, one or more simple plicating sutures of catgut will satisfactorily restore the normal anatomy of the outlet.

The approach does not afford adequate visualization of, or ready access to, the posterior aspect of the prostate or its apex in the region of the membranous urethra. Therefore, in cases of early prostatic carcinoma, in which total prostatectomy is indicated, it is our opinion that the prevesical route is much less advantageous than the perineal.

In summarizing the features of the retropubic operation as already outlined, we believe that the Millin technic is particularly suited for treatment of the following types of prostatic disease: benign hypertrophy of the lateral lobes or of lateral lobes and median lobe combined, benign hypertrophy of the median or subtrigonal lobes when intravesical extension is not marked, and calculous disease of the prostate, particularly when associated with benign hypertrophy. With increasing experience and future developments in technic, this approach may also prove to be a good method of performing plastic procedures in the prostatic urethra and at the bladder outlet.

At present we believe that the Millin operation is not indicated for the treatment of patients with obstruction due to sclerosis of the vesical outlet and prostatic fibrosis. In such cases transurethral resection is the preferred procedure. Likewise, in cases of prostatic obstruction associated with disease of the bladder in which surgical therapy of both lesions is required, it is our opinion that some method other than the retropubic approach is indicated. In this category may be grouped patients with prostatic obstruction who also have a vesical tumor, large vesical calculi, a poorly draining diverticulum with or without tumor and any other vesical lesion necessitating surgery. Although small bladder calculi may be removed by the Millin approach without injury to the vesical outlet, stones larger than the intact outlet should be extracted transvesically unless they can be easily crushed and removed transurethrally. For treatment of simple calculous disease or abscess of the prostate without associated benign hypertrophy, the perineal approach is considered preferable to the retropubic one. And finally for the reasons mentioned above, we believe that the retropubic operation is not suited to the treatment of early carcinoma of the prostate.

The actual details of the technic of the retropubic operation, as described by Millin and modified by ourselves and others, will be outlined briefly. After induction of anesthesia, the patient is placed supine on the operating table and in slight Trendelenburg position. If preoperative urethral drainage has been carried out, the bladder is completely

emptied, and the catheter is removed. If the patient has not been on constant urethral drainage, catheterization is performed, and the bladder is evacuated of all residual urine. Failure to comply with this routine immediately prior to operation results in a distended bladder during the operation. As a consequence, the operative field is limited, it is more difficult to expose the prostate adequately, and when the prostatic urethra is opened there is much unnecessary leakage of urine, which not only delays the procedure but also enhances the likelihood of postoperative pelvic sepsis. Subsequent to catheterization, the abdomen, pubes and genitalia are prepared and draped. The penis is covered with a loose sterile towel. A midline suprapubic incision is made, extending from low over the pubis upward for a distance of 10 to 12 cm, depending largely upon the thickness of the abdominal wall and the depth of the bony pelvis. It should be stressed that the lower angle of the abdominal incision must extend well down over the pubis to afford adequate exposure after the self-retaining retractor has been inserted. If the incision is not carried low enough, it later becomes necessary to use an anterior retractor over the pubis to prevent the abdominal wall from obscuring visualization of the depths of the wound. Such a retractor hinders rather than aids the deep dissection. The aponeurosis of the recti is incised longitudinally, the recti are separated in the midline, and the prevesical space is exposed. The prevesical fat and peritoneal fold are then swept upward with finger dissection to expose the anterior surface of the bladder. A self-retaining Balfour retractor with medium-sized curved lateral blades is introduced to keep the edges of the abdominal incision widely separated. Millin advocates the use of a retractor with a self-retaining posterior blade to press the bladder upward and backward, but we have found that by using a broad malleable ribbon retractor, which can be manipulated by an assistant as desired, the exposure is even better. In contrast to the impression of many surgeons that the prostate lies well down beneath the pubic arch, it is surprising how easily and clearly the prostate is exposed in its entirety by this approach. If difficulty in exposure is encountered, gentle upward traction on the bladder accompanied by finger dissection of the fatty tissue surrounding the bladder neck and prostate will bring the entire gland and vesical neck into clear view (Fig. 1).

A variable amount of fatty and areolar tissue lies deep in the retropubic or prevesical space. This is loosely attached to the bladder neck as well as to the anterior and lateral surfaces of the endopelvic fascia which in turn tightly encloses the prostate. By gentle blunt dissection with either a finger or a small swab on the end of a hemostat this tissue may be easily displaced without bleeding except

in an occasional case in which a superficial longitudinal tributary of the pudendal plexus may necessitate ligation. A medium-sized swab or gauze pack, as suggested by Millin, may be pushed into the lateral recess on each side of the prostate to keep the loose fat out of the field as well as to immobilize the gland and control minor venous ooze. The lower portion of the bladder, the vesical neck, and the prostate are clearly exposed, and the distribution of the veins coursing longitudinally across the anterior and lateral aspects of the gland may be noted. These vessels, the prostatic veins, form the prostatic plexus. They lie partly in the fascial sheath of the prostate, the prevesical or endopelvic fascia, and partly between the sheath and the true prostatic capsule. They communicate laterally with the pudendal and vesical plexuses, which in turn drain into the vesical and hypogastric veins. The prostatic veins, as visualized through the retropubic approach, divide themselves into three principal groups, a central longitudinal one whose chief tributary is the deep dorsal vein of the penis and a lateral group on each side of the gland. Anatomic variations are frequent. We have found with increasing experience that the lateral groups of veins generally need not be disturbed. If they are torn during the course of later manipulations, it is a relatively easy matter to clamp them with Kocher clamps and then either transfix and

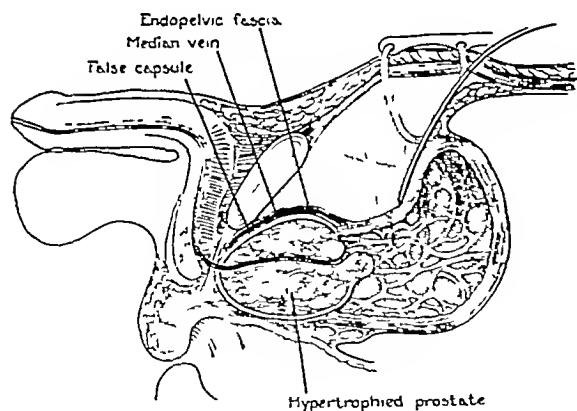


FIGURE 1 Median Sagittal Section of the Male Pelvis Showing the Route of Approach through the Prevesical Space and the Anatomic Relations of the Bladder, Prostate, Pubic Bone and Triangular Ligament

The position of the median prostatic vein between the endopelvic fascia and the true capsule is illustrated

ligate the ends or fulgurate them with the diathermy. The central vein, on the other hand, lies directly in the path of the capsular incision and must be divided. Prompt and effective control of bleeding from this vessel has been our most harassing problem in the retropubic approach,

and we believe that it is best handled in either one of two fashions. The vessel may be doubly transfixed with deep bites of the needle, ligated and then divided — a boomerang needle or a short, strong, curved needle with a long-handled holder may be used. Or the incision through the endopelvic fascia may be made at once, and the bleeding ends

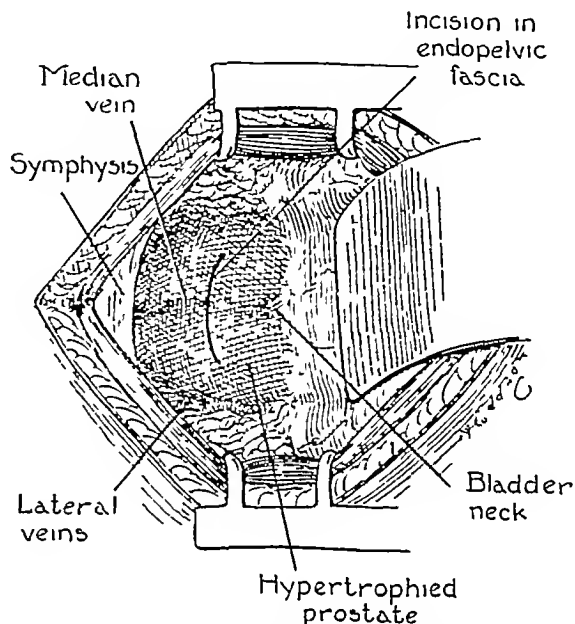


FIGURE 2 Suprapubic View of the Prevesical Space, Showing the Exposure of the Bladder Neck, Prostate and Three Principal Groups of Prostatic Veins, and Illustrating the Site of Incision through the Endopelvic Fascia and True Prostatic Capsule

of the vessel thus exposed are clamped with Kocher hemostats and ligated or fulgured with diathermy. We prefer the former method and have found that in general transfixion and ligation are preferable to the fulgurating current for control of bleeding from this large vessel. Other smaller bleeders can be adequately controlled by diathermy. A 2-cm to 3-cm curved transverse incision, convex downward and approximately 10 to 15 cm distal to the junction of prostate and bladder neck, is made through the endopelvic fascia and true prostatic capsule with a long-handled No. 15 Bard-Parker blade (Fig. 2). Suction is maintained to keep the field dry, and any bleeding vessels in the lips of the capsular incision are grasped with Kocher clamps. With these clamps as tractors the upper and lower flaps are undermined with long dissecting scissors, the upper flap for a distance of not more than 0.5 cm, depending upon the proximity of the incision to the vesical neck, and the lower one for a distance of 1 cm or more, at least for a depth sufficient to expose the lower portion of the gland

except at its very apex. It is often unnecessary to undermine the upper flap at all, since it tends to retract spontaneously during the course of later enucleation. Either the Kocher clamps are touched with the fulgurating current or the vessels are transected and ligated, and the hemostats are then removed. One or two traction sutures of silk are placed in the edge of the upper and lower flaps,

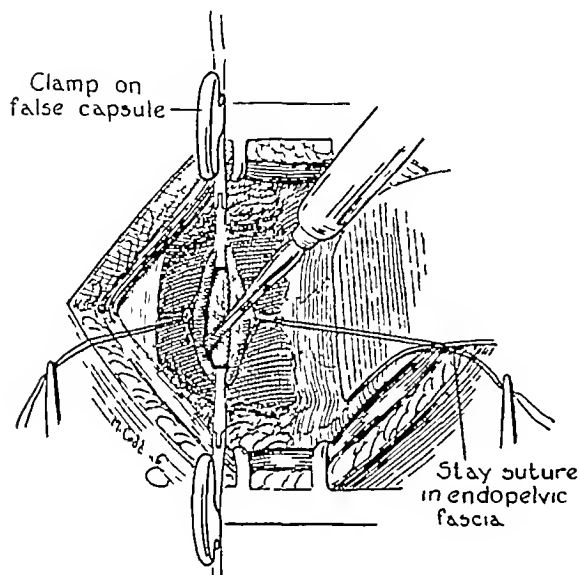


FIGURE 3 The Upper and Lower Flaps of Endopelvic Fascia Have Been Elevated with Traction Sutures, and the Hypertrophied Lateral Lobes Are Exposed through an Inverted V Incision in the False Capsule

and the operator should be able to expose the anterior and part of the lateral aspects of the false capsule for a vertical distance of approximately 2 or 3 cm.

An inverted V incision, with the apex of the V pointing distally in the midline, is made in the false capsule and is carried down to expose the hypertrophied lateral lobes, which are easily recognized by the grayish-white, whorled appearance of the adenomas. If these structures are only slightly enlarged, it is sometimes wiser to continue the incision down into the prostatic urethra. By this means, the line of demarcation between false capsule and adenomas can frequently be more easily recognized. The V-shaped flap is elevated, and a diamond or lozenge-shaped space is opened into which the tip of a finger can be readily inserted. The lateral angles of this incision are grasped with Allis clamps to bring the prostate up toward the operator and at the same time to immobilize it during the course of subsequent enucleation. With a blunt spatula or long curved dissecting scissors the lower lateral margin of the right or left lateral lobe is freed from the false capsule toward the apex

of the gland, and a similar procedure is carried out on the opposite side either then or after one lateral lobe has been more completely exposed (Fig 3). The enucleation of one and then the other lateral lobe is continued with the finger. We have found that the actual digital enucleation is greatly aided by temporary removal of the bladder retractor. The lateral blades of the self-retaining retractor are not disturbed. The lateral lobes having been freed at the apex from below upward, the finger is passed across the midline beneath the distal third of the prostatic urethra, and that structure is then cut with a scalpel or scissors. The severed distal end of the prostatic urethra will retract without bleeding. Lobe forceps are applied to the presenting apical portions of the lateral lobes, and by continued traction and finger dissection posterolaterally from below upward, the lateral lobes, as well as the median lobe when present, are brought up into the capsular wound, being now attached only in the region of the bladder neck (Fig 4). The fibrovascular pedicle of each lateral lobe is clamped with a Kocher hemostat, and the adenomas are detached distal to the clamp with scissors or

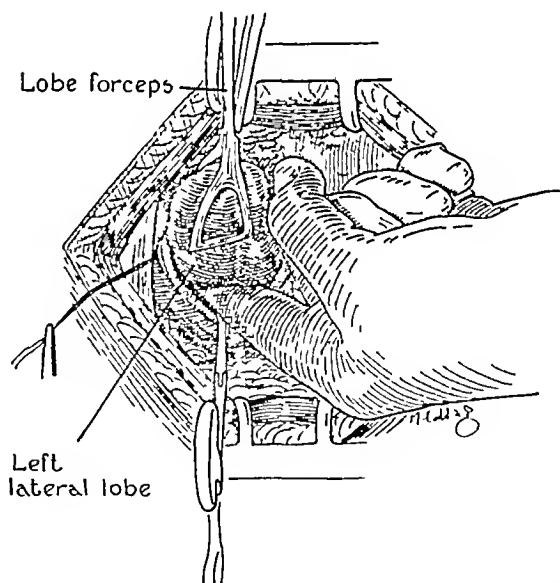


FIGURE 4 The Apexes of the Lateral Lobes Have Been Freed from the Capsule Distally and Posterolaterally, Have Been Grasped with Lobe Forceps and Are Then Enucleated from Below Upward

the scalpel. The median lobe is now enucleated digitally or by sharp dissection from below and behind the floor of the vesical outlet (Fig 5). Any ragged ends of mucous membrane of the proximal urethra or posterior vesical lip are removed cleanly at the bladder outlet with scissors. The pedicles of the lateral lobes are ligated with No. 00 plain catgut, and the hemostats are removed.

In cases in which one is dealing with a sclerotic bladder neck or fibrosed gland or in which the hypertrophy of the lobes is minimal, the technic described above is modified to a certain extent. Since the prostate is small and mobile in such cases, finger enucleation is difficult because the gland tends to fall away from the operator. However, by the application of Allis clamps at the four angles of the capsular incision and by upward lifting of the prostate, the gland is immobilized so that sharp dissection of either small lobes or fibrosed tissue may be performed with relative ease. As suggested above, the use of a rectal balloon or a finger in the rectum to push the prostate upward and forward is of benefit in cases such as these.

The bladder retractor is now replaced, and by traction on Allis forceps secured at the angles of the capsular incision the prostatic bed and vesical outlet are completely exposed to direct inspection. Any bleeders may be seen with ease and are ligated or fulgurated with the coagulating current. By placing an Allis forceps on the edge of the pos-

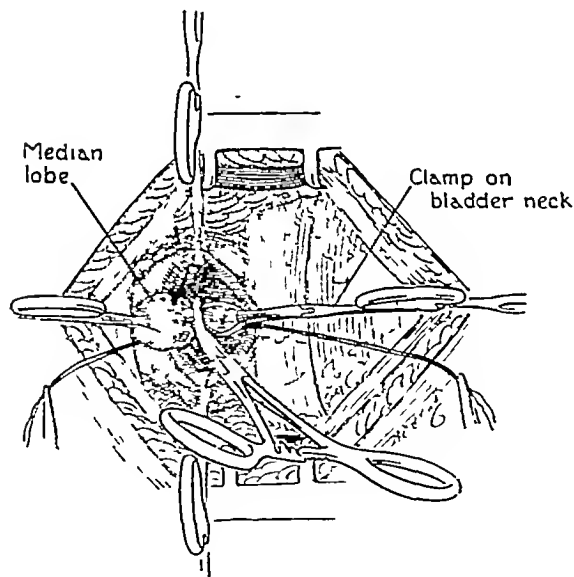


FIGURE 5 *The Lateral Lobes Have Been Removed, and the Prostatic Cavity Is Exposed*

*A small median or subtrigonal lobe has been enucleated from beneath the posterior vesical lip, and its attachment to the mucous membrane of the bladder outlet has been clamped prior to complete removal.*

terior vesical lip, one may lift up the bladder neck and readily control any bleeding in this region, particularly that which may occur from the prostatic arteries in the posterolateral recesses of the prostatic cavity. Furthermore, this exposure allows one to see and remove any tags or small nodules that might otherwise be overlooked. Hemostasis having been completed, the finger is

inserted into and through the bladder outlet. Unless the outlet seems smaller than normal, in which case the vesical neck fits very snugly about the finger, we do not enlarge it. However, if the outlet is snug, a wedge-shaped triangle is removed from its posterior lip with either a punch forcep or the scissors. Minor bleeding in the edges of this wound are easily controlled with the coagulat-

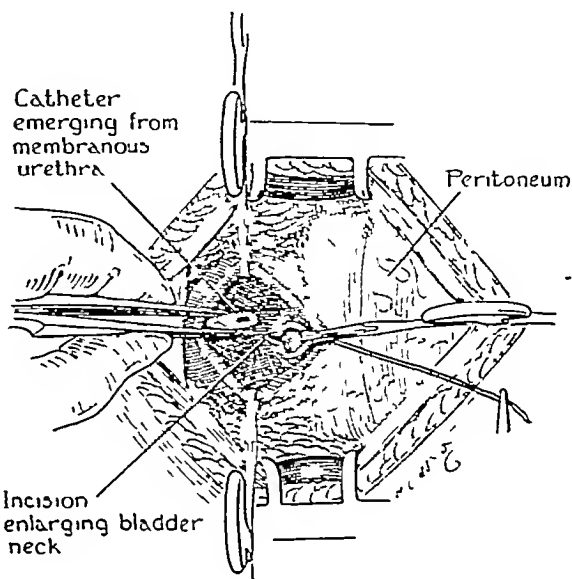


FIGURE 6 *The Prostatic Cavity and Bladder Neck Are Completely Exposed after Removal of All Obstructing Tissue*

*A wedge resection of the posterior vesical lip has been made, to enlarge the bladder outlet. A No. 20 to 24 Fr Foley balloon catheter is being passed into the bladder preparatory to closure of the prostatic capsule.*

ing current. It should be pointed out that in this operation the bladder neck is normally left intact after enucleation of hypertrophied lobes. It thus hangs free in the upper margin of the prostatic cavity, unsupported by any immediate peripheral attachments and with healing of the wound contracture of the outlet may result. Because of the occurrence of postoperative bladder-neck obstruction in 5 of his first 75 cases, Millin now apparently does a wedge resection almost routinely unless the outlet has been unduly stretched or torn. In the latter event, it is a simple matter to close the outlet to the proper caliber by one or two plicating sutures of No. 00 chromic catgut.

With the prostatic cavity still exposed, a No. 20 to 24 Fr Foley balloon catheter (30-cc capacity) is inserted into the external meatus of the penis and is passed through the urethra into the prostatic cavity. Its tip is grasped with forceps and thereby guided into the bladder (Fig. 6). The balloon is distended with 25 to 30 cc of sterile water or saline solution, and the catheter is then pulled down so that the distended balloon rests lightly against

except at its very apex. It is often unnecessary to undermine the upper flap at all, since it tends to retract spontaneously during the course of later enucleation. Either the Kocher clamps are touched with the fulgurating current or the vessels are transfixed and ligated, and the hemostats are then removed. One or two traction sutures of silk are placed in the edge of the upper and lower flaps,

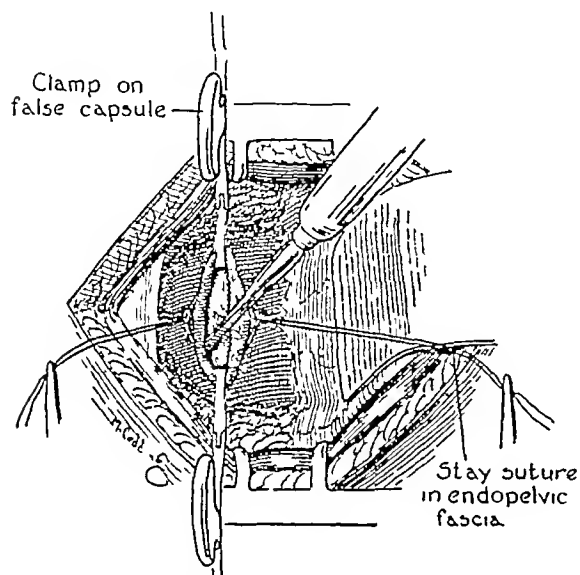


FIGURE 3 The Upper and Lower Flaps of Endopelvic Fascia Have Been Elevated with Traction Sutures, and the Hyper-trophied Lateral Lobes Are Exposed through an Inverted V Incision in the False Capsule

and the operator should be able to expose the anterior and part of the lateral aspects of the false capsule for a vertical distance of approximately 2 or 3 cm.

An inverted V incision, with the apex of the V pointing distally in the midline, is made in the false capsule and is carried down to expose the hypertrophied lateral lobes, which are easily recognized by the grayish-white, whorled appearance of the adenomas. If these structures are only slightly enlarged, it is sometimes wiser to continue the incision down into the prostatic urethra. By this means, the line of demarcation between false capsule and adenomas can frequently be more easily recognized. The V-shaped flap is elevated, and a diamond or lozenge-shaped space is opened into which the tip of a finger can be readily inserted. The lateral angles of this incision are grasped with Allis clamps to bring the prostate up toward the operator and at the same time to immobilize it during the course of subsequent enucleation. With a blunt spatula or long curved dissecting scissors the lower lateral margin of the right or left lateral lobe is freed from the false capsule toward the apex

of the gland, and a similar procedure is carried out on the opposite side either then or after one lateral lobe has been more completely exposed (Fig 3). The enucleation of one and then the other lateral lobe is continued with the finger. We have found that the actual digital enucleation is greatly aided by temporary removal of the bladder retractor. The lateral blades of the self-retaining retractor are not disturbed. The lateral lobes having been freed at the apex from below upward, the finger is passed across the midline beneath the distal third of the prostatic urethra, and that structure is then cut with a scalpel or scissors. The severed distal end of the prostatic urethra will retract without bleeding. Lobe forceps are applied to the presenting apical portions of the lateral lobes, and by continued traction and finger dissection posterolaterally from below upward, the lateral lobes, as well as the median lobe when present, are brought up into the capsular wound, being now attached only in the region of the bladder neck (Fig 4). The fibrovascular pedicle of each lateral lobe is clamped with a Kocher hemostat, and the adenomas are detached distal to the clamp with scissors or

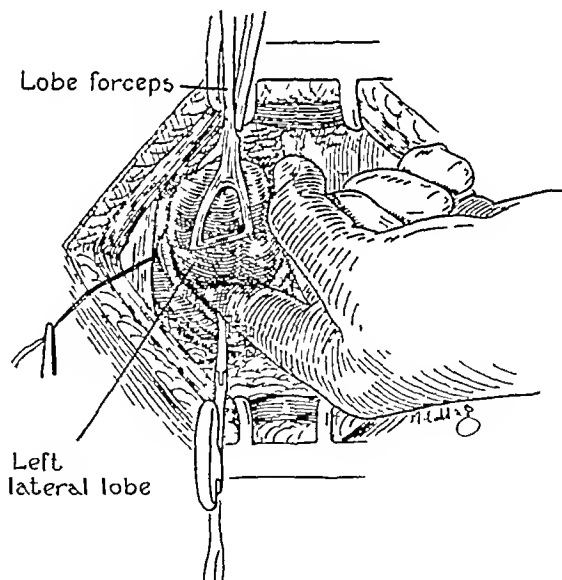


FIGURE 4 The Apexes of the Lateral Lobes Have Been Freed from the Capsule Distally and Posterolaterally, Have Been Grasped with Lobe Forceps and Are Then Enucleated from Below Upward

the scalpel. The median lobe is now enucleated digitally or by sharp dissection from below and behind the floor of the vesical outlet (Fig 5). Any ragged ends of mucous membrane of the proximal urethra or posterior vesical lip are removed cleanly at the bladder outlet with scissors. The pedicles of the lateral lobes are ligated with No. 00 plain catgut, and the hemostats are removed.

In cases in which one is dealing with a sclerotic bladder neck or fibrosed gland or in which the hypertrophy of the lobes is minimal, the technic described above is modified to a certain extent. Since the prostate is small and mobile in such cases, finger enucleation is difficult because the gland tends to fall away from the operator. However, by the application of Allis clamps at the four angles of the capsular incision and by upward lifting of the prostate, the gland is immobilized so that sharp dissection of either small lobes or fibrosed tissue may be performed with relative ease. As suggested above, the use of a rectal balloon or a finger in the rectum to push the prostate upward and forward is of benefit in cases such as these.

The bladder retractor is now replaced, and by traction on Allis forceps secured at the angles of the capsular incision the prostatic bed and vesical outlet are completely exposed to direct inspection. Any bleeders may be seen with ease and are ligated or fulgurated with the coagulating current. By placing an Allis forceps on the edge of the pos-

inserted into and through the bladder outlet. Unless the outlet seems smaller than normal, in which case the vesical neck fits very snugly about the finger, we do not enlarge it. However, if the outlet is snug, a wedge-shaped triangle is removed from its posterior lip with either a punch forcep or the scissors. Minor bleeding in the edges of this wound are easily controlled with the coagulat-

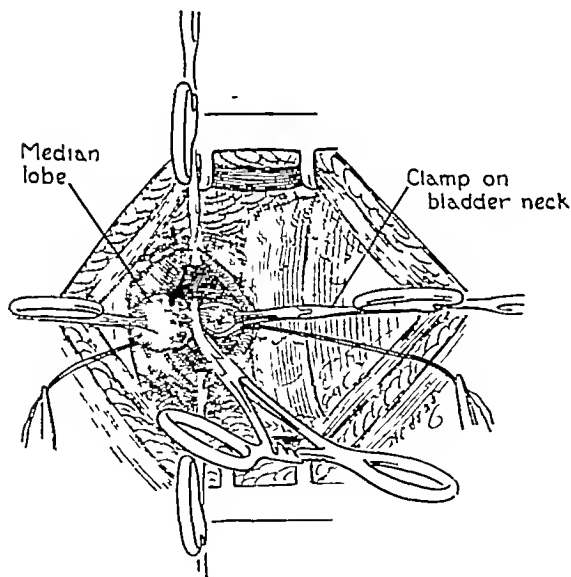


FIGURE 5 *The Lateral Lobes Have Been Removed, and the Prostatic Cavity Is Exposed*

*A small median or subtrigonal lobe has been enucleated from beneath the posterior vesical lip, and its attachment to the mucous membrane of the bladder outlet has been clamped prior to complete removal*

terior vesical lip, one may lift up the bladder neck and readily control any bleeding in this region, particularly that which may occur from the prostatic arteries in the posterolateral recesses of the prostatic cavity. Furthermore, this exposure allows one to see and remove any tags or small nodules that might otherwise be overlooked. Hemostasis having been completed, the finger is

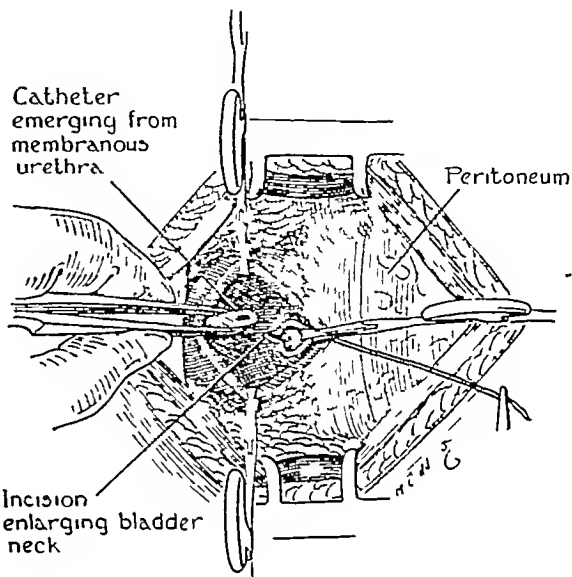


FIGURE 6 *The Prostatic Cavity and Bladder Neck Are Completely Exposed after Removal of All Obstructing Tissue*

*A wedge resection of the posterior vesical lip has been made, to enlarge the bladder outlet. A No. 20 to 24 Fr. Foley balloon catheter is being passed into the bladder preparatory to closure of the prostatic capsule*

ing current. It should be pointed out that in this operation the bladder neck is normally left intact after enucleation of hypertrophied lobes. It thus hangs free in the upper margin of the prostatic cavity, unsupported by any immediate peripheral attachments and with healing of the wound contracture of the outlet may result. Because of the occurrence of postoperative bladder-neck obstruction in 5 of his first 75 cases, Millin now apparently does a wedge resection almost routinely unless the outlet has been unduly stretched or torn. In the latter event, it is a simple matter to close the outlet to the proper caliber by one or two plicating sutures of No. 00 chromic catgut.

With the prostatic cavity still exposed, a No. 20 to 24 Fr. Foley balloon catheter (30-cc. capacity) is inserted into the external meatus of the penis and is passed through the urethra into the prostatic cavity. Its tip is grasped with forceps and thereby guided into the bladder (Fig. 6). The balloon is distended with 25 to 30 cc. of sterile water or saline solution, and the catheter is then pulled down so that the distended balloon rests lightly against

the vesical neck. This maneuver not only assures one of the integrity of the balloon but also demonstrates any abnormal disparity between size of balloon and caliber of outlet. A final inspection of the prostatic bed is made. Should oozing be unusual and not controlled by previous ligature or fulguration, the cavity may be packed with fibrin foam or some similar hemostatic agent as described by Quinby<sup>16</sup> and others. We have resorted to this procedure in 7 cases of our series, the wounds in the remaining patients being almost completely dry at the time of closure.

With an assistant steadying the Allis forceps on the margins of the false capsule, the opening in

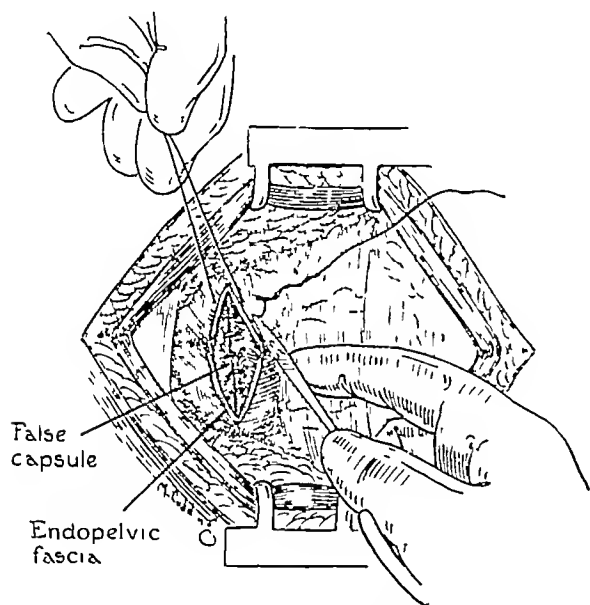


FIGURE 7 *Transverse Closure of the False Capsule and Endopelvic Fascia, Two Layers of Interrupted Sutures Being Used*

this structure, now converted into a more or less transverse one by the stretching subsequent to enucleation, is closed transversely with interrupted sutures of No. 00 chromic catgut. The incision in the true capsule and endopelvic fascia is closed in a similar fashion with fine silk sutures (Fig. 7). The bladder retractor is removed, and the catheter is irrigated with sterile saline solution. If the catheter is properly adjusted and the capsular wound closed tightly, there should be no leakage when irrigation is performed. All swabs and packs are removed, and the prevesical space is irrigated with saline solution and sucked dry to remove clots. An empty Penrose drain is placed down to the suture line in the prostatic fascia and is brought out through the lower angle of the abdominal wound. The self-retaining retractor is removed, and the rectus sheath, the subcutaneous tissue and the skin are approximated with interrupted silk

sutures. A dry sterile dressing is applied. Bilateral vasectomy may be performed either before or after prostatectomy. In our cases vasectomy has not been done, and we have had 2 cases of epididymitis. The catheter is again irrigated to establish its patency, at which time the returns are generally only faintly or moderately blood tinged, and is then connected to a sterile, constant-drainage system.

During the fifteen-month period from June, 1946, to September, 1947, we have treated at the Peter Bent Brigham Hospital 20 cases of prostatic obstruction by the retropubic method of Millin. These cases do not represent a consecutive series. Inasmuch as the method was new and relatively untried, the selection of patients was in general limited to those with a preoperative diagnosis of benign hypertrophy of the prostate without other major complicating diseases of the lower urinary tract. One patient had coexisting bladder calculi, 4 had pathological evidence of associated chronic prostatitis, another had small prostatic calculi in a hyperplastic gland, and 2 were discovered on microscopic examination of the removed specimens to have small previously unsuspected islands of carcinoma in situ. In neither of the last 2 cases was there any evidence of local or distant extension of tumor cells.

The operative risk of the patient, relative to his renal and cardiovascular equilibrium, was not a factor in the choice of these cases for operation by this method. Seven of this group had severe arteriosclerotic heart disease with cardiac arrhythmias or decompensation, while 3 had permanently impaired renal function of mild to moderate degree. On the other hand, the retropubic approach was not chosen for patients with marked intravesical median-lobe hypertrophy, pure fibrosis or contraction of the bladder neck, or prostatic carcinoma.

The ages of the 20 patients varied between 53 and 86 years, with an average age of 70.2 years. The average duration of symptoms of prostatism was 3.65 years. In 2 cases a transurethral resection had been performed for similar symptoms 6 years and 2.5 years respectively prior to the present hospital admission.

Four patients were admitted to the hospital with complete obstruction, 8 had partial retention, and 8 carried only a small amount of residual urine. There was a mild to moderately severe lower-urinary-tract infection in 12 cases, and upon admission to the hospital the blood urea nitrogen was appreciably elevated in 6. In 3 of the latter group the blood urea nitrogen dropped to normal after the institution of drainage, but the other 3 maintained a reading persistently above normal in spite of adequate drainage.

Preoperative drainage of the bladder was effected through a small urethral catheter in 12 cases, the duration of preliminary drainage varying between

6 and 25 days, with an average of 14.4 days. A No 16 Fr Foley catheter with a 5-cc balloon was found to be quite effective, and the drainage was accompanied by very little evidence of local irritation.

The smallest prostate gland weighed 13.5 gm, and the largest 125 gm, the average being 42.1 gm. The majority of glands were the site of trilobar enlargement, the median lobe being of a size equal to or smaller than the lateral lobes. In a few cases hyperplasia was confined to the lateral lobes, the median lobe being normal.

During the performance of the operation, several variations in technic were utilized. In 16 cases a transverse capsular incision was made, whereas in 4 cases a linear incision was used. Although there seemed to be less bleeding from the large prostatic veins with the linear incision digital manipulation during enucleation tends to extend this type of incision too far toward the apex of the gland and toward the vesical neck and thus to render subsequent closure of the capsule and fascia more difficult than when a transverse incision is made. Therefore, a transverse capsular incision is favored. As a result of the later development of contracture of the vesical neck in the first 3 patients upon whom we performed this operation, the bladder outlet was dilated digitally prior to closure in 12 of the remaining cases, and a wedge resection of the posterior lip was performed in 3. Plication of the outlet to reduce it to a normal caliber was performed in 2 cases in which removal of large median or subtrigonal lobes had unduly torn or stretched the vesical neck. One patient with benign hypertrophy, multiple vesical calculi and chronic cystitis underwent a combined retropubic prostatectomy and suprapubic cystotomy with removal of the calculi. Both the urethral and the suprapubic transvesical methods of drainage were used postoperatively. Except in 2 cases in which No 20 Fr and No 26 Fr catheters were used respectively, postoperative urethral drainage was maintained with either a No 22 Fr or a No 24 Fr Foley catheter with a 30-cc balloon.

After operation the urine was clear on inspection within twenty-four hours in 9 cases, within forty-eight hours in 8 cases, and within seventy-two hours in 3 cases. The suprapubic drain was removed, in almost all cases, on the second or third day after operation. In 2 cases in which drainage was negligible the drain was removed twenty-four hours postoperatively. There was generally a moderate amount of serosanguineous ooze from the lower angle of the wound for twenty-four to forty-eight hours, but thereafter drainage was slight, and in the majority of patients the wound was dry and completely healed when the sutures were removed on the sixth or seventh day after operation. The urethral catheter was removed, on the average, slightly over six and a half days

after operation, the shortest period of postoperative drainage being four days and the longest period being nine days. It was necessary to reinsert the catheter in 1 case from the ninth to the thirteenth postoperative day because of a large amount of residual urine secondary to an atonic cord bladder, in another from the tenth to the twelfth day because of bleeding and in a third from the twelfth to the sixteenth day because of suprapubic urinary leakage in a patient who had also undergone a cystotomy for removal of bladder stones. The last patient had a rather severe cystitis before and after operation and was the only one in the series to demonstrate partial incontinence, which persisted until the twenty-eighth day after operation.

Suprapubic leakage of urine occurred in 4 of the 20 cases. In 2 of these, the second and third cases of the series, there was slight drainage from the first to the fourth day postoperatively in 1 and from the sixth to the twelfth day in the other. The cause in both was attributed to faulty adjustment of the urethral catheter and inadequate closure of the prostatic capsule and fascia. A mild wound infection, manifested by local induration and tenderness, was noted in both cases. A third patient, who had vesical calculi and a marked cystitis and was subjected to a combined cystotomy and retropubic prostatectomy, had some leakage of urine from the upper angle of the wound on the tenth to twelfth days after operation. His wound was dry on the thirteenth day after urethral catheter drainage had been reinstituted from the twelfth to the sixteenth postoperative day. The fourth patient, an elderly malnourished man with severe cardiac disease, who had been bedridden for two months prior to hospitalization with chronic cystitis and prostatitis as well as prostatic obstruction, developed an infected hematoma of the prevesical space that was drained on the fifth day after operation. This was followed by suprapubic leakage of urine for a period of three weeks, after which the wound healed spontaneously. With increasing experience regarding proper adjustment of the catheter and watertight closure of the capsule we believe that urinary leakage should rarely occur except in cases in which gross infection of the prevesical space supervenes.

Other postoperative complications in this group of patients were infrequent and relatively unimportant. One patient developed transient edema of the penis on the seventh day after operation. This subsided completely in two days after the application of wet heat and elevation of the organ. Mild unilateral epididymitis occurred in 2 cases, in both of which the infection subsided rapidly with conservative measures. Acute unilateral pyelonephritis on the tenth postoperative day was noted in 1 case. Symptoms and signs abated within thirty-six hours, and the patient was discharged.

from the hospital on the seventeenth day after operation with only a moderate number of pus cells in the urine. Two patients, both of whom had a marked cystitis before operation, continued to show a moderate pyuria during their period of postoperative hospitalization. However, within six to eight weeks after discharge from the hospital, the urine of both patients was free of leukocytes. It is noteworthy that in the majority of our cases the urine was unusually clear after prostatectomy by the retropubic approach.

Immediate postoperative hemorrhage occurred in 1 case, and delayed bleeding of minor degree was encountered in 2. In the first excessive bleeding into the bladder persisted for forty-eight hours after operation, and frequent irrigations were necessary to evacuate clots and maintain satisfactory drainage. Thereafter, bleeding rapidly subsided, and the urine was clear within seventy-two to eighty hours. Another patient, whose catheter was removed on the sixth day after operation, had faintly blood-tinged urine on the following day. There were no accompanying symptoms of irritation or obstruction, and bleeding ceased spontaneously within twelve to eighteen hours. A third patient, in whom the catheter was removed on the seventh day after operation, developed sudden bleeding and clot retention on the tenth postoperative day. The use of an indwelling catheter for forty-eight hours sufficed to control this complication. In none of these cases was urinary infection a contributing factor.

One other complication encountered is that related to proper maintenance of urethral-catheter drainage. In 2 cases the urethral catheter was pulled out of the bladder during the first twelve hours after operation. In both, a faulty balloon was responsible for this event, the bag apparently having burst in 1 case and having developed a slow leak in the other. Fortunately, the accident was discovered promptly before the bladder had become distended, and a new catheter on a stylet was reinserted through the urethra without difficulty. No bleeding or other untoward results followed in either case.

In the 20 cases in this series, 12 patients were discharged from the hospital within eleven to fourteen days after operation, and 6 within fourteen to twenty-one days. One patient was discharged on the thirtieth day, and one on the thirty-third postoperative day. There were no deaths. All the patients have been observed closely since discharge from the hospital, the period of follow-up observation varying between two weeks and fourteen months, 6 patients have been followed for 6 months or more, and 14 have been observed for less than six months. One patient, who had benign hypertrophy and carcinoma in situ, died of coronary thrombosis three months after operation.

Immediately prior to the attack it had been noted that his only urinary symptom was mild nocturia associated with a few leukocytes in the sediment. Post-mortem examination revealed an adequate bladder outlet and no evidence of carcinoma. The remaining 19 patients are living and well. Three of these, the first 3 patients operated upon by the retropubic approach, developed a contracture of the vesical outlet within five to twelve weeks after operation, in 1, acute clot retention followed instrumental urethral investigation five and a half weeks after operation. Suprapubic cystotomy and dilatation of the contracted bladder neck were performed, with an uneventful convalescence. The patient was asymptomatic a year later. The second patient was found to have a stenosed outlet three months postoperatively. Urethral dilatation with sounds was performed on several occasions, and this patient was also asymptomatic ten months later. In the third patient symptoms of bladder irritability and infection appeared shortly after discharge from the hospital. Seven weeks after operation examination revealed a "bar" contracture of the posterior vesical lip and a rather marked cystitis. In spite of prolonged chemotherapy and local treatment in the form of dilatations and irrigation, the symptoms and signs persisted. A recent examination, conducted a year after operation, revealed the presence of a vesical calculus as well as a chronic cystitis and stenosis of the bladder neck. It is planned to perform a transurethral litholapaxy and resection of the outlet on this patient in the near future. A fourth patient, who had a chronic epididymitis preoperatively and an exacerbation of the infection postoperatively, developed a recurrent epididymitis a week after discharge from the hospital. This eventually necessitated orchidectomy several days later, approximately a month after prostatectomy. The remaining 15 patients have had no urologic complaints referable to the operation since discharge from the hospital.

#### SUMMARY

The pertinent literature concerning a newly proposed method of retropubic prostatectomy is briefly reviewed, and the advantages and disadvantages of the procedure are discussed.

The indications and contraindications for the employment of this operative approach are presented in the light of a limited experience with the operation.

The technic of the operation is outlined, and a summary of the results obtained in a selected group of 20 cases is recorded.

#### REFERENCES

1. Millin T. Retropubic prostatectomy: new extravesical technique report on 20 cases. *Lancet* 2:693-696, 1945.
2. van Stockum W. J. Prostatectomia suprapubica extravesicalis. *Zentralbl f. Chir.* 36:41-43, 1909.

- 3 Jacobs L. C. and Casper E. J. Pre vesical prostatectomy *Urol & Cutan Rev* 37 729-732 1935
- 4 Maier O. Inguinale extravascale Prostatektomie *Arch klin Chir* 132 296-302 1924
- 5 Millin T. Retropubic prostatectomy *Brit J Urol* 18 33 1946
- 6 *Idem*. Treatment of benign enlargement of prostate *Brit J Urol* 18 105-108 1946
- 7 *Idem*. *Retropubic Urinary Surgery* 216 pp Baltimore Williams & Wilkins Co 1947
- 8 Loughnane F. McG. Retropubic prostatectomy *Brit J Urol* 18 38 1946
- 9 Jacobs A. Treatment of benign enlargement of prostate *Brit J Urol* 18 112-114 1946.
- 10 Hey W. Treatment of benign enlargement of prostate *Brit J Urol* 18 108 1946
- 11 Jacobs A. Retropubic prostatectomy *Brit J Urol* 18 36 1946
- 12 Riches E. W. Treatment of benign enlargement of prostate *Brit J Urol* 18 115 1946
- 13 Galbraith W. W. Treatment of benign enlargement of prostate. *Brit J Urol* 18 116 1946
- 14 Ward O. Treatment of benign enlargement of prostate *Brit J Urol* 18 121 1946
- 15 *Idem*. Retropubic prostatectomy *Brit J Urol* 18 34 1946
- 16 Quinby W. C. Hemostasis by thrombin and fibrin foam in suprapubic prostatectomy: analysis of 40 cases *Tr New Eng Surg Soc* 26 64-72 1945

## AMEBIC ABSCESS OF THE LIVER\*

### Therapeutic Problems in Various Types of Late Hepatic Amebiasis

EMERSON H. DRAKE, M.D.,† AND THOMAS A. WARTHIN, M.D.‡

WEST ROXBURY, MASSACHUSETTS

THE problem of late complications of disease acquired by military personnel in distant parts of the earth is now facing the medical profession throughout the United States. In all probability it will continue to do so for some years to come. In the six-month period from November 1, 1946, to May 1, 1947, at the Veterans Administration Hospital, West Roxbury, Massachusetts, 6 patients were treated for amebic liver disease secondary to amebiasis acquired while on overseas duty one or two years before. It seems likely that, with the long delay that may take place between the initial infection and the late complication, new cases will continue to appear in areas of the country where the disease is customarily considered as being relatively uncommon. We present these 6 cases, discussing the signs and symptoms, the forms of treatment used, and suggest a plan of treatment that utilizes all aids now currently available.

It has long been known that the high mortality that follows open drainage of an amebic abscess is due to secondary infection entering through the draining site. In 1871 MacLean<sup>1</sup> pointed out that the death rate was lowest in liver abscesses that discharged through the lungs and highest in those draining through the abdominal wall. He advocated the removal of the pus by means of a Bowditch syringe without the admission of air. This method of treatment was abandoned because there was usually a reaccumulation of the material in the abscess cavity, probably owing to the lack of suitable antiamebic chemotherapy. The discovery of the specific effect of injections of emetine by Rogers<sup>2</sup> in 1912 led to a readoption of the closed aspiration method of treatment in conjunction with

the use of emetine to prevent reformation of the abscess. Ochsner and DeBakey<sup>3</sup> reported that in patients treated by open drainage without amebicides the mortality was 48.2 per cent. On open drainage in addition to emetine, the mortality was 16.6 per cent. Of those treated on emetine alone, only 5.4 per cent died. They also stated that in cases in which drainage through a bronchus had already been established, antiamebic treatment was sufficient. Walters et al.<sup>4</sup> recommend that open drainage be reserved for cases in which the abscess cavity obviously has become secondarily infected, or in which rupture into either the pleural or the peritoneal cavity is impending. The latest edition of *Stitt's Diagnosis, Prevention and Treatment of Tropical Diseases*<sup>5</sup> recommends open drainage in a well established abscess. Berne<sup>6</sup> concluded that closed aspiration and emetine treatment reduced the mortality to its lowest level. In the early stages of amebiasis of the liver, Klatskin<sup>7</sup> has clearly shown that repeated courses of emetine alone were sufficient to effect cure.

#### MATERIALS AND METHODS

For discussion of therapy our clinical material is divided into three groups: simple amebic hepatitis, possibly with small abscess formation, a large liver abscess that remained localized within the abdomen, and a large abscess that penetrated through the diaphragm.

Only 1 patient (Case 1) was classified as having diffuse hepatitis without significant abscess formation. He was treated with chemotherapy alone, surgical measures being unnecessary.

Two patients (Cases 2 and 3) had abscesses of significant size that had not drained spontaneously into either the pleural or peritoneal cavities. Both exhibited tender, palpable masses beneath the right costal margin. They were treated by chemotherapy and aspiration. After the institution of emetine therapy, an incision was made in the abdominal

\*From the Medical and Surgical Services, Veterans Administration Hospital.

Published with the permission of the chief medical director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or the conclusions drawn by the authors.

†Assistant chief Surgical Service, Veterans Administration Hospital.

‡Assistant in medicine, Harvard Medical School; chief Medical Service, Veterans Administration Hospital.

from the hospital on the seventeenth day after operation with only a moderate number of pus cells in the urine. Two patients, both of whom had a marked cystitis before operation, continued to show a moderate pyuria during their period of postoperative hospitalization. However, within six to eight weeks after discharge from the hospital, the urine of both patients was free of leukocytes. It is noteworthy that in the majority of our cases the urine was unusually clear after prostatectomy by the retropubic approach.

Immediate postoperative hemorrhage occurred in 1 case, and delayed bleeding of minor degree was encountered in 2. In the first excessive bleeding into the bladder persisted for forty-eight hours after operation, and frequent irrigations were necessary to evacuate clots and maintain satisfactory drainage. Thereafter, bleeding rapidly subsided, and the urine was clear within seventy-two to eighty hours. Another patient, whose catheter was removed on the sixth day after operation, had faintly blood-tinged urine on the following day. There were no accompanying symptoms of irritation or obstruction, and bleeding ceased spontaneously within twelve to eighteen hours. A third patient, in whom the catheter was removed on the seventh day after operation, developed sudden bleeding and clot retention on the tenth postoperative day. The use of an indwelling catheter for forty-eight hours sufficed to control this complication. In none of these cases was urinary infection a contributing factor.

One other complication encountered is that related to proper maintenance of urethral-catheter drainage. In 2 cases the urethral catheter was pulled out of the bladder during the first twelve hours after operation. In both, a faulty balloon was responsible for this event, the bag apparently having burst in 1 case and having developed a slow leak in the other. Fortunately, the accident was discovered promptly before the bladder had become distended, and a new catheter on a stylet was reinserted through the urethra without difficulty. No bleeding or other untoward results followed in either case.

In the 20 cases in this series, 12 patients were discharged from the hospital within eleven to fourteen days after operation, and 6 within fourteen to twenty-one days. One patient was discharged on the thirtieth day, and one on the thirty-third postoperative day. There were no deaths. All the patients have been observed closely since discharge from the hospital, the period of follow-up observation varying between two weeks and fourteen months, 6 patients have been followed for 6 months or more, and 14 have been observed for less than six months. One patient, who had benign hypertrophy and carcinoma in situ, died of coronary thrombosis three months after operation.

Immediately prior to the attack it had been noted that his only urinary symptom was mild nocturia associated with a few leukocytes in the sediment. Post-mortem examination revealed an adequate bladder outlet and no evidence of carcinoma. The remaining 19 patients are living and well. Three of these, the first 3 patients operated upon by the retropubic approach, developed a contracture of the vesical outlet within five to twelve weeks after operation, in 1, acute clot retention followed in instrumental urethral investigation five and a half weeks after operation. Suprapubic cystotomy and dilatation of the contracted bladder neck were performed, with an uneventful convalescence. The patient was asymptomatic a year later. The second patient was found to have a stenosed outlet three months postoperatively. Urethral dilatation with sounds was performed on several occasions, and this patient was also asymptomatic ten months later. In the third patient symptoms of bladder irritability and infection appeared shortly after discharge from the hospital. Seven weeks after operation examination revealed a "bar" contracture of the posterior vesical lip and a rather marked cystitis. In spite of prolonged chemotherapy and local treatment in the form of dilatations and irrigation, the symptoms and signs persisted. A recent examination, conducted a year after operation, revealed the presence of a vesical calculus as well as a chronic cystitis and stenosis of the bladder neck. It is planned to perform a transurethral litholapaxy and resection of the outlet on this patient in the near future. A fourth patient, who had a chronic epididymitis preoperatively and an exacerbation of the infection postoperatively, developed a recurrent epididymitis a week after discharge from the hospital. This eventually necessitated orchidectomy several days later, approximately a month after prostatectomy. The remaining 15 patients have had no urologic complaints referable to the operation since discharge from the hospital.

#### SUMMARY

The pertinent literature concerning a newly proposed method of retropubic prostatectomy is briefly reviewed, and the advantages and disadvantages of the procedure are discussed.

The indications and contraindications for the employment of this operative approach are presented in the light of a limited experience with the operation.

The technic of the operation is outlined, and a summary of the results obtained in a selected group of 20 cases is recorded.

#### REFERENCES

1. Millin T. Retropubic prostatectomy: new extravesical technique: report on 20 cases. *Lancet* 2: 693-696, 1945.
2. van Stockum W J. Prostatectomia suprapubica extravesicalis. *Zentralbl f Chir* 36: 41-43, 1909.

adherent to the anterior abdominal wall was entered. Over 30 cc. of thick, pinkish-red, purulent material evacuated itself through the incision, and, after irrigation, 200,000 units of penicillin was instilled before the incision was closed. No amebas were found in the pus. The temperature was normal thereafter, and all symptoms rapidly disappeared. Emetine was discontinued after 9 days because of electrocardiographic changes, which proved to be of a temporary nature. A course of vioform was followed immediately by 6 more days of emetine. Changes in the T waves recurred, but on complete bed rest, these were greatly lessened. The patient was discharged on April 2. Follow-up examinations have been negative.

CASE 4 J Z, a 19-year-old veteran, was first admitted to the hospital on August 16, 1946, complaining of right-upper-quadrant pain, chills and fever of 4 days' duration. In 1945 he had had a cystotomy for removal of paraffin, which had been introduced into the bladder through the urethra. From early 1945 to June, 1946, he had been on active duty in Guam and China, but there was no history of dysentery while he was in the service. About 1 week prior to admission he suffered an attack of diarrhea lasting 1 week. Four days before admission he complained of chills and a feeling of oppression in the right anterior portion of the chest and the right upper quadrant. The temperature was 103°F on admission. A tender liver was palpated three fingerbreadths below the right costal margin. Urinalysis revealed a ++ test for albumin and 50 to 60 pus cells per high-power field. The white-cell count was 12,850, with 81 per cent neutrophils. Examination of the stools was negative. Because of acute pain in the right lower quadrant with tenderness and spasm, an exploratory laparotomy was performed on the day after admission. An attempt at liver aspiration yielded no pus, and a fibrotic retrocecal appendix was removed. Postoperatively, on penicillin therapy alone, the high temperature subsided to normal within 7 days. The patient was discharged on the nineteenth postoperative day, entirely asymptomatic.

Five days later he returned, complaining of a chill, which had appeared 2 days prior to readmission, a feeling of discomfort in the right side of the abdomen and a pain in the right shoulder and neck. Physical examination showed some tenderness in the right upper quadrant, with slight voluntary spasm. The temperature was 103°F. A moderate polymorphonuclear leukocytosis was present. The urine was normal. Examination of the stool was again negative for amebas, and a protoscopic examination was negative. Both penicillin and sulfadiazine therapy were begun. On the 17th day the sulfadiazine was stopped because of lack of improvement, and a course of emetine was given. The temperature and white-cell count promptly fell to normal. The emetine was followed by a course of vioform. A retrograde pyelogram was done on September 15 because of urinary symptoms, which revealed a right hydronephrosis and blunting of the pelvic calyces on the right. A culture of the urine from the right kidney grew colon bacilli. After the temperature had been normal for 2 weeks, the patient was discharged to be continued as an outpatient on sulfadiazine.

Two weeks later he was readmitted, having developed a fever 2 days previously, and having coughed up what he thought to be blood. On admission the temperature was 103°F, and the pulse 120. Dullness and absent breath sounds were present in the right axilla and over the right lower portion of the chest anteriorly. The abdomen showed marked tenderness and spasm in the right upper quadrant. The white-cell count was 5400, with 68 per cent neutrophils. Fluoroscopy showed elevation of the anterior mid-portion of the right leaf of the diaphragm, haziness of the diaphragmatic angle and an immobile diaphragm. Penicillin therapy was begun. On the 2nd day he coughed up a considerable amount of thick, reddish sputum in which small trophozoites resembling *E. histolytica* were found. A course of emetine was started immediately. The patient remained acutely ill. On the 6th hospital day an open drainage of a right subdiaphragmatic abscess was performed below the right costal margin. Cultures of the pus obtained were sterile.

Postoperatively the temperature continued to spike. Cultures obtained at subsequent packing of the abscess showed *Staphylococcus albus*. On the 21st postoperative day a second operation was performed, a segment of the seventh

rib in the right anterior axillary line being resected. The temperature at first fell to normal, but again became elevated, leading to the recognition of a supradiaphragmatic abscess pocket, which was drained through the lateral incision on December 23. This left the patient with a small bronchial fistula. The temperature fell to normal, and 18 days later penicillin was stopped.

Twelve days later, profuse purulent drainage, with many motile amebas, again appeared. In addition, a positive culture of *Staph. albus* was obtained. Penicillin was resumed, the drainage wound enlarged, and another course of emetine given. The temperature again fell to normal, and the drainage decreased. A second course of vioform was administered. Gain in weight and improvement in general health continued. The external drainage wound required subsequent revision 2 months later. The patient was discharged on June 27, 1947, after 7 months' hospitalization, with a bronchial fistula, but drainage sites otherwise healed. Subsequent follow-up examination showed closure of the fistula and no further symptoms.

CASE 5 T C, a 34-year-old woolen worker, had been hospitalized with the diagnosis of bacillary dysentery in the Philippine Islands in June, 1945. Hospitalization for right-sided abdominal pain and a high temperature was initiated at this hospital in November, 1945, when tenderness and rigidity in the right upper quadrant were noted. A downhill course, with the appearance of signs over the lower lobe of the right lung, was halted by a single combined course of emetine and penicillin, after which the patient was discharged on January 7, 1946.

He was readmitted late in February for recurrence of the abdominal pain. The findings over the right lower lobe and upper part of the abdomen were again present. The white-cell count was 26,000, and for the first time, typical cysts of *E. histolytica* were found in the stool. Two alternate 8-day courses of emetine and vioform without penicillin were given during the next month without permanent effect. On March 27 under local anesthesia, a trocar was inserted through an incision over the eleventh intercostal space, and 2000 cc of thick, reddish-brown material aspirated. Subsequently the high temperature persisted, the cavity became filled with air, and open drainage was performed on the basis that secondary infection was probably present.

Emetine and penicillin were again administered, with temporary improvement, but the high temperature and profuse drainage promptly reappeared when the therapy was discontinued. In spite of various revisions of the incision, the patient failed markedly, and the wound drained profusely during the next ten weeks, the exudate literally teeming with motile trophozoites of *E. histolytica*. Repeated intramuscular courses of emetine and emetine irrigations did not affect the number of these parasites. Resistance studies of the amebas were performed by Dr. Quentin Geiman, of the Department of Comparative Pathology, Harvard Medical School. Amebas cultured from this patient grew in concentrations of emetine that were much higher than the control strains tested, indicating resistance to the drug in vitro.

On June 25 a thoracotomy with resection of part of the eighth rib was performed, and a pleural empyema cavity with a bronchopleural fistula effectively drained. Disappearance of the trophozoites from the exudate, loss of fever and other improvement occurred from this point on. Convalescence was slow, but the wounds had healed sufficiently for discharge on December 9. Follow-up examinations have shown complete healing of all incisions. During the year of hospitalization the patient received a total dose of 3 gm (45 gr) of emetine intramuscularly without any evidence of toxicity.

CASE 6 J W, a 22-year-old printer, was first admitted to the hospital on December 18, 1946, complaining of fever, cough productive of bloody sputum and pain in the right side of the chest of 2 weeks' duration.

While on overseas duty in Iran during 1944 and 1945, he had suffered two brief bouts of diarrhea not requiring hospitalization. In the month prior to admission to this hospital, 1 year after returning from overseas, he had been hospitalized elsewhere on three occasions for fever of unknown origin. He had been treated with penicillin and

wall to permit, under direct vision, the introduction into the abscess of a large aspirating needle on a syringe. Aspiration was followed by the instillation of penicillin into the abscess cavity and closure of the abdominal wall without drainage. At least one additional course of emetine was administered before discharge from the hospital.

Two of the abscesses that had penetrated through the diaphragm (Cases 4 and 5) were considered to be secondarily infected. These were treated with open drainage.

In another case (Case 6) the abscess had drained spontaneously into the right pleural cavity and through the bronchial tree. The patient was treated with chemotherapy and aspiration of the empyema fluid by thoracentesis.

All patients were treated with intramuscular emetine in a single daily dose of 60 mg (1 gr). The initial course lasted for at least eight days, and subsequent courses were of six days' duration. At least two courses were given to each of the patients. The pulse and blood pressures were recorded three times a day, and electrocardiograms were taken before and on every second day of treatment to determine the existence of drug toxicity. After each course of emetine, all patients received vioform (iodochlorohydroxyquinoline) in oral dosage beginning at 0.25 gm (4 gr) three times daily, and slowly increasing to 1.0 gm (15 gr) three times a day. Dosage at this level was maintained for seven to ten days. Penicillin was injected intramuscularly in doses of 30,000 to 50,000 units every three hours, concurrent with or prior to the initiation of the first course of emetine. It was continued as long as fever or signs of secondary infection were present. The arsenical amebicides were not used.

### CASE REPORTS

**CASE 1** L K, a 25-year-old man, was admitted to the hospital on October 1, 1946, complaining of chills, fever and right-upper-quadrant pain of 7 days' duration. In June, 1945, while serving in the Philippines, he had experienced an intermittent episode of watery diarrhea of 3 weeks' duration, which had subsided spontaneously. Chills and fever due to a malarial infection had been experienced in December, 1945, and April, 1946. One week before admission, while riding in a truck, he had noted sharp, knife-like periumbilical pain, which had later shifted to the right upper quadrant. The pain was aggravated by deep breathing and pressure.

Physical examination revealed the patient to be acutely ill. A tender liver was palpable on inspiration.

The temperature was 102°F, the pulse 100, and the respirations 20.

Examinations of the blood showed white-cell counts of 12,000 to 18,000, with a marked increase in neutrophils. The sedimentation rate was 20 mm per hour. Blood cultures were sterile. Urinalysis was negative. Except for an elevated urobilinogen, routine liver-function tests were within normal limits. After several unsuccessful attempts, typical cysts of *Endamoeba histolytica* were found in the stool. X-ray examination of the chest and fluoroscopy were not remarkable.

The patient ran a daily spiking temperature from 99 to 103°F. On the 4th hospital day penicillin therapy, consisting of 30,000 units intramuscularly every 3 hours, was begun. The temperature was lower on the 7th to 9th days,

but the symptoms remained unchanged. On the 9th hospital day, emetine therapy was instituted, with slow improvement, the temperature falling to near normal by the 3rd day of this treatment. Emetine and penicillin were continued for a total of 10 days without evidence of drug toxicity and were followed by a course of vioform for a similar period. On October 31 and November 2 a high spiking temperature recurred. Thick blood smears revealed *Plasmodium vivax*, and the fever promptly responded to therapy with chloroquin. A second course of emetine was instituted for 6 days after completion of the antimalarial therapy. The patient was discharged November 20, with the diagnoses of amebic hepatitis and malarial fever. During the succeeding month he experienced occasional fever and a constant dull ache in the right upper quadrant. Readmission on December 27, for a third course of emetine and a second course of chloroquin, was followed by the disappearance of all symptoms. When last seen in September, 1947, he was working and in good health.

**CASE 2** W M, a 24-year-old laborer, was first admitted to the hospital on November 30, 1946, complaining of right upper-quadrant pain of 2 days' duration. He had had mild abdominal cramps and watery stools on several occasions while on duty with the United States Army in New Guinea and the Philippines in 1944-1945. He had been evacuated to the United States in 1945 because of skin lesions of the legs and feet. Symptoms had first appeared 2 days before admission, when he had suddenly developed a pressing pain in the right upper quadrant radiating across the back. A temperature of 102°F developed, and he was treated at home with sulfadiazine before being admitted to the hospital. His appetite had remained unaffected.

Physical examination showed moderate tenderness and spasms over a mass in the right upper quadrant. The temperature was 101°F, the pulse 100, and the respirations 25.

The white-cell count was 18,000, with 63 per cent neutrophils. A chest film was normal. It was believed that the diagnosis lay between an acute cholecystitis and an amebic abscess presenting beneath the right costal margin. A preliminary dose of emetine was given, and an exploratory laparotomy performed. The liver was found to be enlarged, the edge extending to the level of the umbilicus. An aspirating needle removed 70 cc. of thick, reddish, purulent material typical of an amebic liver abscess from the right lobe. Penicillin, 50,000 units in 10 cc. of saline solution, was injected into the abscess cavity, and the abdomen was closed without drainage. Smears of the aspirated fluid were negative for amebas, and a culture grew out *Proteus vulgaris*. Postoperatively, penicillin was continued intramuscularly for 19 days. The course of emetine was discontinued after six doses because of changes in the electrocardiogram. The temperature fell to normal on the 4th postoperative day and remained at that level. On December 13 a course of vioform was initiated. On January 6 a second course of emetine was begun, being discontinued after 6 days because of recurrence of the electrocardiographic changes. This was followed by two further courses of vioform and another course of emetine. At no time were amebas found in the stools. The patient was discharged, asymptomatic, on February 4, 1947. He has remained well.

**CASE 3** W K, a 25-year-old musician was admitted to the hospital on February 26, 1947, complaining of sudden onset of fever and a severe, sharp, catching pain across his upper abdomen, increased by cough or pressure. In July, 1945, while serving in the Philippine Islands, he had experienced a severe episode of diarrhea of 10 days' duration, followed by 6 weeks' hospitalization for jaundice and malaria. Loose stools, two or three times a day, and monthly malarial attacks had been noted since 1945.

Physical examination revealed a temperature of 100°F, and a hard, markedly tender liver edge three fingerbreadths below the right costal margin near the midline. There was a moderate polymorphonuclear leukocytosis, and the stools contained numerous actively motile trophozoites of *E. histolytica*. A course of emetine was begun on February 28 and penicillin on March 3. On the following day under nitrous oxide, oxygen and ether anesthesia, a 2.5-cm incision was made over the point of greatest tenderness beneath the right costal margin. An abscess that had become

acute cholecystitis. In others the signs of perihepatitis were outstanding. Restriction of the movement of the adjacent diaphragm without deformity of shape on x-ray examination was often an early sign, and was frequently followed by subsequent pleural involvement.

Laboratory studies in similar types of cases showed the white-cell count to vary from normal to marked elevation. Examination of the stools was positive for amebas in 3 cases, or 50 per cent. Characteristic sputums, after spontaneous drainage of the abscess by hepatobronchial fistula, contained trophozoites in the 2 cases of that group. The exudate from abscess cavities that received inadequate open drainage contained large numbers of motile trophozoites.

#### SUMMARY

Six cases of late amebiasis of the liver are described. None of these patients had previously been diagnosed as having amebiasis. The time of onset of symptoms after returning to the United States from overseas was variable. The onset was usually acute, with signs referable to the liver.

Three problems in therapy are described. These include diffuse hepatitis or small abscesses that heal on chemotherapy alone, large abscesses that require aspiration in addition to chemotherapy — this is most safely performed as a surgical procedure, and large abscesses penetrating above the diaphragm, which may drain spontaneously and be cured by chemotherapy with or without thoracentesis. Occasionally, open drainage may become

necessary, but this should be reserved as a last resort, for it is likely to be followed by prolonged hospitalization.

The best results of chemotherapy were obtained by a combination of emetine and penicillin in two or more courses, alternately with vioform in large doses. Toxic effects of emetine on the heart as revealed by electrocardiogram were noted in 3 cases, but were apparently not serious.

All six patients are alive and well at present, but only a more prolonged follow-up will determine whether or not they have been permanently cured of the disease. The early follow-up study appears to be just as satisfactory in patients treated conservatively as in those treated by radical surgery. The former had a more benign clinical course and a shorter hospital stay than those on whom open drainage was performed.

#### REFERENCES

- 1 Maclean W. C. Cited by Rogers L. Lettsomian Lectures on amoebic liver abscess: its pathology, prevention and cure. *Lancet* 1:463-469, 569-575 and 677-684, 1922.
- 2 Rogers L. Rapid cure of amoebic dysentery and hepatitis by hypodermic injections of soluble salts of emetine. *Brit. M. J.* 1:1424, 1912.
- 3 Ochsner A. and DeBakey M. Surgical consideration of amebiasis: collective review. *Internat. Abstr. Surg.* 69:392-403, 1939.
- 4 Walters W., Watkins C., Butt H., and Marshall J. Amebic abscess of liver unsuspected until perforation. *J. A. M. A.* 125:963-966, 1944.
- 5 Strong R. P. *Stitis: Diagnosis, Prevention and Treatment of Tropical Diseases*. Seventh edition, 2 vol. 174 pp. Philadelphia: Blakiston Co., 1944. Vol. 1, p. 539.
- 6 Berne C. J. Diagnosis and treatment of amoebic liver abscess. *Surg., Gynec. & Obst.* 75:235-238, 1942.
- 7 Klatkin G. Amebiasis of liver: classification, diagnosis and treatment. *Ann. Int. Med.* 25:601-631, 1946.
- 8 Dack S. and Moloshok R. E. Cardiac manifestations of toxic action of emetine hydrochloride in amoebic dysentery. *Arch. Int. Med.* 79:228-238, 1947.

sulfadiazine, and had received 1 unit of plasma. One week before admission he entered a second hospital with pain in the right side of the chest, a productive cough and fever. A needle aspiration of the right side of the chest revealed fluid typical of an amebic abscess, and he was transferred to this hospital.

The temperature was 101°F, and the pulse 96. There were signs of fluid at the right base, and a tender liver edge was palpable three fingerbreadths below the right costal margin. The white-cell count was 8750, with 56 per cent neutrophils. The stools were negative for amebas, but a sputum examination was positive for trophozoites resembling *E. histolytica*. X-ray study of the chest showed obliteration of the lower two thirds of the right lung field. Aspiration from the right side of the chest yielded 260 cc of sterile bloody fluid containing no identifiable amebas.

Intramuscular penicillin therapy was begun, and a course of intramuscular emetine given. Two subsequent chest aspirations yielded a further 500 cc of fluid. The liver returned to its normal position. On the 12th hospital day the temperature had fallen to normal, where it remained. Penicillin was continued for 26 days, followed by a course of vioform. This was followed by a second course of emetine, which was discontinued after 6 days because of electrocardiographic changes and the development of jaundice. Laboratory studies at that time showed an icteric index of 19, cephalin flocculation of + + + +, a van den Bergh reaction of 2.1 mg per 100 cc, later rising to 5.8 mg (4.2 mg direct, 1.6 mg indirect). This was interpreted as a homologous serum jaundice caused by the plasma received during the previous hospitalization. Over the succeeding month the jaundice cleared, the liver-function tests improved, and the electrocardiogram quickly returned to normal. The patient was discharged, asymptomatic, on March 22, 1947. He was readmitted on April 21, when an x-ray film of the chest, an electrocardiogram, liver-function studies and blood counts were all within normal range. He was discharged without further therapy. Follow-up examinations have been negative.

### Discussion

Patients suffering from diffuse hepatic involvement or from multiple small liver abscesses (as in Case 1) appear to respond well to adequate doses of chemotherapy alone.<sup>7</sup> If an accurate diagnosis can be made and proper treatment instituted, it seems likely that the complications due to penetration of the abscess into the surrounding tissues can be avoided. Single courses of chemotherapy in late larger abscesses proved inadequate. In Cases 4 and 5, if proper diagnoses had been made and adequate treatment instituted at the time of the first admission, it seems probable that many of the subsequent complications would have been prevented.

Needle aspiration of moderate-sized, individual abscess cavities readily localized by physical or x-ray examination, in conjunction with adequate chemotherapy, gave good results in Cases 2 and 3. The period of hospitalization was short, with a relatively benign postoperative course. There was suggestive clinical evidence that penicillin somehow appreciably supplemented the amebicidal action of emetine. No studies in vitro were performed to confirm this impression.

Abscesses draining spontaneously into the bronchial tree may heal on chemotherapy alone, as in Case 6. The presence of a bronchial fistula does not, in itself, necessarily mean that sufficient secondary infection has taken place to require open drain-

age. In the light of subsequent experience we should now treat Case 4 for a longer period with chemotherapy before resorting to open drainage. Similarly, earlier aspiration in Case 5 might have been successful. Patients who had open drainage (Cases 4 and 5) suffered a stormy postoperative course, with a prolonged convalescence. This is in contrast with the results obtained in Case 6 by aspiration and chemotherapy without surgical drainage. Open drainage is indicated only when a thorough trial with chemotherapy and aspiration has proved inadequate. When performed, open drainage must be wide and complete, or repeated drainage procedures will be necessary. In the presence of open drainage and secondary infection, penicillin appears to be beneficial in decreasing systemic reaction and in lessening the quantity of purulent discharge, which is in itself a culture medium for amebas.

All cases should be observed for evidence of emetine toxicity. The electrocardiographic changes were the only ones noted in our series, being present in 3 of the 6 cases. Changes in contour and direction of the T waves in the limb and chest leads were noted in varying degree. They persisted for a few weeks only, were greatly lessened by absolute bed rest and were not associated with tachycardia, arrhythmia, changes in blood pressure or symptoms referable to the heart. The occurrence of such changes in the initial course was not regarded as a contraindication to further courses of emetine. Treatment continued after the development of these changes was not followed by serious effects. This varies considerably with the experience of Dack and Moloshok.<sup>8</sup>

The development of resistance of the parasite to emetine may take place. This was demonstrated by the studies in vitro and the clinical observations in Case 5.

Vioform was found to be an extremely satisfactory means of eradicating the cyst forms. By a gradual increase of the dose to 1.0 gm three times daily, a highly effective intestinal concentration of the drug was attained without producing irritant or toxic symptoms. No parasites were found in stool examinations made during the follow-up studies.

It appears that the primary infection in these cases was acquired while the patients were on overseas duty, 4 having served in the Philippines, 1 in China, and 1 in Iran. Not all had had previous symptoms of intestinal disease, and in none had a diagnosis of amebic dysentery been made. The lapse of time between departure from the overseas duty and the admission to the hospital for hepatic disease varied from two to eighteen months, it can, of course, be much longer.

The onset of symptoms referable to the abscess was often acute and without premonitory symptoms. In 2 cases the physical signs suggested an

The second method may be considered complementary to the first. It consisted of polls inquiring of two types of population groups whether they remembered ever having received tetanus antitoxin. One type consisted of young adults of moderately high economic level, the majority of whom could be said to have medical attention more readily available than the average person. These were the current group of Harvard medical students\*. The information was obtained by checking the routine medical-history forms filled out on admission to the school. The other type of population group was the total adult medical and surgical ward patients of two Massachusetts hospitals. Information was obtained by personal questioning of each patient. In addition to the query about prior tetanus antitoxin, the patients were also asked whether they had ever received a severe burn or a penetrating wound (the example of stepping on a

TABLE 1 Case Mortality in Various Series

AUTHOR	NO OF CASES	NO OF DEATHS	MORTALITY %
G-nicht	289	137	47.4
Vinnard <sup>2</sup>	352	158	44.9
Huntington <sup>3</sup>	642	405	63.1
Bruce <sup>4</sup>	1,437	500	34.8
Gessler <sup>5</sup>	121	65	53.7
Press <sup>6</sup>	100	49	49.0
Totals	2,941	1,314	44.7

nail was used) without the administration of tetanus antitoxin.

Similar information on the prevalence of prior inoculation of horse serum (not limited in this series to tetanus antitoxin) was gathered from an article by Lyall and Murdick.<sup>6</sup> In 1000 consecutive cases of accident in which tetanus antitoxin was given, a history of whether or not prior horse serum had been received was obtained from 815 patients. Of these, 110 (13.5 per cent) had had serum before. This percentage is similar to that noted in the ward cases. Both series are definitely significant from the statistical standpoint.

It is thus noted that from 11 to 27 per cent of the general population remember having had antiserum inoculations. In addition, a large number may have received it during the first five or six years of life, when it would rarely be remembered. It is during that time that accidental injuries associated with falling and creeping and often necessitating tetanus antitoxin are especially frequent.

A factor further highlighting the allergic potentialities is brought out in the above series of Lyall and Murdick,<sup>6</sup> many persons receive more than one dose of antitoxin during their lifetime.

For example, the 110 persons mentioned above with a history of prior administration of horse serum were not denied a dose of tetanus antitoxin because of this history. They constitute a portion of the growing group of persons that have had two or more doses of foreign proteins parenterally. Each succeeding dose greatly increases the risk of severe

TABLE 2 Prior Injections of Antiserum among Medical Students\*

DATA ON INJECTIONS	NO OF STUDENTS
History of 1 or more	109 (27.7%)
None admitted	242
No reply	49
Total	400

\*The subjects questioned were second-year, third-year and fourth-year students at Harvard Medical School.

reactions and anaphylaxis. In the series of 1000 cases referred to,<sup>6</sup> generalized reactions occurred in 23.6 per cent of those giving a history of prior serum injection and in only 8.8 per cent of those without such a history.

Frequency of Injuries that May Result in Tetanus

To estimate the frequency of these injuries it is necessary to arrive at a definite understanding of the types concerned. It has been rather generally believed until recently that penetrating wounds and embedded foreign bodies, especially if contaminated with rural soil, as well as severe burns, accounted for the large majority of cases of tetanus. These wounds, in addition to gunshot wounds and those in which there was considerable maceration

TABLE 3 Prior Injections of Antiserum among All Surgical and Medical Ward Patients in Two Massachusetts Hospitals, according to a Personal Poll

DATA ON INJECTIONS	NO OF PATIENTS
Prior tetanus antitoxin	17 (11.0%)
No tetanus antitoxin but history of penetrating injury or severe burn in past	29 (18.8%)
Total	154

and destruction of tissue, were the ones for which tetanus antitoxin was recommended.

An approximate gauge of the frequency with which this type of wound is remembered can be obtained from Tables 2 and 3, if one assumes that the persons who received tetanus antitoxin did so because of the above type of wound. This is a reasonable assumption, and in the 154 patients personally polled (Table 3) it was corroborated. It is thus noted that approximately 30 per cent of the population can recall such an injury. Again, it is to be expected that many persons had such in-

\*Permission to examine these records was obtained through the courtesy of Dr. Myles P. Baker.

## DESIRABILITY OF THE ROUTINE USE OF TETANUS TOXOID

EDWARD PRESS, M D , M P H \*

CHICAGO

**D**URING the last few years a considerable amount of additional information regarding the effectiveness and hazards of active immunization against tetanus has become available. The war, with its many casualties among unimmunized, partly immunized and fully immunized civilian and military personnel, contributed greatly to this fund of information. In the light of this added knowledge and in view of the continuing diversity of opinion and practice regarding the routine active immunization of children and adults, it was believed that the entire problem deserved re-evaluation. An effort was made to analyze objectively all the factors involved and to arrive at a definite conclusion whether active immunization as a public-health procedure should be limited to special groups or be administered routinely to all children or adults, or both.

## METHOD

The various factors pro and con are enumerated below and analyzed on the basis of a review of the pertinent available literature supplemented by the following procedures.

A series of 100 consecutive cases of tetanus was culled from the records of five Massachusetts hospitals† and analyzed from the standpoint of the type of injury preceding the disease, the use of prophylactic tetanus antitoxin at the time of the injury and whether recovery occurred. I bear the responsibility for any errors in the presentation and interpretation of these figures.

Pools of two sample population groups were carried out to determine the prevalence of penetrating injuries and the frequency of prophylactic use of tetanus antitoxin.

Personal correspondence with all the private and public laboratories licensed to distribute tetanus antitoxin was carried on to estimate the amount used annually in the United States.

The accident-room records of 250 successive cases of injury in a representative, reputable urban hospital were examined to determine the frequency with which tetanus antitoxin is given and the type of injuries in which it is currently considered indicated.

## FACTORS FAVORING ROUTINE IMMUNIZATION

The factors favoring routine immunization are as follows: the high case mortality in tetanus, the fre-

quency of administration of tetanus antitoxin when active immunization is limited, the marked frequency of accidental injuries that may be precursors of tetanus, the wide distribution of tetanus spores and evidence that they are not limited to soil in rural areas, the allergic reactions to tetanus antitoxin, and the not infrequent failure of tetanus antitoxin prophylactically and the almost universal effectiveness of toxoid.

*High Case Mortality*

In spite of the advent of tetanus antitoxin, sulfonamides and antibiotics, a definitely effective therapeutic agent remains to be found.

In the last twenty to thirty years there has been little, if any, change in the over-all case mortality. The best rate in any statistically significant series is about 35 per cent, and the average is 44.7 per cent (Table 1).

*Frequency of Administration of Tetanus Antitoxin*

To keep the incidence of tetanus low when active immunization is limited, it is necessary to give many doses of tetanus antitoxin. It is obvious that if a sufficiently large number of doses were given, the undesirable effects of this mass sensitization might well overbalance the advantage of omitting routine inoculations of tetanus toxoid.

Two separate methods were used to estimate the frequency of administration of tetanus antitoxin. The first was correspondence with all private and public laboratories licensed to distribute tetanus antitoxin through the Biologics Control Laboratory of the United States Public Health Service. Replies were received from nine out of ten of the private concerns, and annual reports supplemented by correspondence elicited similar figures from all the health departments concerned. From these figures an estimate of the total distributed annually could be made. This would not include tetanus antitoxin packaged for therapeutic use. Undoubtedly, some of this is used prophylactically. It would also exclude any private laboratories whose products were not sold in interstate commerce.

As the replies from many of the private companies were confidential, an individual breakdown could not be given. However, the over-all figures of public and private laboratories amounted to approximately 2,125,000 doses of 1500 units annually, exclusive of returns when the expiration date was exceeded.

\*Regional medical director, Chicago Regional Office, United States Children's Bureau, Federal Security Agency.

†The institutions concerned are the Massachusetts General, Beverly, Beth Israel, Boston City and Peter Bent Brigham hospitals. The courtesy and assistance of the administrative staff and record room workers are gratefully acknowledged.

study was able to isolate tetanus bacilli from only about half the cultures obtained from wounds (not feces) of 200 patients with clinical tetanus. In the light of this, it is easier to understand the discrepancy in reported investigations. In addition, varying geographic, occupational and sanitation features may be involved.

Table 5 presents a summary of most of the reported studies on this subject.

In the presence of conflicting evidence and a difficult technical procedure, it is reasonable to place more weight on the isolation of tetanus bacilli than on the failure to isolate them. This conclusion is strengthened by the commonly accepted empiric observation that severe burns and wounds with considerable necrosis are likely to result in tetanus if no prophylactic antitoxin is given, regardless of the absence of contamination with rural soil. Study of Table 5 reveals the rather startling fact that tetanus spores are frequently found more often in the feces of human beings than in those of horses.

#### *Allergic Reactions to Tetanus Antitoxin*

In addition to local reactions at the site of injection, generalized allergic reactions, palsies of the peripheral and central nerves and deaths due to anaphylactic shock have repeatedly been described. The incidence of these reactions varies with the purity of the antitoxin, the method of administration, the use of concomitant epinephrine, the criteria of what constitutes a generalized allergic reaction and many other things. It is therefore exceedingly difficult to estimate the frequency of deleterious reactions.

The use of enzyme-digested antitoxins, such as that prepared by Parfentjev,<sup>25</sup> has considerably decreased the number of reactions. Top and Watson<sup>26</sup> believes that this "despeciated" antiserum has reduced allergic reactions—formerly observed in about 40 per cent of cases—to less than 10 per cent in a large number of unselected cases. However, even with the use of these modified serums an irreducible minimum of reactions that is fairly high exists.

#### *Greater Effectiveness of Tetanus Toxoid Prophylactically*

Tetanus antitoxin when given at the time of an injury is usually effective in preventing tetanus. However, to ensure success, it is necessary to continue administering the antitoxin every ten to fourteen days until complete healing has taken place. This is usually not done, and in the majority of cases only a single dose is given, often resulting in a false sense of security. Practically every study of the illness reveals many cases in which tetanus antitoxin failed to prevent tetanus (Table 6). Particularly outstanding is the great number of cases mentioned by Kirschner<sup>28</sup> as occurring in

the German forces in World War I, in spite of the administration of tetanus antitoxin.

Tetanus toxoid when properly and thoroughly administered provides almost complete protection. A review of the experience of the British Expeditionary Forces in the African and European theaters in World War II, presented by Boyd,<sup>27</sup> revealed that only 6 cases of tetanus developed in soldiers who had previously had over three inoculations of tetanus toxoid. In the American experience during the same war on all fronts, including the zone

TABLE 6 *Development of Tetanus in Spite of Prophylactic Administration of Tetanus Antitoxin*

AUTHOR	CASES OF TETANUS	PATIENTS RECEIVING TETANUS ANTITOXIN	
		NO	PERCENTAGE
Gessler <sup>1</sup>	121	11	9.1
Gruich <sup>2</sup>	249	3	1.04
Boyd <sup>27</sup>	105	2	2.3
Vinnacott <sup>3</sup>	352	10	2.8
Huntstock <sup>4</sup>	642	72	11.2
Bruce <sup>5</sup>	1478	609	61.7
Kirschner <sup>28</sup>	—	20,000	—
Press <sup>6</sup>	100	6	6.0
Total†	7055	1024	53.4
Average			
To all nonmilitary	1504	102	6.8
Average			

\*Studies based on wounded military personnel.

†Exclusive of Kirschner's<sup>28</sup> cases.

of interior as well as overseas, Long<sup>29</sup> found that only 12 cases of tetanus had occurred in the entire Army personnel. Of these, only 4 followed both the basic course of toxoid and the stimulating dose, 2 additional cases followed the basic course in which the stimulating dose was omitted. The United States Army procedure for immunization consisted of three 1-cc injections of fluid toxoid at three-week intervals followed by a routine stimulating dose in one year and an "emergency" stimulating dose at the time of injury. The 12 cases in the American Army represent a frequency of 0.44 case per 100,000 wounded (0.22/100,000 if only the immunized are counted). Bruce<sup>5</sup> found that among unprotected personnel about 9 cases of tetanus per 1000 wounded occurred—that is, 900 per 100,000. On the basis of these figures toxoid is over 99.9 per cent effective. Bruce reported an incidence of about 1.12 per 1000 among men protected with prophylactic tetanus antitoxin.

#### FACTORS AGAINST ROUTINE IMMUNIZATION

The factors against routine immunization are as follows: the relative rarity of the disease and the lack of communicability, the availability of antitoxin as a safeguard for injuries customarily causing tetanus, the reactions to tetanus toxoid, the cost of tetanus toxoid, and the possibility of preventing the majority of cases and avoiding in-

juries at too early an age to recall them. Indeed, if splinters are included in penetrating injuries, it is reasonable to believe that the majority of the people have had such episodes.

Recently, evidence has become more prevalent that tetanus very frequently is preceded by non-

TABLE 4 Frequency of Trivial Injuries and "Unknown Injuries" Preceding Tetanus

AUTHOR	TOTAL CASES OF TETANUS	INJURY UNKNOWN		INJURY TRIVIAL	
		NO OF CASES	PER CENTAGE	NO OF CASES	PER- CENTAGE
Vinnard <sup>2</sup>	352	38	10.8	*	*
Pratt <sup>8</sup>	56	16	28.6	18	32.1
Dean <sup>5</sup>	25	*	*	5	20.0
Francisco <sup>10</sup>	100	16	16.0	28	28.0
Silverthorne <sup>11</sup>	70	15	21.4	37	52.9
Spaeth <sup>12</sup>	276	37	13.4	*	*
Dietrich <sup>13</sup>	28	13	46.4	*	*
Press <sup>14</sup>	100	14	14.0	33	33.0
Totals for un- known in- juries	982	149	15.2		
Totals for trivial in- juries	351			121	34.5

\*Information not stated

penetrating wounds and that often a trivial injury results in the disease. Moreover, in a moderately large proportion of the cases, no history of any injury can be obtained. This implies that any wound sustained was so slight that it went unnoted. This concept is not really a new one and has been recognized by a few physicians for many years. In 1923

was the first to place strong, definite emphasis on this point.

Of the 100 consecutive patients with tetanus admitted to the five metropolitan Massachusetts hospitals, 33 had injuries of a nonpenetrating type that were so trivial that medical attention would not have been sought even by the patients in the highest income levels. Examples of this type of injury are infected mosquito or chigger bites, superficial cuts or scratches on the palms, soles, wrist or the dorsum of the hands and slight abrasions of the knee or elbow. In addition, 14 patients in spite of careful questioning could recall no injury whatsoever in the five or six months preceding the onset of the illness.

It is unquestionably true that the vast majority of trivial injuries are not followed by tetanus, and even most of the penetrating wounds might not result in tetanus if unprotected. However in view of the fact that about 50 per cent of the cases of tetanus are preceded by very slight wounds or "no" wounds and the case mortality is about 45 per cent, the conscientious physician would find it difficult to avoid administering tetanus antitoxin in such cases. The problems inherent in such frequent use of tetanus antitoxin are obvious and constitute an excellent point favoring routine use of tetanus toxoid.

#### Wide Distribution of Tetanus Spores

In the majority of cases, medical teaching has transmitted from one textbook to the next the

TABLE 5 Distribution of Tetanus Spores

AUTHOR	DATE	LOCATION	SPECIMENS EXAMINED		POSITIVE NO	SPECIMENS PER- CENTAGE
			NO	TYPE		
Pizzini <sup>15</sup>	1898	Italy	100	Human feces	5	5.0
Tulloch <sup>16</sup>	1919	England	52	Human feces	12	23.1
Tenbroeck and Bauer <sup>17</sup>	1922	China	78	Human feces	28	35.9
Tenbroeck and Bauer <sup>17</sup>	1926	China	539	Human feces	153	28.4
Fildes <sup>18</sup>	1925	England	200	Human feces	2	1.0
	1925	England	200	Horse feces	34	17.0
	1925	England	70	Soil	33	27.1
Buzello and Rahmel <sup>19</sup>	1924	Germany	50	Human feces	20	40.0
Bauer & Meyer <sup>20</sup>	1926	California	487	Human feces	120	24.6
Kerrin <sup>21</sup>	1928	England	204	Human feces	0	0.0
Kerrin <sup>21</sup>	1929	England	53	Horse feces	5	9.4
	1929	England	37	Dog feces	9	24.3
	1929	England	141	Rat feces	23	16.3
	1929	England	100	Human feces	0	0.0
Kahn <sup>22</sup>	1924	New York City	72	Human feces	0	0.0
Gilles <sup>23</sup>	1937	Baltimore	63	Street dust	9	14.3

\*Seven positive specimens were found in 21 soldiers returned from the European Theater.

†No separate test was reported to distinguish toxic from nontoxic strains.

‡Controlled by one specimen from human tissue and not by known positive feces.

Miller<sup>7</sup> stated that it was to be noted that tetanus could come from wounds so slight and so superficial that they were hardly noticeable, and that it was not at all unheard of to have a clear-cut clinical case and yet be unable to find the focus of the disease. Many studies of tetanus reported in the literature reveal no injury or very slight injuries (too slight to implicate a physician) and several of these series are listed in Table 4. Pratt,<sup>8</sup> in 1945,

concept that tetanus spores are generally associated with horses and other grazing animals. More recent investigations using refined anaerobic techniques combined with animal inoculation fail to give uniformly conclusive results. The technique involved is a rather intricate one, and this probably accounts for the difficulty in isolation of the spores from feces and the diversity of the results obtained. For example, Tulloch,<sup>14</sup> in a very detailed and thorough

### *Cost of Tetanus Toxoid*

The cost is the same for both alum-precipitated and fluid toxoid, varying from \$1.12 to \$1.60 per immunizing dose. This is the retail price to the patient. The analogous price of tetanus antitoxin is from 45 to 85 cents. The cost and ease of administration would be reduced if the tetanus toxoid were combined with another toxoid.

### *Limitation of Active Immunization to Specially Susceptible Groups*

If one can assume that the majority of cases of tetanus result from injuries sustained in and around barnyards, ranches and in the proximity of grazing animals, it seems feasible to limit immunization to this group, as well as military personnel. Unfortunately, this assumption is not warranted, as pointed out above.

### SUMMARY AND CONCLUSIONS

An attempt has been made to present impartially the evidence for and against routine active immunization for tetanus. Several of the facts noted are contrary to current general opinion. It was found that about 50 per cent of all injuries leading to tetanus in the civilian population were exceedingly trivial or completely unknown. In addition, it was noted that the majority of bacteriologic studies revealed that tetanus spores were very widely distributed and more frequently found in human feces than in those of horses.

It was noted that the mere presence of tetanus spores in a wound was not sufficient to cause the disease, and the discrepancy between the amount of injuries capable of resulting in tetanus and the number of cases actually occurring was stressed. Several possible explanations for this, including evidence for the existence of a natural immunity, were mentioned.

Statistical evidence was demonstrated to show that less than 20 per cent of the cases of tetanus are reported in the United States. There were at least 910 deaths due to tetanus in the United States in 1940. This compares with 1457 due to diphtheria, 1378 to typhoid fever and 706 to measles.

It was further pointed out that in addition to the number of cases and deaths due to tetanus, one must take into account the number of people sensitized to horse serum by prophylactic tetanus antitoxin as an explanation of the small number of fatal cases. It was estimated that well over two million doses of tetanus antitoxin are given annually and that at least a seventh and probably much more of the entire population receive one or more doses during life. However, if past concepts of proper treatment of injuries are carried out—that is, tetanus antitoxin for penetrating injuries and severe burns—about a third of the population should receive tetanus antitoxin. If present knowl-

edge of the distribution of tetanus spores and the type of injuries associated with the disease were generally publicized, the problem would be greatly intensified. The conscientious physician, aware of the widespread distribution of tetanus spores, knowing the potentiality of tetanus with trivial injuries and being unable to determine which cases might go on to develop it, would be forced to give tetanus antitoxin for nearly all injuries. In view of the definite effectiveness of tetanus toxoid and its almost complete freedom from adverse reactions, its use seems to be indicated.

The not infrequent failure of tetanus antitoxin prophylactically is indicated by the fact that about 7 per cent of civilian and over 50 per cent of military cases developed in spite of its use.

To avoid the increased risk of anaphylaxis and the more frequent allergic reactions to repeated doses of tetanus antitoxin, it is advisable to give toxoid concurrently with each inoculation of tetanus antitoxin. If this active immunization is then completed, it should be unnecessary to use antitoxin for any future injuries in a person by then sensitized to horse serum.

It is my opinion that active immunization against tetanus as a practical public-health measure is indicated. Until further information regarding the pathogenesis of the disease or a simple method of estimating the natural antitoxin level is available, it should be given routinely by private physicians and should also be included in health-department programs for all children. The toxoid should be given to children combined with diphtheria or pertussis vaccine, or both. In addition, children who have been immunized for diphtheria and pertussis, but not for tetanus, should have tetanus toxoid available and be encouraged to use it. Adults with increased accident hazards, such as manual laborers in both rural and urban areas, should also be immunized.

I am indebted to Drs. Stuart S. Stevenson and Carl R. Doering for their advice and suggestions. Particular thanks are due Dr. Harold C. Stuart for his services in helping to make the clinical records available and for general guidance in the study.

188 W. Randolph Street

### REFERENCES

1. Grulich, F. G. Present status of use of tetanus toxoid. *New Orleans M & S J* 98:420-427 1946.
2. Vinnard, R. T. Three hundred and fifty-two cases of tetanus. *Surgery* 18:482-492 1945.
3. Huntington, R. W. Jr., Thompson, W. R., and Gordon, H. H. Treatment of tetanus with antitoxin: analysis of outcome in six hundred and forty-two cases. *Ann. Surg.* 105:93-96 1937.
4. Bruce, D. Tetanus: analysis of 1458 cases which occurred in home military hospitals during years 1914-1918. *J. Hyg.* 19:1-33 1920.
5. Gessler, C. N. Clinical study of tetanus: analysis of 121 cases of tetanus. *J. Tennessee M. A.* 38:363-365 1945.
6. Lyall, H. W., and Murdick, P. P. Tetanus antitoxin serum reactions following prophylactic injection. *New York State J. Med.* 38:882-885 1938.
7. Miller, R. H. Tetanus: report of 116 cases at Massachusetts General Hospital. *Surg., Gynec. & Obst.* 36:90-96 1923.
8. Pratt, E. L. Clinical tetanus: study of 55 cases with special reference to methods of prevention and plan for evaluating treatment. *J. A. M. A.* 129:1243-1247 1945.
9. Dean, H. R. Report on twenty-five cases of tetanus. *Lancet* 1:673-680 1917.

discriminate immunization of millions by limitation of active immunization to specially susceptible groups

### *Relative Rarity and Lack of Communicability*

Tetanus is definitely not a common disease in civilian life at present. In 1945 only 439 cases were reported in the United States<sup>30</sup>. Because the illness is not contagious, it can hardly be much of a public-health threat.

In examining these figures more closely, it was found that tetanus was not a reportable disease in four states and that, even in the states in which it was reportable, some cases were not being reported. This could be determined by the fact that more deaths due to tetanus were being reported in some areas than cases. Since death certificates were necessary for burial, this was understandable. Moreover, a large percentage of the deaths due to tetanus followed injuries, and when two or more diagnoses appeared on the death certificate the death was charged to the injury and not to tetanus. According to the *Manual of Joint Causes of Death* whenever tetanus coexists with accidental injuries including burns, cutting or piercing injuries, firearms or abortion, conditions of pregnancy, childbirth or puerperium, the death is not charged to tetanus but to the other cause.

A study by the National Office of Vital Statistics<sup>31</sup> reveals that in 1940 there were 560 certificates recorded in which tetanus was given as the primary cause of death. In an additional 350, it was listed as secondary. This gives a total of 910 tetanus deaths for that year. Assuming the case mortality to be 40 per cent, there should have been 2275 cases in 1940. However, only 411 cases were reported for that year. During the same year, deaths resulting from other diseases for which active immunization is available were diphtheria (1457 cases), whooping cough (2926 cases), typhoid fever (1378 cases) and smallpox 14 cases. As an item of additional interest, it may be noted that there were 706 deaths attributed to measles, 1026 to poliomyelitis and 1725 to acute rheumatic fever.<sup>32</sup>

Another factor opposing routine use of toxoid and related to the relative rarity of the disease is that tetanus fails to follow many injuries that might be expected to cause it. Everyone is familiar with the great many cases in which penetrating wounds or severe burns have failed to result in tetanus in spite of the absence of any precautions. In an attempt to estimate the frequency with which injuries fail to result in tetanus and also the proportion of injuries sustained for which the average well trained physician would give tetanus antitoxin, the following procedure was carried out. The records of 250 consecutive cases of accidental injuries treated in the outpatient department of a reputable metropolitan hospital in Boston were examined. During that time, 20 injuries were treated

with tetanus antitoxin or tetanus toxoid. One hundred lacerated injuries severe enough to require suturing were not given tetanus antitoxin or toxoid, and 130 additional lacerations, abrasions and minor puncture wounds were treated that were not serious enough to merit either suture or any prophylactic measure for tetanus. During, and for an ample time after, this period, no patients with tetanus were admitted to the same hospital for treatment. This experience corroborated the belief that many injuries that are potential precursors of tetanus fail to result in tetanus in spite of the omission of prophylactic measures.

Some experimental work has been done in animals to indicate that the mere presence of tetanus spores in a wound is not sufficient to cause the disease. Other changes of some type are considered to be necessary for the spores to germinate. Space does not permit a detailed description of this work, but among the theories advanced are a change in oxidation-reduction potential of the tissue or tissue necroses, or both, and the presence of ionizable calcium salts.

The large number of human beings harboring tetanus bacilli in their intestines suggests the possibility of circulating antitoxin in the blood stream. This has been corroborated by Tenbroeck and Bauer,<sup>33</sup> who found the antitoxin in about 25 per cent of the persons tested, and also by Van der Reis.<sup>34</sup> This represents another possible factor in explaining the discrepancy between the plentiful distribution of tetanus spores and the scarcity of the disease.

### *Efficiency of Tetanus Antitoxin*

There is ample scientific evidence that tetanus antitoxin, if given repeatedly at intervals of ten to fourteen days from the time of injury until complete healing, will prevent tetanus. This is available in practically every city and village in the United States wherever physicians are located. It does not apply, however, to injuries in which physicians are not in attendance or to those in which physicians do not use it.

### *Reactions to Tetanus Toxoid*

Most of the relatively few adverse generalized allergic reactions were found to be due to Witte and Berna peptones, which were part of the culture mediums commonly used in the preparation of the toxoid. When these were removed, the number of reactions dropped considerably. For example, Long,<sup>35</sup> in a study of about 10,000,000 soldiers, found that the ratio of significant reactions dropped from 46/100,000 to less than 2/100,000. The recently reported crystallization of tetanus toxoid<sup>36</sup> gives promise of a toxoid practically free of any impurities and therefore even less susceptible to allergic reactions.

had no bowel evacuation for 2 days and had expelled very little flatus. Intestinal obstruction was feared, and she was admitted to the New Hampshire Memorial Hospital on December 3. From that time to the day she was operated on for the second time she was treated as a hopeless case. Consultants advised taps and morphine and believed that x-ray therapy would be of no help. The patient was treated accordingly until about June 1, 1942. She was tapped 63 times and from 5000 to 10,000 cc. of fluid removed every 2 or 3 weeks. She was kept comfortable with morphine, the dosage being increased to 30 mg. every 3 hours.

The patient at that time begged to be operated on again, no matter what the outcome might be. The only intention was to explore and insert a mushroom catheter to relieve her of further taps. On June 1 she was operated on at her request. Her weight was about 80 pounds. The abdomen was opened, and there were no peritoneal implants. A fair amount of straw-colored fluid was found. The appearance of the pelvis was altogether different. All the papillary growths were encapsulated in one large mass to the left and two other smaller ones to the right. All were adherent to the adjacent organs, rectum, uterus and bladder. The growths were dissected and removed with great difficulty except for a small portion about the size of a silver dollar in the right fossa. Some of the contents were spilled in the abdominal cavity and removed with care. The uterus was not removed because of the difficult and long operation. One mushroom drain was left in place, and the abdomen was closed in the usual way.

The pathological diagnosis was papillary cystadenocarcinoma of both ovaries (Fig. 1), with extension to the peritoneum.

The postoperative recovery was fair and rather stormy because the patient was deprived of morphine. She was given two 500-cc. transfusions. The drain was removed on June 27. The abdomen was not healed before September 12, and until that time the temperature went as high as 102°F. The patient was then transferred to the medical service. She improved, gradually gained weight and was discharged November 22, after having spent 1086 days in the hospital.

The patient has been checked regularly every 6 months. She had one scant menstrual period and occasional hot flashes after the second operation. She was checked for the last time 2 months ago, with no apparent recurrence. Her weight is now 140 pounds, she feels well and works every day.

When Dr. George Van S. Smith, of Brookline, Massachusetts, was told about this case in 1946, he thought that there might have been an error in the pathological diagnosis, but after studying the slides himself, he was convinced that the diagnosis was correct and that the case was out of the ordinary and difficult to understand and explain.

#### SUMMARY

Papillary cystadenocarcinoma of the ovary is a malignant epithelial growth. The prognosis is very poor. Early diagnosis is essential, and treatment

should be as radical as circumstances permit, followed by x-ray therapy.

A case of papillary cystadenocarcinoma of the ovary, diagnosed approximately one year after the onset of symptoms, is reported. The patient



FIGURE 1 Photomicrograph of Section of Ovary, Showing Papillary Cystadenocarcinoma

had actual surgical, but not radical, treatment four years after the onset of symptoms and without postoperative x-ray therapy. Yet after more than eight years she feels well, works every day and is apparently cured.

#### REFERENCES

1. Meigs, J. V. Cancer of ovary. *Surg. Gynec. & Obst.* 71: 44-53, 1940.
2. Jones, F. H. Papillary cystadenoma of ovary. *Am. J. Surg.* 52: 246-259, 1941.
3. Pemberton, F. A. Cancer of ovary. *Am. J. Obst. & Gynec.* 40: 751-763, 1940.
4. Curtis, A. H. *A Textbook of Gynecology*. Fifth edition. 755 pp. Philadelphia: W. B. Saunders Company, 1946. P. 400.

- 10 Francisco R. Clinical and epidemiological study of tetanus in Puerto Rico: study of 100 cases seen at Arecibo Charity District Hospital in 2½ year period. *Clinics* 3 373-414 1944
- 11 Silverthorne N. Tetanus. *J Pediat* 30 195-198 1947
- 12 Spaeth R. Therapy of tetanus: study of 276 cases. *Arch Int Med* 68 1133-1160 1941
- 13 Dietrich, H. F. Tetanus in childhood, with special reference to treatment. *Am J Dis Child* 59 693-710 1940
- 14 Tulloch, W. J. Report of bacteriological investigation of tetanus carried out on behalf of War Office Committee for Study of Tetanus. *J Hyg* 18 103-202, 1919-1920
- 15 Pizzini, L. Il bacillo de tetano nelle feci dell'uomo. *Riv d'ig e san pubb* 9 170-173 1898
- 16 Tenbroeck, C. and Bauer, J. H. Tetanus bacillus as intestinal saprophyte in man. *J Exper Med* 36 261-271 1922
- 17 *Idem*. Cited by Bauer and Meyer<sup>25</sup>
- 18 Fildes, P. Tetanus.—I. Isolation, morphology, and cultural reactions of *B tetani*. *Brit J Exper Path* 6 62-70 1925
- 19 Buzello, A. and Rahmel, O. Der Nachweis von Tetanusbacillen im Darm und den inneren Organen Gesunder nicht tetanuskranker Menschen. *Arch f klin Chir* 130 660-676 1924
- 20 Baner, J. H. and Meyer, K. F. Human intestinal carriers of tetanus spores in California. *J Infect Dis* 38 295-305, 1926
- 21 Kerrin, J. C. Incidence of *B tetani* in human feces. *Brit J Exper Path* 9 69-71 1928
- 22 *Idem*. Distribution of *B tetani* in intestine of animals. *Brit J Exper Path* 10 370-373 1929
- 23 Kahn, M. C. Anaerobic spore bearing bacteria of human intestine in health and in certain diseases. *J Infect Dis* 35 423-478, 1924
- 24 Gilles, E. C. Isolation of tetanus bacilli from street dust, its bearing on surgical practice. *J A M A* 109 484-486 1937
- 25 Weil, A. J., Parfentjev, I. A., and Bowman, K. L. Antigenic qualities of antitoxin. *J Immunol* 35 399-413, 1938
- 26 Top, F. H. and Watson, E. H. Reduction of serum reactivity of antitoxins of which protein specificity has been altered by enzymic digestion. *Am J Dis Child* 62 548-554 1941
- 27 Boyd, J. S. K. Tetanus in African and European theaters of war 1913-1945. *Lancet* 1 113-119 1946
- 28 Kirchner, M. Tetanus. Bemerkungen zu den Ausführungen des Herrn Prof. Dr. Lehmann in Nr. 24 dieser Zeitschrift "Ausgabe: Notwendigkeit der Tetanusprophylaxe". *Med. Klin.* 352 (113) 1141 1939
- 29 Long, A. P. and Sartwell, P. E. Tetanus in United States Army in World War II. *Bull U S Army M Corps* 7 371-385 1941
- 30 Incidence of diseases. *Pub Health Rep* 62 400-412 1947
- 31 United States Public Health Service. Federal Security Agency. Unpublished data.
- 32 United States Department of Commerce. Bureau of the Census. *Vital Statistics of the United States 1946*. Part 1. Natality and Mortality Data for the United States Tabulated by Place of Occurrence with Supplemental Tables for Hawaii, Puerto Rico, and the Virgin Islands. 657 pp. Washington, D. C. Government Printing Office 1943
- 33 Tenbroeck, C. and Bauer, J. H. Studies on relations of tetanus bacilli in digestive tract to tetanus antitoxin in blood. *J Exper Med* 37 479-489 1923
- 34 Van der Reis. Cited by Tenbroeck and Bauer<sup>22</sup>
- 35 Pillemer, L., Wittler, R. and Grossberg, D. B. Isolation and crystallization of tetanin toxoid. *Science* 103 615 1946

## PAPILLARY CYSTADENOCARCINOMA OF BOTH OVARIES

### Report of a Case with Apparent Cure Eight Years after Operation

GERARD L. GAUDRAULT, M.D.\*

CONCORD, NEW HAMPSHIRE

THE following case appears to be one of those mysterious cases that cannot be explained. After reading textbooks and journals I came to the conclusions that the patient had had actual surgical treatment four years after the onset of symptoms, that she had not been given x-ray therapy and that a hysterectomy had not been performed.

Meigs<sup>1</sup> states that cancer of the ovary of the malignant papillary cystadenoma type is about as malignant as any other epithelial growth and that bilateral oophorectomy and hysterectomy are the proper treatment. Jones<sup>2</sup> reported 30 cases of papillary cystadenoma of the ovary and stated that the prognosis is extremely poor. Another authority, Pemberton,<sup>3</sup> writes that cancer of the ovary should be treated by as radical an operation as circumstances permit, followed by x-ray therapy. The results of treatment are poor, and early diagnosis is essential.

Curtis<sup>4</sup> states that prognosis with frank carcinoma of the ovary is not good. Five-year salvage is obtained in 60 per cent of the patients with unilateral growths and in 20 per cent of those with cancer of both ovaries, but this includes many small early cancers discovered at operation and cases with slowly developing tumors and relatively benign peritoneal implants.

The comments of other authorities indicate that upon the advent of such symptoms as discomfort,

pain or free fluid in the abdomen, the patient is very seriously handicapped and that the chances of recovery are extremely poor.

A S., a 26-year-old housewife, entered the Margaret Pillsbury General Hospital on November 7, 1939, complaining of discomfort in the lower abdomen, distention, menstrual irregularity and loss of weight, as well as pain in the lumbar region and legs.

The past and family histories were irrelevant. The patient was married, and her husband was well. She had had no pregnancies. For 1 year prior to admission she had complained of some discomfort in the lower abdomen, back and legs. During the last 2 months before admission the discomfort increased markedly, and since other distressing symptoms appeared, admission was advised.

Physical examination showed the patient to be pale and cachectic. The abdomen was distended and tender, and on percussion the presence of fluid was detected. No masses were felt. Pelvic examination revealed a small uterus in normal position, not movable, and a tender, diffuse mass in the pelvis. A tentative diagnosis of tuberculous peritonitis or adenocarcinoma was made.

Examinations of the blood were within normal limits. The urine showed a trace of albumin, sugar and acetone.

On November 9 a laparotomy was performed, and about 2 liters of straw-colored fluid drained from the abdominal cavity. Exploration of the pelvic cavity revealed a small uterus in good position and large papillary growths of both ovaries, with extensive papillary peritoneal implants in the entire pelvic cavity.

Three other physicians were called in for advice, and it was decided that the disease was too extensive and advanced for surgery to be of any benefit. A biopsy was taken, and the abdomen was closed.

The pathologist reported metastases of a papillary cystadenocarcinoma of the ovary. The patient was discharged on November 22, still complaining of some abdominal discomfort.

On December 2 the patient was seen at home. She complained of severe abdominal distress and distention, she had

\*Chief of obstetric and gynecologic staff, Concord Hospital.

need for therapeutic malaria. This belief has not been substantiated by results of extensive series of treatments using penicillin alone.<sup>61</sup>

The mode of action of malaria therapy and of penicillin on *Treponema pallidum* is not known. Since penicillin has no effect on either malarial parasites or clinical malaria, malarial and penicillin therapy either given simultaneously or in sequence have been used extensively.<sup>61</sup> That these procedures will continue to be utilized for some time is entirely possible in view of the 5 per cent increase of syphilis reported for the first half of 1947<sup>61</sup> and the expected subsequent increase in neurosyphilis. Thus, a brief review of procedures for handling therapeutic malaria is warranted.

The infection of choice for therapy of white patients is *P. vivax*. Various strains, such as the McCoy, St. Elizabeth's<sup>62</sup> and Chesson's,<sup>63, 64</sup> are generally available for therapy. Except for the use of infected anopheline mosquitoes to produce experimental infections, the infection is induced in man by passage of 2 to 5 cc of infected blood, and the incubation period, depending on dosage, is approximately two to six days. Wherever reliable parasite counts can be obtained, definite dosages give more consistent incubation periods and predictable course of infection. Kaplan et al.<sup>65</sup> recommend a dosage of 1,000,000 *P. vivax* parasites for susceptible white patients. In our experience with the McCoy and St. Elizabeth's strains,<sup>66</sup> a dosage of 500,000 parasites per kilogram of body weight gives desirable results. There is also evidence that the compatibility of the parasitized blood to be inoculated affects the incubation period. When compatible blood is used the incubation period is approximately two days shorter.<sup>64</sup> The determination of parasite densities during the infection helps also to predict onset, clinical course and spontaneous control of parasitemia.

American Negroes have varying degrees of natural resistance to certain but not all strains of benign tertian malaria.<sup>67</sup> Hence, if Negroes fail to develop clinical malaria after inoculation with *P. vivax*, quartan malaria (*P. malariae*) should be used to obtain the desired hyperpyrexia. If available, the latter species should be the original organism of choice for Negroes. This infection has some disadvantages, such as a longer incubation period (given variously as twelve to fifteen days<sup>68</sup> in a series of 92 patients and as an average of slightly over nineteen days in a series of 38 patients<sup>69</sup>) and intervals of seventy-two hours between paroxysms. These characteristics lengthen the time of hospitalization considerably and tend to eliminate the use of quartan infection in other than resistant Negroes and white patients.

*P. falciparum* of malignant tertian malaria is considered too dangerous for use in treating paretics without laboratory control. This type of malaria is less severe in Negroes than in white patients,

and it can be used to obtain hyperpyrexia without great risk if the parasitemia is not allowed to exceed approximately 100,000 per cubic millimeter. If this infection is used in paretics, parasite densities should be determined at least twice a day because of the rapidity of multiplication of the parasite during the primary attack.

In numerous hospitals, the supply of paretics is not great enough to ensure continuous passage of malaria. Since infected blood loses its viability within two weeks when stored at ordinary refrigerator temperatures, the problem of keeping and obtaining infected blood for new patients constantly arises. The technic of using low-temperature freezing to preserve human malarial parasites has been developed.<sup>66, 70</sup> The method was originally devised for the preservation of simian and avian plasmodia.<sup>29, 71, 72</sup> If a dry-ice cabinet or a mechanical deep freeze is available to maintain the temperatures below  $-50^{\circ}\text{C}$  infected blood containing *P. vivax* or *P. falciparum* can be frozen and stored for lengths of time up to at least six months. Attempts have been unsuccessful with *P. malariae*. One or two cubic centimeters of the infected blood is sealed in thin-walled, 5-cc vials or ampoules and frozen quickly by twirling of the vials in a bath of alcohol precooled to  $-50^{\circ}\text{C}$  or below or in a bath of dry ice and alcohol at a similar temperature. At no time should the temperature of the stored blood be allowed to rise above  $-50^{\circ}\text{C}$ . In use, the vials of infected blood are transported from the storage cabinet in a bath of alcohol and dry ice ( $-50$  to  $-70^{\circ}\text{C}$ ) to the bedside where it is to be used. The vials of blood are thawed quickly in water at  $37^{\circ}\text{C}$ , a syringe is filled, and the blood is injected immediately. Two to five cubic centimeters of thawed blood has been injected without any reaction. In our laboratory, at the Department of Comparative Pathology and Tropical Medicine, Harvard Medical School, where human and simian parasites are maintained constantly in a deep-freeze, best results have been obtained with blood taken during the last half of the cycle before a paroxysm, when the parasites are half or full grown. Sterile precautions and sterile equipment must be used throughout the procedure.

In the previous review,<sup>1</sup> the use of thiobismol was discussed as an aid in inhibiting one of the paroxysms in debilitated patients who have daily rises in temperature during *P. vivax* infections. Many inquiries have been received about this procedure. When the directions for its use as recommended by Young, McLendon and Smarr<sup>73</sup> are followed, desired results are obtainable. But when thiobismol is injected at the wrong part of the parasite cycle, the results are disappointing. No information is available about the exact mode of action of this drug on *P. vivax*, but it is known that the half-grown parasites or trophozoites are affected. Thus to derive maximum effects, 0.1 to 0.2 gm

## MEDICAL PROGRESS

### MALARIA (Concluded)\*

QUENTIN M. GEIMAN, PH.D. †

BOSTON

#### TRANSFUSION MALARIA

Unexpected clinical malaria has occurred in many nonendemic malarious areas when patients receive transfusions of blood from donors who had previously lived or had been exposed to infection in endemic malarious areas<sup>54-58</sup>. In New England the majority of such cases of transfusion malaria before World War II resulted from transfusions from adults who had previously lived in the Mediterranean area. With few exceptions, quartan malaria was the type that was contracted by the recipients of such donor blood. Rubenstein et al.<sup>59</sup> recorded some of these cases, which were reported to the Massachusetts Department of Public Health. In the list of cases, only two of the twelve infections were caused by *Plasmodium vivax*. With the exception of one unidentified case, the other cases were definitely identified as quartan malaria.

The basic reason for the incidence of quartan malaria among these cases resulting from transfusion is the long-lived latency of this type of malaria. This characteristic is not typical of *P. vivax* or of *P. falciparum*.

Two results of World War II and increasing air travel to tropical areas have tended to focus attention on this problem of transfusion malaria. In the first place, relatively great numbers of men were stationed at one time or another during World War II in endemic or hyperendemic malaria areas. In the second place, blood banks have been organized at hospitals for transfusion purposes. This blood is stored for varying periods up to two weeks before it is used.

Although very little quartan malaria occurred in the armed forces during World War II, the high incidence of *P. vivax* and *P. falciparum* prompted a review of the danger involved in using blood from such persons after they have had malaria. *P. falciparum* is not a seriously relapsing type of malaria, and it tends to be cured or to stop spontaneously within a year after the initial infection, provided there is no reinfection or transmission by mosquitoes. On the other hand, the vivax malaria that occurred among the forces in the Pacific theater of war was a seriously relapsing type. There are still a number of these men who continue to have relapses although they had their initial infection two to four

years previously. Available records show that vivax malaria seldom persists beyond three to six years after the initial infection. Thus, blood for transfusion purposes should be refused even in cases of emergency from persons who have given a previous history of any type of malaria. If the species causing the previous infection were known, this statement could be modified, but the intended donor seldom knows more than that he had malaria. It must be realized that the blood during the intervals between relapses of vivax malaria is infective and should not be used for direct transfusion or for storage in blood banks. There is no reason, however, to exclude persons with a previous history of malaria from giving blood for the production of plasma.<sup>60</sup> The parasites live within the red cells, and these cells are discarded during the processing of the plasma for therapeutic use.

The incubation period for transfusion malaria depends upon the numbers of parasites present in the donor's blood and the species of plasmodium. The incubation of quartan malaria as passed by inoculation of infected blood to paretics ranges from one to four weeks. Thus, with submicroscopic parasitemia existing in latent malaria, the incubation period might be as long as three months. This is not so, however, with *P. vivax* from patients who have had relapses of tertian malaria within a few months. In these cases, there are greater numbers of circulating parasites and hence the incubation period in the recipient would be five to fourteen days.

Thus, it should be emphasized that donors of blood for transfusion or for the replenishment of supplies in the blood bank should be asked about a previous history of malaria. If they have had malaria at any time in the past or recall symptoms that might have been due to malaria, their blood should be refused. Their blood can be used, as stated above, for the production of plasma.

#### INDUCED MALARIA

The paradox of using one disease therapeutically to treat another exists in the practice of using human malaria to obtain hyperpyrexia in patients with paresis or neurosyphilis. This therapeutic procedure dates from the successful experiments of Wagner-Jauregg in 1917.<sup>48</sup> The effects of hyperpyrexia produced by induced malaria, mechanical fever cabinets or typhoid vaccines in the hands of many clinicians appear to favor the use of malaria.

The discovery of penicillin, however, and its efficiency in the treatment of paresis was originally believed sufficient to supersede and eliminate the

\*From the Department of Comparative Pathology and Tropical Medicine, Harvard Medical School.

The material reviewed in this paper was compiled in connection with a malaria research project supported by a grant-in-aid to Harvard Medical School from the Division of Research Grants and Fellowships of the National Institute of Health, United States Public Health Service.

†Assistant professor of tropical diseases, Harvard Medical School.

"to have more meaning than that based on plasma concentration"

Studies by another research unit of the Army<sup>51</sup> tend to oppose this view. This group determined the range of plasma concentrations, obtained in a group of men on various dosage schedules, concentrations after completion and after interruption of drug courses, the variation of concentration in persons on the same schedule, the influence of environment on the plasma concentration and the toxicity of the drug. The important results for this discussion are the wide variations of plasma concentrations obtainable in a group on the same dosage schedule and the relative nontoxicity of the drug.

Fairley and his collaborators<sup>52</sup> in Australia studied the build-up, equilibrium level and die-away concentrations of quinacrine after certain dosage schedules, and the effect of such levels on suppression and clinical and radical cure of benign tertian and malignant tertian malaria. These studies established the fact that quinacrine in a dosage of 0.1 gm (1½ gr) daily suppressed falciparum malaria. When the dosage was continued for a required period of approximately a month after the last exposure to infection, a radical cure was obtained. The dosage schedule, furthermore, suppressed benign tertian malaria, but clinical malaria will develop at varying intervals of a few days up to a year<sup>53</sup> after the drug has been discontinued. The prophylactic or suppressive dosage for adults is as follows: one tablet of 0.1 gm (1½ gr) daily, preferably beginning two weeks in advance of exposure, and continuing for at least four weeks after the last possible exposure in a malarious area.<sup>54</sup> When quinacrine is to be taken as an antimalarial drug, administration should be started up to two weeks before a malarious area is entered. This procedure is essential to get an effective plasma level for suppression of clinical malaria.

The thorough review of toxicity of this antimalarial agent by Findlay<sup>54</sup> deserves comment. A comprehensive reference list was covered to record the severe toxic reactions associated with quinacrine therapy before and during the war. This paper should be read by those passing on claims for compensation or pension by persons who have a history of toxic effects following quinacrine therapy.

The primary toxic reactions to quinacrine involved the skin, central nervous system, hematopoietic system and eyes. Lichenoid dermatitis contracted by American and Australian troops in the Pacific area is considered in detail. The incidence of toxic psychoses, frequently exaggerated during the war, was found to be quite low. In a collected series of 89,168 persons receiving quinacrine, 126 developed psychotic symptoms. Unique corneal lesions are described that developed in a small series of industrial workers handling the drug in

quantity and in persons taking large doses of the drug.

The author emphasizes the fact that "hundreds of thousands of persons in the services were given quinacrine without ill effects."

### *Chloroquine*

Another compound, chloroquine diphosphate (synonyms, SN-7618, resochin and aralen) has been found to be a more potent antimalarial drug than quinacrine.<sup>55</sup> This compound—7-chloro-4-(4-diethylamino-1-methylbutylamino) quinoline diphosphate—was first synthesized and patented in Germany.<sup>56</sup> Two years later the patent granted in this country was assigned to Winthrop Chemical Company. During the North African Campaign, sontochin (SN-6911), a relative of chloroquine, was captured from the Germans, who were using it against malaria. This led to an extensive investigation of both drugs in this country.

Surrey and Hammer<sup>57</sup> synthesized samples of chloroquine and sontochin for testing, and additional samples were synthesized later by "several University laboratories under OSRD contract."<sup>58, 56</sup> Screening tests with avian malaria and extensive pharmacologic, clinical and field tests showed that both drugs had valuable antimalarial properties but that chloroquine was superior, with approximately the same antimalarial properties as quinacrine. The rapidity of absorption and lesser localization of chloroquine in tissues and organs contributed to the greater potency on lower dosage schedules and hence with lower plasma concentrations. One dose of chloroquine per week (0.5 gm) will suppress *P. vivax* and *P. falciparum* infections, and clinical malaria can be treated successfully in three to five days. Furthermore, the drug does not lead to discoloration of the skin. The toxic symptoms developing from therapeutic dosages parallel those of quinacrine. Mild and transient headache, visual disturbances, pruritus and gastrointestinal disturbances are the most common complaints. In the words of Loeb et al.,<sup>58</sup> "none of these manifestations have been constitutionally serious and all have been readily reversible."

Most and his associates<sup>58</sup> treated more than 1000 cases of acute vivax malaria, and compared the control of symptoms and toxicity by quinine, quinacrine and chloroquine. As might have been expected, each drug gave different results, but in general chloroquine controlled fever more quickly, reduced the parasitemia faster, lengthened the interval between relapses and gave less toxic symptoms.

Chloroquine will effect a complete cure of malignant tertian malaria. When taken prophylactically, this drug will not prevent infection, but it is effective as a suppressive. Clinical cures of vivax malaria are readily obtained, but relapses are not prevented.

of the drug is injected intramuscularly sixteen to twenty-eight hours after the last paroxysm. Also, this drug appears to be effective only in inhibiting *P. vivax* and not *P. malariae* or *P. falciparum*. Kaplan, Read and Becker<sup>74</sup> have studied the action of thiobismol in therapeutic quartan malaria more recently. This study shows that the drug has a predictable action in reducing the frequency of paroxysms in double or quotidian quartan malaria if the parasitemia prior to injection is below 10,000 per cubic millimeter. Again the drug was not effective on young or mature parasites. The absence of laboratory control of infections in most hospitals and the unpredictable interruptions of paroxysms when injections are not properly timed with the parasite cycle make the use of thiobismol against quartan infections impracticable.

### CHEMOTHERAPY

Advances in the chemotherapy of malaria are almost entirely the result of an extensive wartime research program. The program was dictated by the necessity of fighting in malarious areas and by the urgent need of prophylactic and curative drugs that would offset the grave loss of the source of quinine from the Netherlands East Indies. Although the losses from World War II are beyond calculation, mankind will benefit for years to come by the vision, skill and co-operation of American and British workers, who demonstrated how to use quinacrine most effectively, who synthesized and tested thousands of drugs and who proved the value of new antimalarial drugs.

Therapeutic problems with malaria involve the need of a drug to act as a prophylactic preventive of infection by killing the infective stages, or sporozoites, injected when the mosquito bites or by preventing the parasites from entering and from developing in the blood stream to cause the disease. In benign tertian malaria, a drug to be of specific value must produce not only a clinical cure but also a radical cure by destroying the hypothetical tissue stages of parasites that are responsible for relapses. The same requirement applies to drugs needed to produce a radical cure with latent malaria (*P. malariae*).

As previously stated<sup>1</sup> there was no agreement among clinicians in malarious areas about the dosage of quinine and quinacrine to be used in the treatment of malaria and about the results. It should also be pointed out that the dosages then in use for man were largely arrived at on empirical grounds. Little was known about their fundamental pharmacology, range of tolerance, most effective dosage schedules, mode of action on parasites and strain susceptibility to the two drugs.

### Quinacrine

At the beginning of World War II, quinacrine was the most effective antimalarial drug available.

The drug had an unfortunate reputation for toxicity, and no large quantities were being produced. Fortunately, the results of a concentrated pharmacologic and clinical testing program, combined with pharmaceutical skill, which enabled the manufacture of great quantities of this drug, made the difference between success and failure of military operations in tropical and subtropical theaters of war. New drugs were produced before the end of the war, but screening for antimalarial properties by animal injections, clinical testing, field trials and manufacture consumed too much time to make them a factor in field operations. Perhaps they can now be considered weapons to benefit the public health in peace.

The extensive synthesis of new compounds and the pharmacologic and clinical testing program in this country have been documented.<sup>75</sup> The broad organization that guided the emphasis and reasoning of the research projects will not be discussed here. The contributions, the majority of which are still unpublished, are so numerous that they can be discussed only briefly. To the discussion will be added the antimalarial studies and discoveries of British investigators that are of interest and practical application to clinicians.

Extensive pharmacologic, clinical, laboratory and field studies have made quinacrine one of the better known drugs. The pharmacologic behavior, advantages and disadvantages of this antimalarial agent are now known. The studies of Shannon and his collaborators<sup>76-78</sup> showed that the efficacy of quinacrine as a suppressive and as a clinical cure for malaria depended upon the plasma concentration of the drug. Analyses of blood concentration in man after the previously recommended dosage schedules revealed the difficulty and inadequacy of obtaining effective blood levels quickly. However, when a priming or loading dose of the drug was given on the first day, high plasma concentrations were obtained more quickly. The dosage is then lowered on the second day, and the required level can easily be maintained to complete the course.

Thus, the recommended therapeutic dosage of quinacrine for clinical malaria in adults is now two tablets of 0.1 gm (a total of 3 gr) and 1 gm (15 gr) of sodium bicarbonate by mouth every six hours for five doses and then one tablet of 0.1 gm three times daily for six days (total dosage, 2.8 gm in seven days).<sup>79</sup> Each dose should be taken with a full glass of water, sweetened tea or fruit juice after a meal to avoid gastric discomfort.

The principles involved with the correlation of plasma concentration for suppressive or therapeutic effects have been questioned.<sup>80</sup> Available data show that on the basis of plasma concentration quinacrine is over a hundred times more active than quinine. On the basis of oral dosage quinacrine is only three times more active. Thus, dosage schedules appear, in the words of Marshall,<sup>81</sup>

When great numbers of relapsing vivax malarial infections developed during the Pacific war, the extent and seriousness of the problem led to a reconsideration of the properties of existing antimalarial drugs. The revised dosage schedule with quinacrine provided radical cures with falciparum malaria, but the relapse rate with vivax malaria was not affected. Thus, plasmochin combined with quinine was the only known therapy that lowered relapse rates of vivax malaria. The high toxicity of plasmochin prevented its general use, but Most et al.<sup>104</sup> and Warthin and his co-workers<sup>105</sup> have used the combined plasmochin-quinine therapy to reduce relapses in vivax malaria. Nevertheless, less toxic analogues were sought. That search has now resulted in the discovery of two new and less toxic 8-aminoquinoline compounds<sup>106,107</sup> called pentaquine (SN-13,276) and SN-13,274. The latter drug has not been named officially, but the name isopentaquine has been suggested.<sup>107</sup> These drugs when used singly in combined therapy with quinine are said to reduce the relapse rate of vivax malaria by 85 per cent. The compounds are not commercially available at the time of writing, but they should become available in the near future.

The recommended dosage applies only to clinical and radical cures of vivax malaria with pentaquine and quinine. The drugs are too toxic for suppressive or prophylactic use. "A daily dose of 60 mg base (equivalent to 80 mg of diphosphate) and 2 gm of quinine administered concurrently" in divided doses every four hours for fourteen days is sufficient to produce radical cure of severe infections due to *P. vivax*. The drug is to be given only under close medical supervision and in a hospital if possible.<sup>106</sup>

Thus, we now have new drugs for the prophylaxis, suppression and treatment of malaria. Each drug appears to have special attributes against certain species and stages of plasmodia, but no drug answers the ideal requirements. The evidence is not sufficient to offer a final evaluation of any one of the new drugs. Furthermore, the claims made by some clinicians or malarialogists will probably be discredited later by others. When those who test new drugs realize that malaria occurs in many races of people having different body weights, habits and diets, and natural or acquired immunity, the results of clinical trials can be compared more readily. The conditions of trial in various parts of the world are also dissimilar. Thus, to avoid controversy when results are compared, the many and varying factors of the drug tests should provide the foundation for interpretation.

## REFERENCES

- 54 McClure R. D. and Lam C. R. Malaria from bank blood trans-  
fusions. *Surg. Gynec. & Obst.* 80:261 1945.
- 55 Sbaroff, J. G. Geiger J. and Selzer I. Malaria transmitted by  
bank blood transfusion report of two cases. *Am. J. Clin. Path.*  
15:494 1945.
- 56 Fischer W. J. H. and York C. L. Quartan malaria occurring sub-  
sequent to blood transfusion report of case. *New Eng. J. Med.*  
235:411-413 1946.
- 57 Schrack W. D. Jr. Malaria infection acquired through blood  
transfusion report of case. *Pub. Health Rep.* 61:1630 1946.
- 58 Teasley G. H. Malaria following blood transfusion report of case.  
*Proc. Staff Meet. Mayo Clin.* 21:289-295 1946.
- 59 Rubenstein A. D. Shulman M. H. and Merrill, D. Hazard of  
transfusion malaria after war. *New Eng. J. Med.* 233:234-237  
1945.
- 60 Lozner E. L. and Newhouser L. R. Studies on transmissibility  
of malaria by plasma transfusions. *Am. J. M. Sc.* 206:141-146  
1943.
- 61 Crawford, G. M. Syphilis. *New Eng. J. Med.* 238:87-93 121-128  
and 152-159 1948.
- 62 Coatsney G. R. and Young M. Taxonomy of human malaria  
parasites with notes on principal American strains. In *A Sym-  
posium on Human Malaria with Special Reference to North America  
and the Caribbean Region* 398 pp. Publication No. 15. Wash-  
ington D. C. American Association for the Advancement of  
Science 1941. Pp. 19-29.
- 63 Ehrman, F. C., Ellis J. M. and Young M. D. *Plasmodium vivax*  
Chesson strain. *Science* 101:377 1945.
- 64 Whorton C. M., et al. Chesson strain of *Plasmodium vivax* malaria.  
*J. Infect. Dis.* 80:223-227 1947.
- 65 Kaplan L. I. Read H. S. and Becker, F. T. Use of quantitative  
parasite inoculation doses in *Plasmodium vivax* malaria therapy.  
*Arch. Neurol. & Psychiat.* 56:65-73 1946.
- 66 Geiman Q. M. Cobbe, T. S. Jr. and Caskey W. H. Unpublished  
data.
- 67 Butler F. A. and Sapero J. J. Pacific vivax malaria in American  
Negro. *Am. J. Trop. Med.* 27:111-115 1947.
- 68 Boyd M. F. Observations on naturally and artificially induced  
quartan malaria. *Am. J. Trop. Med.* 20:749-798 1940.
- 69 Becker F. T. Kaplan L. I. and Read H. S. Variations in suscep-  
tibility to therapeutic malaria. *Am. J. M. Sc.* 211:680-685  
1946.
- 70 Saunders G. M. and Scott V. Preservation of *Plasmodium vivax*  
by freezing. *Science* 106:300, 1947.
- 71 Coggeshall L. T. Preservation of viable malaria parasites in frozen  
state. *Proc. Soc. Exper. Biol. & Med.* 42:499-501 1949.
- 72 Maxwell R. D. Low temperature freezing of malaria parasites.  
*Am. J. Trop. Med.* 23:123-131 1943.
- 73 Young M. D. McLendon S. B. and Smart R. G. Selective ac-  
tion of thioisomol on induced malaria. *J. A. M. A.* 122:492-  
494 1943.
- 74 Kaplan L. I. Read H. S. and Becker F. T. Action of thioisomol  
on therapeutic quartan malaria. *J. Lab. & Clin. Med.* 31:735-  
741, 1946.
- 75 *A Survey of Antimalarial Drugs 1943-1945*. Two volumes. Edited  
by F. Y. Wiselogle. Ann Arbor Mich. J. W. Edwards 1946.
- 76 Shannon J. A. Earle D. P., Jr. Brodie B. B., Taggart, J. V. and  
Berliner R. W. Pharmacological basis for rational use of at-  
abrine in treatment of malaria. *J. Pharmacol. & Exper. Therap.*  
81:307-350 1944.
- 77 Shannon J. A. and Earle D. P. Jr. Recent advances in treatment  
of malaria. *Bull. New York Acad. Med.* 21:467-481 1945.
- 78 Shannon J. A. Study of antimalarials and antimalarial activity  
in human malaras. *Harvey Lect.* (1945-1946) 41:43-89 1947.
- 79 *Malaria Chemotherapy with Atabrine Dihydrochloride* 56 pp.  
Winthrop Chemical Co., 1945.
- 80 Marshall E. K. Jr. Scientific principles, methods and results of  
chemotherapy 1946. *Medicine* 26:155-166 1947.
- 81 Armed Medical Research Laboratory. Plasma quinacrine con-  
centration as function of dosage and environment. *Arch. Int.  
Med.* 78:64-107 1946.
- 82 Fairley H. Chemotherapeutic suppression and prophylaxis in  
malaria experimental investigation undertaken by medical re-  
search teams in Australia. *Tr. Roy. Soc. Trop. Med. & Hyg.* 38:  
311-365 1945.
- 83 London I. M. Kane C. A., Schroeder, E. F., and Most, H. De-  
layed primary attack of vivax malaria. *New Eng. J. Med.* 235:  
405-410 1946.
- 84 Findlay G. M. Toxicity of mepacrine in man. *Trop. Dis. Bull.* 44:  
763-779 1947.
- 85 Board for the Coordination of Malarial Studies. Activity of new  
antimalarial agent, chloroquine (SN 7618). *J. A. M. A.* 130:1069  
1946.
- 86 Blanchard K. C. Antimalarial drugs. *Ann. Rev. Biochem.* 16:  
587-604 1947.
- 87 Surrey A. R. and Hammer H. F. Some 7 substituted 4-amin-  
quinoline derivatives. *J. Am. Chem. Soc.* 68:113-116 1946.
- 88 Most H. et al. Chloroquine for treatment of acute attacks of vivax  
malaria. *J. A. M. A.* 131:963-967 1946.
- 89 *Malaria Chemotherapy with Atabrine Dihydrochloride* 24 pp.  
Winthrop Chemical Company 1946. Pp. 1-24.
- 90 Rice J. B. Dosage of antimalarial drugs. *J. A. M. A.* 132:104  
1946.
- 91 Editorial. Triumph against malaria. *Brit. M. J.* 2:653 1945.
- 92 Editorial. Paludrine. *Lancet* 2:639 1945.
- 93 Warrington Yorke memorial number. *Ann. Trop. Med.* 39:137-  
236 1945.
- 94 Chlorguanide hydrochloride. 11 pp. *Bull. Abbott Laboratories* 1948.

The effective dosage of chloroquine (aralen) for suppression of malaria is 0.3 gm of the base, but the manufacturers produce the drug as a diphosphate in tablets of 0.25 gm, and hence 0.5 gm (two tablets of 0.25 gm) in a single dose once in a week is recommended<sup>88, 89</sup>. In clinical malaria, an initial dose of 1 gm followed by an additional 0.5 gm in six to eight hours and then a single dose of 0.5 gm on each of two consecutive days is recommended<sup>88, 89</sup>. (The total dosage of 2.5 gm, or ten tablets of 0.25 gm each, in three days is higher than that used by Most et al<sup>90</sup>—1.5 gm—for acute vivax malaria, but the higher dosage is calculated to make allowance for the salt content of the commercial preparation.)

### Paludrine

An entirely different type of antimalarial drug was discovered during the war by British investigators and announced in 1945<sup>91, 92</sup>. This drug, originally called paludrine (synonyms-M-4888, SN-12,837 and chlorguanide hydrochloride),<sup>75, 93, 94</sup> represents another milestone in the efforts of man to find an ideal drug for true causal prophylaxis and treatment of malaria.

A series of researches<sup>93</sup> was initiated in an effort to explore compounds with different ring structures that would give antimalarial activity against the tissue stages of the parasites. The pyrimidine compounds were selected because of the need for this ring structure as a building block for nucleoproteins and because of the importance of nuclear components for cell growth and multiplication. The chance that analogues of essential pyrimidines might interfere with growth in the way that sulfonamides interfere with utilization of para-aminobenzoic acid seemed worth investigation.

Anilino-pyrimidines were prepared and tested and the compound "2666" was found to have antimalarial activity against *P. gallinaceum* in chicks. After the synthesis and testing of many more compounds, it was found that compounds containing a guanidine group and without the pyrimidine ring exhibited outstanding antimalarial properties. Thus, the new drug N<sub>1</sub>-p-chlorophenyl-N<sub>1</sub>-isopropylbiguanide acetate, called paludrine, was developed<sup>95</sup>. The salt of this drug now in use is the hydrochloride.

This drug was screened against four species of avian plasmodia and then tested in England<sup>96, 97</sup> and Australia<sup>98, 99</sup> against types of malaria in human beings. The clinical testing in Australia involved 200 volunteers infected with the highly virulent New Guinea strains of parasites. The results of clinical trials in this country have not been published, but reports of more recent field trials are beginning to appear. The results of comparative trials with chloroquine and paludrine under identical conditions and in a variety of patients of different age groups will be awaited with interest.

The prime advantage of paludrine over other antimalarial drugs is that it is a true causal prophylactic for falciparum malaria, giving complete protection against this parasite when the proper dosage is taken. The drug will also give radical cures of this lethal type of malaria. Although the drug will suppress and give clinical cures of vivax malaria, relapses will occur. The drug acts against the hypothetical tissue stages of falciparum malaria and against the asexual stages of *P. falciparum* and *P. vivax* in blood that are responsible for the clinical symptoms. The action against the circulating stages consists of prevention of multiplication and sterilization of gametocytes so that they cannot develop into infective stages in the anopheline mosquito. The rapid excretion of the drug within forty-eight hours<sup>100, 101</sup> and its failure to stop gametocyte production in falciparum malaria<sup>94, 102</sup> are disturbing findings that need more complete investigation.

The toxic dose is approximately two hundred times the therapeutic dose, so that the drug is relatively harmless. Dosages over 1 gm daily may give rise to gastrointestinal disturbances such as vomiting, abdominal pain, diarrhea and urinary symptoms including hematuria, sheets of epithelial cells and hyaline or granular casts. The symptoms subside when the drug is discontinued<sup>94, 99</sup>.

The dosage for causal prophylaxis of *P. falciparum* infection is 0.1 gm twice weekly. A single dose of 0.3 gm once weekly is usually effective in suppressing clinical symptoms and parasitemia of both malignant and benign tertian malarias. In a radical cure of falciparum malaria, 0.3 gm once daily for ten days is usually effective. For vivax malaria, the same dosage may be employed, but no radical cure can be obtained and clinical improvement is very much slower than that after administration of quinacrine or chloroquine. Viswanathan and Bailey<sup>102</sup> treated 8 patients with quartan malaria and found that the temperature persisted from two to five days after the first dose of the drug, which was in contrast to the short duration of temperature and parasite prevalence in falciparum malaria. More field trials are needed before the efficacy against quartan malaria can be assessed.

### Pentaquine

Before World War II, the only drug that was effective against the gametocytes of *P. falciparum* was plasmochin (synonym, pamaquine). The relatively low relapse rate with vivax malaria after combined therapy with plasmochin and quinine had been noted by a number of investigators in India and Panama<sup>103</sup>. Although plasmochin was included in the initial recommended therapy for malaria by the Army, high toxicity and little need for gametocidal properties caused its use to be discontinued.

suggests that she could have been pregnant. She then had a heavy flow. How long that lasted, whether she assumed that that was a menstrual period, or whether it was accompanied by pain, we do not know. Presumably it means that she had a very diffuse period and then had re-establishment of the menses, because nothing is said about further irregularity of bleeding until finally she is said to have missed the last period. In other words, two weeks before admission she was due to have a period but did not have one. What could have become of this pregnancy, if she were pregnant? It seems unlikely that she could have had an abortion of a living two months' fetus during the "heavy flow," because that would have impressed her sufficiently for her to have reported it as a miscarriage. She could, however, have had a blighted ovum and completely aborted it during the period of "diffuse flowing." It seems rather unlikely that she could have had a so-called missed abortion — that is, a blighted ovum that remained in the uterus, otherwise we would not expect her to have had re-establishment of periods, which we are assuming although it is not so stated.

She could also have had a tubal pregnancy six months earlier, which ended with the death of the fetus. That might well be followed by a profuse flowing and then by re-establishment of the menses. One can hardly believe that she terminated a tubal pregnancy with tubal abortion or tubal rupture because there is no history of pain or shock or anything of that sort. I think we can be quite sure that, whatever sort of pregnancy she may have had then, the fetus did not go on growing. As for the recently missed period, she was about two weeks overdue, and we will leave the possible significance of that until later. I notice that no information about the size of the uterus is given. Is there anything in the record about its size? Presumably it was not particularly enlarged or, I suppose, it would have been mentioned.

DR DANIEL S. ELLIS: Dr Meigs did a pelvic examination after the fluid had been withdrawn, but he did not think the uterus was abnormally large, this mass in the left vault was something very vague.

DR SMITH: I do not believe that the laboratory work has much bearing on the diagnosis. I see, however, that there is no report on the urine examination, presumably, it was negative since nothing is said about it.

The essential points about this patient are that she developed ascites with bloody fluid, possibly a pelvic mass, occurring in a woman who was previously healthy without any history of cardiac, renal or liver disease. To my mind, that is strongly suggestive of a malignant tumor in the abdomen. However, she had missed a period recently and she had a positive test for pregnancy. Furthermore, she had not only bloody fluid in the ab-

domen but also a great deal of bleeding, and I presume that we have to stop and consider whether the recent pregnancy was concerned in this condition at all. I do not recall ever hearing of ascites developing in a normal intrauterine or any sort of extrauterine pregnancy. It is worth noting perhaps that the ascites began almost as soon as this hypothetical recent pregnancy, because she noticed swelling of the abdomen ten days before admission, and presumably the ascites had begun some few days before she had noticed it. The period was due two weeks before admission, but at the time she noticed the abdominal swelling she was only four days over the period and that puts the onset of ascites back to a time when she could not have been more than ten to fourteen days' pregnant. I do not believe that we need dwell on a possible pregnancy having anything to do with the ascites.

It is quite possible, of course, that she had a coincidental pregnancy. Suppose that she had a malignant abdominal tumor, with bloody ascites, and just happened to become pregnant at that time. In that case the pregnancy would not be of any particular importance at the moment. However, there are one or two suspicious things about the case. One of them, of course, is that an obstetrician has been invited to discuss it, and it is hard to escape the feeling that we have to tie this up with pregnancy somehow. But there is another, more objective suspicion, and that is the extent of the bleeding. The woman had not only bloody fluid but also a fairly profuse intraperitoneal hemorrhage. According to the count, I should think there was a good deal more blood in the fluid than one ordinarily gets with a malignant lesion of the abdomen, such as a cancer of the ovary. This bleeding, of course, occurred after admission to the hospital — at least, the greater part of it did, because on admission she had a large, distended abdomen, but she had a normal blood pressure and pulse and the hemoglobin was 12.2 gm, which is not far below normal. What possible connection could a recent pregnancy have with this? Could a pregnancy in any way have contributed to this bleeding? Could she perhaps have had a pelvic tumor with ascites, either benign or malignant, and could the bleeding have occurred into this ascitic fluid from the pregnancy, whatever the pregnancy may have been? In that event, of course, there would have been the disadvantage of having to make two entirely separate diagnoses, which is somewhat hazardous as a rule. Furthermore, the only way that this amount of blood in the abdomen could have resulted from a pregnancy would be rupture of the uterus or an ectopic pregnancy. In the first place, the pregnancy as I pointed out earlier, was at the most four weeks along. Spontaneous rupture of a uterus with a normal intrauterine pregnancy is exceedingly rare as early as that. It does occur, but usually in the third or

- 95 Curd F H S, Davey D G and Rose F L. Studies on synthetic antimalarial drugs. X. Some biguanide derivatives as new types of antimalarial substances with both therapeutic and casual prophylactic activity *Ann Trop Med* 39 208-216 1945
- 96 Adams, A R. D. et al. Studies on synthetic antimalarial drugs. XIII. Results of preliminary investigation of therapeutic action of 4888 (paludrine) on acute attacks of benign tertian malaria *Ann Trop Med* 39 225-231 1945
- 97 Macgraith B G, et al. Studies on synthetic antimalarial drugs. XIV. Results of preliminary investigation of therapeutic action of 4888 (paludrine) on acute attacks of malignant tertian malaria. *Ann Trop Med* 39 232-236, 1945
- 98 Land Headquarters Medical Research Unit Cairns. Researches on "Paludrine" (M. 4888) in Australia. *M J Australia* 1 234-236 1946.
- 99 Fairley, N H et al. Researches on paludrine (M 4888) in malaria experimental investigation undertaken by L.H.Q. Medical Research Unit (A I F) Cairns Australia *Tr Roy Soc Trop Med. & Hyg* 40 105-162 1946
- 100 Macgraith B G, Tottey, M M, Adams A R D, and Andrews W H. Absorption and excretion of paludrine in human subject. *Ann Trop Med* 40 493-506, 1946
- 101 Schmidt L H, Hughes H B and Smith C C. On pharmacology of N-Parachlorophenyl, -N-isopropylbiguanide (Paludrine). *J Pharmacol & Exper Therap* 90 233-253 1947
- 102 Viswanathan D K and Bailey J D. Experiments with paludrine in chemotherapy of malaria. *Indian J Malariol* 1:10-17, 1947
- 103 Napier L E. Present status of antimalarial drugs. *New Eng J Med* 233 38-43 1945
- 104 Most H et al. Combined quinine plasmoquin treatment of virus malaria. effect on relapse rate. *Am J M Sc* 212:50-60 1945
- 105 Warthin T A, Levine S A, and Evans R. R. Observations on treatment with chloroquine (SN 7618) and combined quinine and plasmoquin. *New Eng J Med* 238 467-469 1948.
- 106 Board for the Coordination of Malarial Studies. Activity of antimalarial agent pentaquine (SN-13 276). *J A M A* 137 321-323, 1946
- 107 Coatsney G R. Personal communication

## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

TRACY B MALLORY, MD, *Editor*

BENJAMIN CASTLEMAN, MD, *Associate Editor*

EDITH E PARRIS, *Assistant Editor*

### CASE 34281

#### PRESENTATION OF CASE

A twenty-seven-year-old housewife entered the hospital because of abdominal swelling.

The patient had felt well until ten days before admission, when she began to notice abdominal swelling and nausea. Five days before admission she had pronounced abdominal fullness with vomiting, belching and passage of flatus. She was unable to take solid food.

She had been married five years and had two children. In the past three years she was unable to become pregnant. Her menstrual periods were regular until six months previously, when she skipped two menses and then had a heavy flow, and two weeks previously, when she missed her expected period.

There was no history of fever, jaundice or edema of the ankles.

Physical examination disclosed a well developed woman in no distress. The chest was clear. There was slight elevation of the right leaf of the diaphragm. The abdomen was enlarged, and there were generalized tenderness and shifting dullness. Pelvic examination revealed a soft, poorly defined, rounded mass in the left fornix. The uterus was freely movable, and there was no tenderness.

The temperature, pulse and respirations were normal. The blood pressure was 115 systolic, 70 diastolic.

Examination of the blood revealed the patient to be Rh+. The hemoglobin was 12.2 gm, and the white-cell count was 8900, with 71 per cent neutrophils. The total serum protein was 4.91 gm per 100 cc, with an albumin-globulin ratio of 1.90. The prothrombin time was 26 seconds (control, 17 seconds). The chloride was 99 milliequiv per liter, and the nonprotein nitrogen 18 mg per 100 cc. A van den Bergh reaction was normal, a cephalin flocculation test was ++ in forty-eight hours, and the bromsulfalein test showed 4 per cent retention of the dye. A blood Hinton test was negative. The stool gave a negative guaiac test.

X-ray examination revealed at least two rounded shadows of increased density in the right lung and another in the left and a small amount of fluid in the right pleural cavity. In the abdomen there was an area of hazy density apparently due to fluid, and a shadow suggesting the possibility of a mass in the pelvis. A gastrointestinal series was negative.

By the third hospital day the abdominal girth had increased from 91 to 96 cm, and there was a greenish discoloration in the umbilicus. An abdominal paracentesis yielded 4 liters of bloody fluid, with a specific gravity of 1.024, and a total protein of 3.73 gm per 100 cc. Cytologic examination disclosed 777,200 red cells, 560 polymorphonuclear leukocytes and 20 lymphocytes per cubic millimeter. By the fifth hospital day the hemoglobin was reduced to 7.5 gm, with a red-cell count of 2,480,000, and later to 6.6 gm, with a red-cell count of 2,200,000 and a white-cell count of 4500. A mouse test of the urine for pregnancy was positive. By this time the patient was beginning to have a low-grade fever. She was given two successive transfusions, and an operation was performed on the twelfth hospital day.

#### DIFFERENTIAL DIAGNOSIS

DR JUDSON A SMITH. Let us pause to analyze the menstrual history. Although it is inadequate we can perhaps make certain deductions from it. In the first place, the fact that the patient had missed two periods six months previously

of the pregnancy. The specimen of the fluid was sent to the cytologic laboratory, and at the time of operation we had a telephone report that no malignant cells had been seen in it.

#### CLINICAL DIAGNOSIS

Ovarian tumor

DR SMITH'S DIAGNOSIS

Chorioepithelioma, extrauterine, with pulmonary metastases

#### ANATOMICAL DIAGNOSES

*Papillary serous adenocarcinoma*

Uterine pregnancy

#### PATHOLOGICAL DISCUSSION

DR TRACY B MALLORY: Dr Meigs, will you tell us what you found at operation?

DR JOE V MEIGS: There were 3 or 4 liters of bloody fluid in the abdomen. The uterus was enlarged and was consistent with an early pregnancy. In the left ovary was an encapsulated, solid tumor, 20 cm in diameter, which on opening was filled with dark reddish, necrotic material. The other ovary was slightly cystic. There was no evidence of metastases anywhere within the abdomen, the lymph nodes were not enlarged, and there were no papillary projections on the peritoneum. A total hysterectomy and bilateral salpingo-oophorectomy were done.

DR MALLORY: The tumor was a solid ovarian carcinoma, with very extensive hemorrhagic necrosis of a large portion of the tumor. The cells microscopically were very anaplastic, but showed a tendency to papillary formation. The uterus disclosed a perfectly normal pregnancy in one corner, with a fetus 15 cm in length.

The patient returned to the hospital four months after discharge because of epileptiform seizures which were undoubtedly due to cerebral metastases, and died at home a few months later.

#### CASE 34282

##### PRESENTATION OF CASE

A twenty-two-year-old unmarried graduate nurse was admitted to the hospital.

She had been well until nine months before entry, at which time she had an attack of fever and abdominal pain associated with prolongation of menstrual periods. At that time she was studied at

another hospital, and some suspicion of paratyphoid infection was entertained but never proved. A low-grade fever persisted for several weeks and then spontaneously disappeared. Eight months before entry she had, for the first time, considerable pain with the catamenia and more profuse flowing both in amount and in duration than she had previously had. Subsequent to this, the periods were irregular, occurring every thirty-four to forty days rather than every twenty-nine days as previously. With each period she had severe lower abdominal cramps and backache. Between the periods she felt reasonably well and was able to continue her work. Five days before admission to the hospital she was examined. At that time it was found that the last menstrual period had begun nine days previously and had been extremely painful, with profuse flow, lasting for seven days. Associated with the period was a temperature as high as 101°F. The patient was unable to work and was so uncomfortable that she had to go to bed. At the time of examination the pain in the abdomen was still present although she had had no menstrual flowing for two days. Physical examination at that time showed diffuse tenderness throughout the lower abdomen, most marked in the right lower quadrant and associated with a moderate degree of resistance in the latter location. On bimanual pelvic examination the pelvic organs were not made out. There was some tenderness in the right vault, no mass was felt. The cervix was normal to inspection and to palpation. On the anterior vaginal wall there was a very tiny nodule, which seemed to be compatible with an endometrial implant. There was some tenderness also in the left vault, but not enough to interfere with the examination, and no masses were felt. Rectal examination gave no additional information. Because of persistence of the symptoms she was admitted to the hospital.

Except for an appendectomy five years before entry, the past history was irrelevant.

On physical examination no additional information was obtained.

The temperature, pulse and respirations were normal. The blood pressure was 130 systolic, 70 diastolic.

The urine was normal. The white-cell count was 10,700, with 53 per cent neutrophils, 1 per cent large lymphocytes, 36 per cent small lymphocytes, 8 per cent monocytes and 2 per cent eosinophils.

fourth month. If the uterus was ruptured, one would have expected some external bleeding. Also, against either a ruptured uterus or ectopic pregnancy is the fact that the bleeding, although profuse, had apparently not been sudden. It occurred over a few days, and it did not produce pain or any symptoms of collapse, which we associate with rupture of a tubal pregnancy or rupture of a uterus. On the whole, I think we can dismiss the idea of a ruptured uterus in any sort of pregnancy.

On the other hand, one cannot get away from the fact that there was very profuse bleeding, as well as a positive Aschheim-Zondek test, and one wonders if the whole thing can be accounted for by a particular type of tumor. A chorioepithelioma will produce all these signs. It is a very rapidly growing tumor and is notorious for invading blood vessels. It could easily produce this amount of bleeding, as well as the mass in the pelvis, and could account for the positive Aschheim-Zondek test. I believe that a malignant tumor, a chorioepithelioma, is the most probable diagnosis. The possible pregnancy six months before admission is an obvious source. Whether it was a blighted ovum or a complete abortion or a pregnancy, a chorioepithelioma could still have developed in the tube or in the uterus. The fact that six months elapsed is not against that diagnosis because it is well known that there may be a long latent period between pregnancy and the development of this tumor. It is also possible, of course, for a chorioepithelioma to develop coincidentally with pregnancy, although I think it is rather unlikely that a chorioepithelioma could have developed during the past month at the onset of this hypothetical recent pregnancy. And, of course, when one gets right down to it the patient was not necessarily pregnant at all because she could have had a teratoma with chorioepitheliomatous elements in it. That is a rather farfetched diagnosis, but it has happened.

There are a number of things that would help us to confirm this diagnosis. Chorioepithelioma is well known to metastasize early and very frequently to the lung. If these pulmonary shadows on the x-ray film are consistent with metastatic tumor, I should think it would go a long way toward confirming that diagnosis. Another procedure, which was not recorded but which I am

sure must have been done, is examination of the fluid for malignant cells. Then there is the question of the quantitative Aschheim-Zondek test. Perhaps that was performed. This tumor frequently metastasizes to the vagina as bluish nodules that are quite diagnostic. I do not suppose that if such nodules had been noticed they would have been included in the record—that would have made the diagnosis too easy. I think that the most important clue we can ask for is from the X-ray Department. If the presence of tumor is not confirmed, I still think that she probably had a malignant tumor, most likely a chorioepithelioma. I do not believe that one can decide where it originated, on the information we have, but one can draw certain deductions. It is quite unlikely, of course, that it was growing inside the uterus because there had been no recent uterine bleeding. It could have been an intramural nodule. In that case, the abdominal symptoms were probably due to the growth of a metastasis because had the tumor grown rapidly through the uterine wall to involve the adjacent structures, I would expect the tumor not to be freely movable and so easily felt. My guess would be, if she had a chorioepithelioma, that it probably originated outside the uterus.

DR STANLEY M. WYMAN: The masses described in the right lung are in the midlung field, the third nodule lies in the left lower-lung field. Examination about three weeks later showed the three nodules to have increased definitely in size. They have an appearance that is quite characteristic of metastatic disease. The film of the abdomen shows nothing more than probable fluid. I cannot make out a definite mass and I can see no evidence of unusual calcification.

DR ELLIS: This patient was admitted to the hospital with a diagnosis of cirrhosis of the liver, primarily because of the ascites and the fact that nausea and vomiting played a predominant role in the symptoms in the ten days prior to admission. When she came in, it was obvious when one saw her and went into the history carefully and from the various laboratory studies that she did not have cirrhosis. Regarding Dr. Smith's questions about the period that she had six months prior to admission, the patient herself described it as a miscarriage although careful questioning did not reveal that she had actually identified the products

spasm and tenderness in the right lower quadrant, and this suggests a dermoid rather than a follicular cyst. I shall make a diagnosis of twisted dermoid cyst of the right ovary

DR BENJAMIN CASTLEMAN The preoperative diagnosis that Dr Leland S McKittrick made was "pelvic pain, cause undetermined" Can you tell us about the operation, Dr McKittrick?

DR JOHN B MCKITTRICK This patient was seen by several doctors, who were unable to make a more accurate diagnosis The question of pregnancy or pelvic inflammatory disease was raised, but there was no reasonable evidence for such a diagnosis She had no vaginal discharge The cervix was perfectly normal, there was no suggestion of pelvic inflammatory disease either clinically or by physical examination Physical examination was difficult because of the mechanical situation She was very large, with an extremely difficult pelvis to examine purely because of the size Even under ether it was not easy to determine what was in the pelvis We approached the situation with no diagnosis except excruciating pelvic pain

#### CLINICAL DIAGNOSIS

Pelvic pain, cause undetermined

#### DR ULFELDER'S DIAGNOSIS

Twisted dermoid cyst of ovary

#### ANATOMICAL DIAGNOSIS

*Tuberculous salpingitis and endometritis*

#### PATHOLOGICAL DISCUSSION

DR MCKITTRICK At the time of operation we were surprised to find that both tubes were involved in the process The left was worse than the right It was swollen, and the fimbriated end obliterated The tube was nodular throughout The right tube was obstructed just proximal to the fimbriated end and was nodular but less swollen and thickened than the left tube Over the anterior surface of the uterus were multiple, white, miliary nodules Our gross diagnosis at operation was tuberculosis A curettage had been performed preliminary to laparotomy, but very little tissue was obtained and nothing characteristic was determined on appearance The diagnosis of tuberculosis was subsequently confirmed grossly by Dr

Castleman, who saw the patient in the operating room

We removed a portion of the left tube for a biopsy Elsewhere in the peritoneal cavity there was no evidence of disease After much discussion it was decided not to do anything more surgically and to send the patient to a sanatorium

DR CASTLEMAN Our permanent microscopical sections showed an active tuberculous process not only in the tube but also in the endometrium

DR MCKITTRICK Within two months after arrival at the sanatorium, the symptoms became so severe and persistent that it was thought advisable to do a hysterectomy At the time of the second operation the disease had spread although the ovaries were not involved A supravaginal hysterectomy was done The patient remained well for about two months after the laparotomy and then had a recurrence of severe excruciating pain, with profuse discharge from the vagina, and later developed urinary symptoms I think it was established that the vaginal discharge was caused by tuberculosis, but the urinary-tract disease was never, to my knowledge, proved to be tuberculosis She was treated with streptomycin for three months, but it was stopped when she developed severe vertigo I have not heard from her recently, but ten months after the operation she was still having a difficult time, still having pain and profuse discharge For a while the streptomycin slowed up the discharge I do not know what the course was from that time on Dr King saw the patient It would be interesting to hear what he has to say

DR DONALD S KING I saw her after her first operation and found no active pulmonary tuberculosis

DR MCKITTRICK We looked hard for generalized tuberculosis but found none whatsoever

DR CASTLEMAN Do you think that the entire uterus should have been taken out?

DR ULFELDER In retrospect, there is no question that she had tuberculosis of the cervix which accounted for the continued vaginal discharge

A PHYSICIAN I saw this patient two days ago, which is just about two years since she was in this hospital She now has a vesicovaginal fistula, and they are finding tubercle bacilli in the urine on each examination There is some discussion now about taking out the kidney It is a rather stormy outlook

The red cells and platelets appeared normal. The photohemoglobin was 15.1 gm. The sedimentation rate was 0 mm in 15 minutes, 1 mm in 30 minutes, 1 mm in 45 minutes, and 2 mm in 60 minutes.

On the third hospital day a laparotomy was performed because of the persistence of abdominal pain.

#### DIFFERENTIAL DIAGNOSIS

DR HOWARD ULFELDER: This is the history of a young unmarried woman who had two attacks of abdominal pain and fever coincident with the menses. The first attack was nine months prior to admission and the second, two weeks before admission. In the interval between attacks she was well enough to work but noticed a change in the menstrual cycle, the interval increased somewhat, and she developed severe cramps, which apparently she had not had before the present illness. The fever and abdominal pain suggest to me that we are presented with either an inflammatory lesion or ischemia, although one occasionally sees tumors with fever. The location of this lesion was apparently the right lower quadrant, probably in the true pelvis because of spasm and tenderness of the right lower quadrant and some tenderness, which prevented an adequate pelvic examination. I wonder if it was unilateral in the pelvis? Certainly the majority of physical findings were on the right side, but we are told that she had some tenderness on the left side also. Is there anything that can help us localize this lesion more precisely? Were any x-ray films taken? Did she have pyelograms or a barium enema?

DR JOHN B. MCKITTRICK: No.

DR ULFELDER: Apparently, the gastrointestinal and the urinary tracts were not believed to be involved. There was a normal sedimentation rate and hemoglobin and an essentially normal differential count, despite elevation of the white-cell count.

Does the past history help? An appendectomy had been performed five years previously. It is conceivable that something incident to the appendectomy produced the present picture. One thinks of a foreign body, either a fecalith or some other foreign body, left at the time of appendectomy, and producing abscess in the right pelvis. I consider these unlikely, however.

Is there anything in the history to suggest pelvic inflammatory disease? We have no history of vaginal discharge or exposure to gonorrhea.

Does the character of onset of this illness suggest a complication of pregnancy? We are not told whether the bleeding with the first attack was at the expected time of menstruation or whether there had been an abnormal interval between the last normal period and the period described as occurring at the time of the original attack of pain and fever. One must consider the possibility that this patient had a pregnancy with an early miscarriage, with the retention of some products of conception and recurrent infection in the endometrium. To try to interpret the menstrual history is almost futile. The menstrual history that this patient gave may be that of anyone, including a girl who has no organic lesion.

We have been presented with the statement that she had a tiny nodule in the anterior vaginal wall, which seemed to be compatible with an endometrial implant. Endometriosis of the vaginal wall is rare. Endometriosis as an explanation of this picture in a twenty-two-year-old woman is extremely rare. I do not consider endometriosis a very strong possibility in this patient.

To summarize, it is my opinion that this patient was suffering from a lesion in the right pelvis connected with the genital tract, which was either inflammatory or ischemic in character. Foreign body is a possibility, I do not consider it very seriously. Pelvic inflammatory disease is a strong possibility. I have mentioned the possibility of a retained placental fragment, that must be considered. Tuberculosis, lymphoma or congenital anomaly might explain the picture. The congenital anomaly that I have in mind, as a possible but not a likely explanation, is a double uterus with a very small uterus on the right side and a normal one on the left side, with some obstruction in the canal from the small right-sided uterus. I do not consider it seriously but merely mention it.

My belief is that this patient suffered from a lesion that was primarily ischemic and recurrent, and, therefore, I believe that a cyst of the right ovary with torsion is the most likely diagnosis. I had hoped an x-ray film might help in deciding whether or not a cyst was present, and if present, whether it contained calcification. The lesion seemed to be anterior, in that the patient had

personnel during the war and has also occurred not infrequently in civilian practice

Attention is now being focused on a new mode of transmission of this serious form of hepatitis — namely by means of the unsterile or inadequately sterilized needle or syringe. British workers have called attention to the frequent occurrence of such transmission during the treatment of syphilitic patients, in whom it is considered to be the chief cause of the so-called arsphenamine hepatitis<sup>1 2</sup>. It has also been implicated as a possible cause of an outbreak of hepatitis in a diabetic clinic<sup>3</sup> and as the cause of similar illnesses in patients who are under treatment with penicillin for a variety of diseases<sup>4-6</sup>. Furthermore infectious hepatitis can be transmitted from one patient to another by syringes used for the collection of blood<sup>7</sup> and this was probably the mode of transmission in the diabetic clinic.

The syringe transmission of hepatitis is made possible by the fact that very little blood or serum of an infected carrier is necessary to transmit the disease and also by the fact that the causative virus is a hardy one that resists the cursory types of sterilization that are often practiced in busy clinics in which numerous blood samples are drawn or many injections have to be given in a short time. Mendelssohn and Witts<sup>8</sup> showed that during an ordinary venipuncture some of the blood is sucked back from the syringe when the tourniquet is released and this permits infected materials previously present in the syringe or needle to enter the blood stream of the patient whose blood is being drawn. It has also been demonstrated that during the course of an injection some blood or serum from the patient may be forced up through the needle during the contraction of the recipient's muscle, thus resulting in contamination of the syringe.

Capps, Sborov and Scheiffel<sup>9</sup> have recently reported an epidemic of infectious hepatitis apparently resulting from the use of the "multiple dose per syringe" for the administration of tetanus toxoid. In this outbreak 20 per cent of the recipients of the toxoid contracted acute infectious hepatitis. It was estimated that about five per cent of the original group of people being vaccinated must have carried the hepatitis virus in their blood, and

it is believed that the syringes became contaminated with the blood from these persons before all the toxoid had been dispensed. Although separate needles were used for subsequent inoculations of the toxoid from these syringes a large proportion of those receiving the later injections were inoculated with the virus and thus later came down with the hepatitis.

The implications of these findings are obvious. Modern medical practice involves considerable use of needles and syringes for bloodletting and also for various types of injections. These facts and the tremendous development of the use of whole blood and blood products and the general system of blood banks being established in this country all point to the importance of this mode of transmitting such a serious disease. From the point of view of syringe transmission the significance of adequate sterilization is obvious. This can be accomplished by dry heat sterilization, autoclaving or boiling for about thirty minutes and the use of individual sterile needles and syringes for every puncture. The need for adequate supplies of needles and syringes in large clinics or when many injections must be given also becomes apparent.

## REFERENCES

1. Bigger, I. W. Jaundice in syphilis under treatment: possible transmission of virus. *Lancet* 1:477, 1947.
2. MacCallum, F. O. and Bauer, D. I. Homologous serum jaundice: transmission experiments with human volunteer. *Lancet* 1:622-627, 1944.
3. Droller, H. Outbreak of hepatitis in diabetic clinic. *Brit. M. J.* 1:627-628, 1945.
4. Howells, L. and Kerr, I. D. O. Hepatitis after penicillin injections. *Lancet* 1:51, 1946.
5. Turner, R. Hepatitis after penicillin injections. *Lancet* 1:108, 1946.
6. Hughes, R. R. Post penicillin jaundice. *Brit. M. J.* 2:685-688, 1946.
7. Sheehan, H. L. Epidemiology of infective hepatitis. *Lancet* 2:8-11, 1944.
8. Mendelssohn, K. and Witts, L. J. Transmission of infection during withdrawal of blood. *Brit. M. J.* 1:625, 1945.
9. Capps, R. B., Sborov, V. and Scheiffel, C. S. Syringe-transmitted epidemic of infectious hepatitis with observations regarding incidence and nature of infectious donors. *J. A. M. A.* 136:819-824, 1948.

## THE LEADING CAUSES OF DEATH

THE mortality statistics recently presented by the United States Public Health Service,<sup>1</sup> indicating "a new record low" for the crude death rate in the United States in 1946 underline the fact that these data should be interpreted with caution. The equivocal significance of such figures has previously been

# The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established 1828

Official Organ of

THE MASSACHUSETTS MEDICAL SOCIETY  
and

THE NEW HAMPSHIRE MEDICAL SOCIETY

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND

PUBLISHED WEEKLY UNDER THE JURISDICTION OF THE  
COMMITTEE ON PUBLICATIONS

James P. O'Hare, M.D. Richard M. Smith, M.D. *Chairman*  
Oliver Copc, M.D. Conrad Wesselhoef, M.D.  
John Fallon, M.D.

Joseph Garland, M.D., Editor

ASSOCIATE EDITORS

Thomas H. Lanman, M.D. Donald Munro, M.D.

Henry Jackson, Jr., M.D.

Clara D. Davies, Executive Editor

Robert O. Leary, Assistant Editor

EDITORIAL BOARD

C. Gay Lane, M.D.  
Henry R. Viets, M.D.  
Robert M. Green, M.D.  
Dwight O'Hare, M.D.  
Fletcher H. Colby, M.D.  
Robert L. Goodale, M.D.  
Chester M. Jones, M.D.  
Harvey R. Morrison, M.D.

Maxwell Finland, M.D.  
James M. Faulkner, M.D.  
Carroll B. Larson, M.D.  
Francis D. Moore, M.D.  
C. Stuart Welch, M.D.  
Vernon P. Williams, M.D.  
Benjamin Castleman, M.D.  
Hugh R. Leavell, M.D.

SUBSCRIPTION TERMS: \$7.00 per year in advance, postage paid for the United States (medical students \$4.00 per year); Canada \$8.00 per year (Boston funds) \$9.50 per year for all foreign countries belonging to the Postal Union.

MATERIAL should be received not later than noon on Thursday three weeks before date of publication.

THE JOURNAL does not hold itself responsible for statements made by any contributor.

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts. Telephone KE 6-2094.

NEW ENGLAND ADVERTISING REPRESENTATIVE: Edwin B. Tyler, 89 State Street, Boston, Massachusetts. Telephone LA 3-5516.

## SMALLPOX TO TETANUS A HUNDRED AND FIFTY YEARS OF IMMUNIZATION

THE value of vaccination against smallpox cannot be questioned, but now, a century and a half after its effectiveness was clearly shown, vaccination is still by no means universally employed, even in certain enlightened areas in the United States. There are protests against its use from those who either cannot or will not see its merit. In earlier years the slowness of its adoption could be explained, in part, by the lack of efficient methods of demonstrating the good results to the public. Also, in the early stages of its use no really large-scale and well controlled figures were possible.

Today, with present methods of broadcasting knowledge, scientific and otherwise, no excuse can be offered for failure to recognize the benefits of immunization against tetanus. The not tabulated results of not thousands, but millions, of cases in the armed forces all over the world furnish conclusive evidence of the efficacy of immunization against tetanus. The procedure is simple, safe and relatively painless. The results admit of no argument regarding its effectiveness, as amply demonstrated by Press elsewhere in this issue of the *Journal*.

Scarcely a day goes by in which a physician does not see a case in which tetanus could result from a minor wound. In the days when tetanus antitoxin was his only recourse he was constantly obliged to make the important and sometimes difficult decision whether the patient should be subjected to such serum therapy, with its discomforts and its dangers, or whether by withholding it, to obviate these discomforts at the risk of the disease. Such a difficulty is no longer necessary.

There are, of course, those who protest against any and all progress in medicine. As there are conscientious objectors to vaccination against smallpox, so there are inevitably those who would object to any advance, even though the known facts of its efficacy permitted of no dispute.

It is most desirable, therefore, that general practitioners do what they can, and as much as they can, to promote the acceptance by the public of active immunization against tetanus. Tetanus toxoid will protect the individual person, and its universal use may greatly ease the burdens of the physician.

## SYRINGE-TRANSMITTED HEPATITIS

THE occurrence of a severe form of hepatitis often referred to as "homologous serum jaundice" following injections of normal or immune plasma, serum or whole blood or after inoculations of certain vaccines containing normal serum or plasma is now well recognized. This type of hepatitis was observed in widespread epidemics in military

These new proposals represent a considerable willingness to compromise since even his own party is not entirely in sympathy with them

The Government according to Mr Bevan's parliamentary secretary, now recognizes that a full-time salaried service is incompatible with free choice of physician by the patient more, it recognizes the importance of the principle of free choice of physician and therefore puts forward the compromise of payment partly by capitation fee and partly by salary Further, although the buying and selling of public practices will still be forbidden, every doctor will be free to practice where he wishes except in professionally overcrowded areas and will have the right to choose his partner or assistant

A few strands of democracy will remain in Britain's anchor line, although, as the *British Medical Journal*\* phrases it, "Mr Bevan's machinery may provide that justice will be done, but we doubt whether it will make it possible that justice 'may manifestly be seen to be done'

A plebiscite on the amendments proposed by the Government indicates that approximately 64 per cent of the British Medical Association members still disapprove of the Act, with 36 per cent approving Only 52 per cent, however, are against serving under the Act whether they like it or not, a majority so bare that further organized resistance seems impossible

There is no question that, with Britain's peculiar genius for compromise, the doctors of England will now unite in an organized effort to make the new system effective

\*Editorial Plebiscite. *Brit M J* 1 791-793 1948

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

FLAGG — Elisha Flagg, M D , of Boston, died on June 8 He was in his eighty-third year  
Dr Flagg received his degree from Harvard Medical School in 1901 He was formerly treasurer of the Boston Medical Library

His widow, a daughter and two grandchildren survive

SMALL — Albert E. Small, M D , of Melrose, died on June 9 He was in his seventy-third year

Dr Small received his degree from Harvard Medical School in 1900 He was formerly president, secretary and treasurer of Middlesex East District Medical Society, and was chairman of the Melrose Board of Health He was a fellow of the American Medical Association

Two children survive

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR MAY 1948

DISEASES	RÉSUMÉ		
	MAY 1948	MAY 1947	SEVEN YEAR MEDIAN
Chancroid	2	0	2*
Chicken pox	1612	2599	176
Diphtheria	18	17	16
Dog bite	1260	1259	1289
Dysentery bacillary	8	5	5
German measles	132	107	640
Gonorrhea	218	273	540
C-arcinoma inguinale	0	0	0*
Lymphogranuloma venereum	2	0	2*
Malaria	1	10	12
Measles	5743	1785	4208
Meningitis meningococcal	7	5	16
Meningitis Pfeiffer bacillus	4	10	2
Meningitis pneumococcal	2	2	5†
Meningitis staphylococcal	0	0	0†
Meningitis streptococcal	1	0	2†
Meningitis other forms	2	0	1†
Meningitis undetermined	5	4	4†
Mumps	2404	1095	1450
Pneumonia lobar	70	17	210
Poliovirus	0	0	1
Salmonellosis	6	14	6
Scarlet fever	910	440	1120
Syphilis	182	279	49
Tuberculosis pulmonary	224	248	505
Tuberculosis other forms	1	22	2
Typhoid fever	5	1	2
Undulant fever	4	8	6
Whooping cough	134	495	573

\*Four year median

†Six year median.

COMMENT

Diseases with incidence above the seven-year median were diphtheria, bacillary dysentery, measles, mumps and typhoid fever

Diseases with an incidence below the seven-year median were chicken pox German measles malaria, meningitis, all forms, lobar pneumonia, scarlet fever, undulant fever and whooping cough

Mumps had the highest incidence since 1915 There were more cases of typhoid fever in May than in the last six years Whooping cough and lobar pneumonia were at the lowest level since 1915

GEOGRAPHIC DISTRIBUTION OF CERTAIN DISEASES

Diphtheria was reported from Boston, 7 Brockton, 4, Chelsea, 1 Everett, 1 East Bridgewater, 1, Peabody, 1 Somerville, 1, Watertown, 2, total, 18

Dysentery, bacillary, was reported from Waltham, 1 Worcester, 7, total, 8

Encephalus infectious, was reported from Cambridge, 2, Fitchburg, 1, Lowell, 1, Waltham, 1, total, 5

Malaria was reported from Boston, 1 total, 1

Meningitis meningococcal, was reported from Boston, 2 Everett, 1, Lynn, 1 Medford, 1, Newton, 1, Quincy, 1, total, 7

Meningitis, Pfeiffer-bacillus, was reported from Acton, 1, Lowell, 1 New Bedford, 2 total, 4

Meningitis, pneumococcal, was reported from Brookline, 1, Tewksbury, 1, total, 2

Meningitis, streptococcal, was reported from Cambridge, 1, total, 1

Meningitis, other forms, was reported from Boston, 1 Reading, 1, total 2

Meningitis undetermined, was reported from Braintree, 1, Newton, 1 Worcester, 1 total, 3

Salmonellosis was reported from Beverly, 3, Boston, 1, Haverhill, 1, Otis, 1 total, 6

Septic sore throat was reported from Boston 7 Medford, 1, Milton 1, total, 9

Tetanus was reported from Worcester, 1 total, 1

Typhoid fever was reported from Boston, 3, New Bedford, 1, Westfield, 1, total, 5

Undulant fever was reported from Easton, 1, Hopkinton, 1, Newton, 1, Webster, 1, total, 4

referred to in these columns<sup>2</sup> And the decline in the number of deaths from certain leading causes should be balanced against the increase in other fatal diseases Thus, although the deaths from intracranial lesions of vascular origin and from nephritis decreased, respectively, from 129,144 and 88,078 in 1945 to 125,649 and 81,701 in 1946, the deaths from cancer increased from 177,464 in 1945 to 182,000 in 1946, and those from heart disease from 424,328 to 429,230 One class of preventable deaths (those due to accidents), which rose from 95,918 in 1945 to 98,033 in 1946, remains both a challenge and a disgrace to a nation in which a great part of private and public-health medical practice is devoted to the prolongation of life

Cancer and other malignant tumors continue to take a large toll, accounting for 13 per cent of the total number of deaths in 1946 Although he admits the uncomfortable implications of such a figure, Johnson<sup>3</sup> points out some hopeful trends The rate of deaths from cancer at all ages rose from 60 per 100,000 population in 1900 to 130 per 100,000 in 1940, but this depressing figure should be considered in the light of the 67 per cent increase in the age group over forty-five years, in which the greatest incidence of cancer occurs And although the number of deaths from cancer of the respiratory tract continues to rise each year, deaths due to malignant lesions of the skin, mouth, stomach and liver have steadily decreased in the last twelve years — Johnson suggests an interesting causal relation between the decline in the death rate from gastric cancer and the fact that the decrease began approximately twenty-five years after significant changes in the dietary habits of the American people had taken place

Despite the truly remarkable advances in the control of disease and the prolongation of life, science has not succeeded in making man immortal Johnson<sup>3</sup> questions whether it is desirable to concentrate on that goal alone He expresses what should be a major consideration in the relatively new field of geriatrics, "the enrichment of living rather than the mere prolongation of life" There is no indication for congratulations in the vital statistics referred to above the five leading causes of death, whether they are the causes at present

responsible or others that will take their place, will continue to exact their yearly toll, particularly among the elderly And medical science will continue its campaign not only, by control of the diseases that cause most deaths, to extend the span of life but also to eliminate the physiologic discomforts that plague old age — in short, to avoid a "second age of dependency"<sup>4</sup> and make of old age a period of dignity and mental and physical well-being

#### REFERENCES

- 1 U S Public Health Service National Office of Vital Statistics Micrographed memorandum dated December 30 1947
- 2 Editorial Fallacy of crude death rate *New Eng J Med* 238:577 1948
- 3 Johnson A S Annual Oration Medicine's responsibility in perpetuation of poor protoplasm *New Eng J Med* 238:755-758 1948
- 4 Editorial Second age of dependency *New Eng J Med* 238:340 1948

#### LION ROARS LESS LOUDLY

THE Comitia of the Royal College of Physicians, acting in a spirit of sweet reasonableness, has forwarded two resolutions to the minister of health, Aneurin Bevan, vociferous sponsor of the National Health Service Act of 1946 The first suggests that an act be brought in by the minister of health amending the National Health Service Act of 1946 by discarding full-time medical service by regulation The second recommends a bill to make regulations affecting the National Health Service subject to special parliamentary procedure rather than to ministerial dictation alone

Mr Bevan, departing from his accustomed role, has apparently listened to the voice of the British Medical Association as expressed in its plebiscite of January 31, in which it overwhelmingly rejected the National Health Service Act as it was originally written

He has now proposed his own modifications of the Act In these he relinquishes a full-time service to be brought into effect by regulation and also modifies the proposal for a universal basic salary, limiting such salaries to three years, after which the practitioner may make his own decision whether to continue with salary and capitation fee, or to continue with a capitation fee as the sole source of income from practice

## NOTICES

## AMERICAN OCCUPATIONAL THERAPY ASSOCIATION

The thirty-first annual convention of the American Occupational Therapy Association will be held at the Hotel Pennsylvania, New York City, September 7 to 11. On September 10 and 11, a teaching institute will present recent developments and techniques in the treatment of neuropsychiatric conditions. Various trips to hospitals and other institutions in New York City and surrounding areas, on September 9 and 10, have also been arranged for those attending the convention. A copy of the preliminary program may be obtained from the American Occupational Therapy Association, 33 West 42nd Street, New York 18, New York.

## SOCIETY MEETINGS AND CONFERENCES

## CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, JULY 15

## FRIDAY JULY 16

\*10:00 a.m.-12:00 p.m. Medical Staff Round Peter Bent Brigham Hospital

## TUESDAY JULY 20

\*12:00 p.m. Lunch Conference Margaret Everett Hall Mt Auburn Hospital Cambridge

\*12:15-1:15 p.m. Clinico-oculogenetological Conference Peter Bent Brigham Hospital

\*1:30-2:30 p.m. Pediatric Rounds Burnham Memorial Hospital for Children Massachusetts General Hospital

## WEDNESDAY JULY 21

\*12:00 p.m.-1:00 p.m. Clinical Conference (Children) Hospital Amphitheater Peter Bent Brigham Hospital

\*Open to the medical profession

JUNE 28-JULY 23 Harvard Seminar on Health Education Page 4 issue of June 10

JULY 6-24 Students International Clinical Congress Page 4 issue of March 2

JULY 12-17 First International Poliomyelitis Conference Page 6 issue of January 1

AUGUST 11-21 International Congress on Mental Health Page 44 issue of March 4

AUGUST 23-26 International Society of Hematology Page 41 issue of March 18

AUGUST 26-28 American Association of Blood Banks Page 420 issue of March 18

SEPTEMBER 7-11 American Congress of Physical Medicine Page 52 issue of April 15

SEPTEMBER 7-11 American Occupational Therapy Association Notice above

SEPTEMBER 9 Some of the Advances in Surgery Dr. Frank H. Leber Pentucket Association of Physicians 8:30 p.m. Haverhill

SEPTEMBER 13-15 American Academy of Pediatrics Olympic Hotel Seattle, Washington

SEPTEMBER 16-18 Vermont State Medical Society Annual Meeting Burlington

SEPTEMBER 20-25 American Hospital Association Page 310 issue of February 26

SEPTEMBER 29 Mississippi Valley Medical Editors Association Page 170 issue of January 20

OCTOBER 6-9 American Board of Ophthalmology Page 170 issue of January 29

OCTOBER 18-22 American College of Surgeons Page 34 issue of July 1

OCTOBER 27 New England Obstetrical and Gynecological Society Annual Meeting Hotel Somerset, Boston

NOVEMBER 1-5 American Clinical and Climatological Association Page 582 issue of April 15

NOVEMBER 8-12 American Public Health Association Page 420 issue of March 18

NOVEMBER 10-13 Association of Military Surgeons of the United States Page 722 issue of May 13

NOVEMBER 20-23 American Academy of Pediatric Annual Meeting Chalfonte-Haddon Hall Hotel Atlantic City New Jersey

DECEMBER 7-9 Southern Surgical Association Annual Meeting Page 543 issue of April 8

DECEMBER 9 and 10 New York State Society of Anesthesiologists Page 34 issue of July 1

## Valleyhead Hospital

CONCORD, MASSACHUSETTS

For the treatment of psychoneuroses, alcoholism, mild mental disorders and chronic diseases. Pleasant pastoral setting near historic Concord. Accepted modern therapies used. Complete occupational and recreational facilities available including outdoor swimming pool and tennis court.

S. GAGNON, M.D.  
Superintendent

J. BUTLER TOMPKINS, M.D.  
Director of Clinical Psychiatry

I. P. THORNTON, M.D.  
Consultant in Neuro-psychiatry

IRVING KAUFMAN, M.D.  
Psychiatrist

Post Office, Box 151, Concord, Mass. Tel. Concord 1600

## Washingtonian Hospital

41-43 WALTHAM STREET, BOSTON, MASS

Incorporated 1859

Conditioned Reflex, Psychotherapy, Semi-Hospitalization  
For Rehabilitation of Male Alcoholics

Treatment of Acute Intoxication and Alcohol Psychoses  
Included

Outpatient Clinic and Social-Service Department for  
Male and Female Patients

JOSEPH THIMANN, M.D., Medical Director

Visiting Psychiatric and Neurologic Staff  
Consultants in Medicine, Surgery and the Other Specialties  
Telephone HA 6-1750

## Tablets Ferplate-B with C

High in vitamin B complex content to quicken hemoglobin response to iron therapy

## EACH TABLET CONTAINS

Ferrous Gluconate (5 grains)	0.375 gm	Pyridoxine HCl	0.15 mg
Thiamin HCl	3 mg	Calcium Pantothenate	0.5 mg
Riboflavin	2 mg	Ascorbic Acid	30 mg
Niacinamide	20 mg	Yeast Liver Base	q.s.

## INDICATIONS

Iron deficiency and nutritional anemias as a source of iron and B complex factors

Write Department N12 for Professional  
Sample and Literature

## KENMORE PHARMACAL CO.

500 COMMONWEALTH AVENUE  
BOSTON 15, MASS.

## The Boston Children's Friend Society

offers its services to physicians for the care of a limited number of unmarried mothers arranging for the adoption of their infants

Address communications to

GENERAL SECRETARY

BOSTON CHILDREN'S FRIEND SOCIETY  
125 Marlborough Street, Boston 16, Massachusetts  
Telephone KE 6-8070

## CORRESPONDENCE

### COUNCY AND THE ASSOCIATION OF AMERICAN PHYSICIANS

To the Editor The editorial, "Four Hundred and Thirty Years Ago," in the May 20 issue of the *Journal*, which I read with interest, contains a minor error, perhaps of no importance to anybody, but I think you might like to know about it. That concerns the Association of American Physicians and Dr. Councilman. I am sure that Dr. Councilman had very little to do with the founding of the Association of American Physicians, although he was one of sixty-nine original members. The reason I say that is that Dr. Councilman then was only eight years out of medical school, was an associate in pathology at the Johns Hopkins Hospital with Dr. Welch, beginning at a time when the hospital had not been built.

The editorial also states that he was known as "Councey." I never heard this term used. He was affectionately spoken of by the younger men as "Counce" and was known as "Counce" to many of his colleagues. Dr. Welch, of course, was always known to the younger men as "Popsy," though I never heard anyone call him that. He was always known as Dr. Welch, Welch, to a very few as William and to an occasional member of his family as Willie. I never knew who designated him first as Popsy. When I went to Johns Hopkins in the autumn of 1896 he was universally spoken of by the students as Popsy.

HENRY A. CHRISTIAN

#### Brookline

Note Dr. Councilman was later known to his students at Harvard Medical School as "Councey." — Ed

## BOOK REVIEW

*Surgical Treatment of the Abdomen*. Supervising editor Frederic W. Bancroft, M.D. Associate editor Preston A. Wade, M.D. 4<sup>th</sup> ed., cloth, 1026 pp. with 457 illustrations and 3 color plates. Philadelphia: J. B. Lippincott Company, 1947. \$18.00.

This comprehensive and authoritative volume was written by thirty-five eminent physicians. The scope of the book is sufficiently broad to comprise a thorough consideration of fundamental surgical principles applicable to the exacting requirements of gastrointestinal surgery. Adequate coverage is given to the common problems of anesthesia, preoperative and postoperative care and the essential features of a sound surgical technique. The sections relating to the various diseases involving the gastrointestinal tract are well documented and generously illustrated.

The chapter pertaining to the surgical lesions of the small bowel is particularly noteworthy in terms of its broad scope, its ample pictorial documentation and its careful presentation of the controversial aspects of the surgical management of lesions of the small intestine.

Each section, big and large, achieves the purpose of portraying the dominant clinical features of the diseases that are discussed—the diagnosis, an acceptable method of surgical management and a reasonable consideration of the results that can be achieved by the proposed methods of therapy.

Although one might question the urgent need for such a volume, no one could question its authoritativeness or its essential soundness.

## BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

*Atlas of Practical Incisions and Some Operative Procedures*. By Oliver C. Cox, M.D. 4<sup>th</sup> ed., cloth, 85 pp., with 27 illustrations and 61 plates. With drawings by Garnet W. Jex, and photographs by John W. McGuire. Baltimore: Williams and Wilkins Company, 1947. \$3.00.

In this atlas the author presents incisions recommended for various surgical operations on the gall bladder, appendix,

undescended testicle, hernia and pilonidal cyst, and considers the "reverse" Pfannenstiel and the Parker-Kerr aseptic enterocentrostomy. The plates are excellent and self-explanatory. There are short comments with each series of incisions, but otherwise there is no text. The volume is well published and should prove useful to students and beginners in surgery.

*George Crile. An autobiography*. Edited with sidelights, by Grace Crile. In two volumes. 8<sup>vo</sup>, cloth, Vol. I, 306 pp., Vol. II, 317 pp., illustrated. Philadelphia: J. B. Lippincott Company, 1947. \$10.00.

The material for this autobiography of a celebrated physician-scientist was compiled from the notes, letters, diaries and manuscripts of Dr. Crile, who also wrote the material for the early chapters, until his vision became impaired. Here will be found the history of his work on surgical shock, fear, blood pressure, surgery of the respiratory system, hemorrhage and transfusion, the thyroid gland, anemia and resuscitation, phylogenetic association, anoci-association, the emotions, kinetic drive and the bipolar theory. Dr. Crile made a life-long study of surgical shock and perfected a shockless operating technique. He performed the first successful amputation under local anesthesia in 1897 and the first successful blood transfusion in 1906. He perfected the nitrous oxide method of general anesthesia. He was a motivating force in the founding of the American College of Surgeons and the American Society of Clinical Research. Prior to World War I he set up an ambulance service in Paris and organized Red Cross Base Hospital Units. Later he was a member of the first contingent of the United States Army to serve overseas in the war, establishing a hospital at Rouen in 1917 before the arrival of troops. At the end of the war he was director of medical research for the Army. Returning to Cleveland he was instrumental in building and operating the Lakeside Clinic, which pioneered in radiotherapy and biophysics. Dr. Crile was a traveler. He made two European trips previous to his marriage and upon that occasion made a global trip. During the later years he made numerous trips to Europe, Africa, Alaska, California and Florida to study the endocrine functions of the larger animals and marine life. For this and other work he received many honors including the Lanne-longue surgical medal of the Surgical Society of Paris. This work should be in all medical-history collections.

*Hypnotherapy. A survey of the literature*. By Margaret Brennan, Ph.D., director, Division of Psychology, The Menninger Foundation, and professor of psychology, The Menninger Foundation Center of the Department of Psychology, University of Kansas, and Merton M. Gill, M.D., associate psychiatrist and assistant director, Department of Research, The Menninger Foundation. With appended case reports and an experimental study. 8<sup>vo</sup>, cloth, 276 pp. New York: International Universities Press, 1947. \$4.50. The Menninger Foundation Monograph Series No. 5.

This work was originally published by the Josiah Macy Jr. Foundation in 1944 and distributed to psychiatrists and psychologists as part of its wartime services. It is reissued in a commercial edition with two new appendices. The general bibliography lists 295 sources comprising the basis of the survey. The text is divided into six parts and two appendices. The first part is a short sketch on the historical development of hypnotherapy, followed by methods of inducing and terminating hypnosis, susceptibility of hypnosis, therapeutic applications, the theory of hypnosis, and a summary and statement of problems. The first appendix discusses in detail 4 unusual cases of anxiety hysteria, hysterical psychosis in a seventy-one-year-old woman, a case of combined neurasthenia, hysteria and depression, and a case of neurosis in a young girl, illustrating the techniques of hypnotherapy, hypnoanalysis and psychoanalysis. Seventy pages of text are devoted to these cases. The second appendix is devoted to a discussion of the use of hypnotic techniques in the study of tension systems, giving in detail accounts of the experiments used in the study. There are special bibliographies for the case reports and for the experimental study. The volume is well published, with a good type on good light paper. The work should be in all collections on psychiatry.

(Notices on page xv)

# The New England Journal of Medicine

Copyright 1948, by the Massachusetts Medical Society

Volume 239

JULY 15, 1948

Number 3

## EXCESSIVE HYPERTENSION OF LONG DURATION

ALEX M BURGESS, M D \*

PROVIDENCE, RHODE ISLAND

IN THE *Journal of the American Medical Association* of December 21, 1932, under the heading, "Queries and Minor Notes," appears the following question

Can you give me any statistics or other definite information of assistance in the prognosis of blood pressure? For example, how definitely can one say how long a person with a pressure of 200 systolic will survive, or one with 250, or one with a diastolic of 100 or 120? I realize that many factors enter in, but I am especially interested in the effect such high pressures have on individuals who show no cardiac or renal disease.

An answer to this question was prepared in the office of one of the largest insurance companies. Admittedly, it was incomplete and began, "There are no data available from insurance sources on the prognosis of individuals showing such high pressures, whether systolic or diastolic." Actually, the only available data that could give a real answer to the question are buried in the private records of practitioners who have followed hypertensive patients over long periods. If enough material could be obtained from such records by the collaboration of approximately a hundred physicians, real information would become available and the question could be given a definite answer.

The subject has great intrinsic importance, which has been considerably enhanced by public hypertensophobia. Such regrettable popular articles as that entitled "Killer Number One," which appeared in the *Saturday Evening Post* of December 16, 1944, have contributed to this state of affairs. Unfortunately, the medical profession has no reliable information on which to base reassurance of the unfortunate persons to whom the existence of high blood-pressure readings has been made known, and in whom a thoroughly reasonable anxiety state has been created.

When one encounters a young adult whose diastolic pressures range consistently over 120, whose eye grounds show extensive flame-shaped

hemorrhages, exudates or edema, and who already presents evidence of cardiac or renal damage, there is no difficulty in estimating the prognosis. Such frank cases of hypertension of the malignant type are readily recognized and the gravity of the situation is universally understood. When, however, one is confronted by a patient with excessive hypertension (even with systolic pressures from 200 to 300 and diastolic pressures over 120), and when there is evidence that the condition is not progressive, when retinal changes are minimal and cardiac and renal damage not evident, there is no reliable information on which to base a prognosis.

No previously reported studies have attempted, so far as has been determined, to separate the obviously nonprogressive type of hypertension from the obviously malignant type, and to study the prognosis in the nonmalignant group alone. Although fairly large series have been studied by Janeway in 1913,<sup>1</sup> Rice in 1933<sup>2</sup> and several others<sup>3-5</sup> there has been no unanimity in the method of approach, and the results are difficult to evaluate. A recent communication by King, Carlile and Blackford,<sup>6</sup> which includes a follow-up study of 481 patients, is perhaps the most valuable that has yet been published. In their tabulations "essential" and "malignant" hypertension have been classed together. Their results, therefore, do not indicate what may be expected in the nonmalignant, relatively nonprogressive condition.

Furthermore, the importance of the diastolic pressure has not been sufficiently stressed. Most investigators have, however, pointed out that the presence of a relatively high diastolic pressure is a definitely unfavorable sign although in their statistics they have evaluated the degree of hypertension in terms of systolic as well as diastolic levels and therefore have failed to demonstrate the significance of high diastolic values. The conclusion that a high diastolic pressure carries with it a definitely poor prognosis is, I believe, in accord with the experience of clinicians generally, based

\*Professor of health and hygiene Brown University Medical Department formerly physician-in-chief Department of Medicine Rhode Island Hospital.

This baby's mother learned  
about Mead's Oleum Percomorphum from her physician, not from  
public advertising or displays

*"Servamus Fidem"*

## HOW much sun does the infant really get?

*Not very much* (1) When the baby is bundled to protect against weather or (2) when shaded to protect against glare or (3) when the sun does not shine for days at a time Mead's Oleum Percomorphum is a prophylactic against rickets available 365½ days in the year, in measurable potency and in controllable dosage *Use the sun, too*

Mead Johnson & Co , Evansville, Ind , U S.A

chances that any patient with excessive hypertension of long duration will live to his normal life expectancy are considered, the first factor of which one thinks is the age when the condition developed. In the patients reported it is notable that every person who was sixty-five years or over when excessive hypertension first was noted has outlived his life expectancy. The corollary to this statement, of course, is that persons in whom excessive hypertension was discovered relatively early in life and whose normal expectancy is therefore relatively long are unlikely to complete their life span. That this is true is demonstrated in Table 4, which shows what has happened to the 32 patients in whom the condition was discovered at the age of fifty

It is quite evident that an elevated systolic pressure is not, of itself, an unfavorable prognostic sign. In fact, the 27 patients who showed a systolic pressure of 250 or higher at some time while they were being observed lived distinctly nearer to their life expectancy than those in whom such high readings were never obtained. This is further emphasized by the fact that the 5 patients in whom a reading of over 300 was recorded on one or more occasions actually showed an average duration of life slightly in excess of the normal. The most probable explanation of these findings is that many of these patients with very high systolic pressures showed relatively low diastolic pressures. They belong to the group with arteriosclerotic hypertension in

TABLE 4 Data in Patients Twenty-Eight to Fifty Years of Age

STATUS OF PATIENT	NO OF PATIENTS	AVERAGE BLOOD	HIGHEST PRESSURE	AVERAGE BLOOD	LOWEST PRESSURE	LIFE EXPECTANCY	ACTUAL DURATION OF LIFE	DEFICIT
		SYSTOLIC	DIASTOLIC	SYSTOLIC	DIASTOLIC	yr	yr	yr
Living	20	220 6	121 7	160	96 7	29 4	18	11 4
Dead	12	255 7	126 7	175	94 2	26 0	15	11 0

years or younger. This group is of particular interest because it is patients of fifty years or younger who are usually regarded as favorable subjects for dorsolumbar sympathectomy. Of these, the 12 patients who have died had lived an average of fifteen years, or eleven years short of their life spans. The 20 still alive have lived an average of eighteen years, or again about eleven years short of their normal expectancy. They are, all but 3, normal people who are living normal lives without symptoms. They probably will live enough longer to raise the average length of life for the group to a much more favorable figure. A question that should be considered is whether or not the long-range results of surgical treatment can be expected to be of benefit to these patients.

Regarding the influence of sex it must be admitted that a group of 20 patients is far too small to justify any definite conclusions. However, in these 20 male patients the average life expectancy for 8 patients alive in 1947 was nineteen years and the actual duration of life fifteen and three-fourths years, and the average expectancy for 12 dead patients was nineteen and a half years and the actual duration fifteen and a half years. The deficit for patients in the former group was slightly over three years, and that for patients in the latter was four years. The duration of life was slightly longer than the average for the total of 100 patients. The age at which the condition was first observed was one year earlier than the average for the entire group.

The influence of the degree of hypertension on the prognosis is demonstrated in Tables 5 and 6

whom a loss of elasticity of the arteries, rather than degeneration of the arterioles, has led to excessive pulse pressures but not to marked organic damage other than cardiac hypertrophy.

This conclusion is upheld by a study of the facts presented in Table 6, which clearly indicate the unfavorable influence of a high diastolic pressure. In exactly 50 patients the diastolic pressure was found to have been, on one or more occasions, 120 or higher. In these patients the actual duration of life fell short of the normal expectancy by a considerably longer period than it did in the whole group. The other 50 patients, those whose diastolic pressure was never found to reach 120, showed,

TABLE 5 Influence of Systolic Blood Pressure of More than 250 \*

STATUS	NO OF PATIENTS	AVERAGE LIFE EXPECTANCY	ACTUAL DURATION OF LIFE	DEFICIT
		yr	yr	yr
Living	9	22 9	19 1	3 8
Dead	18	18 5	16 0	2 5

\*Among 1 living and 4 dead patients with systolic pressures of more than 300 the average life expectancy was sixteen and the actual duration of life sixteen and three-fourths years.

of course, figures for duration of life that were correspondingly more favorable than those of the total group. It is interesting to note, however, that the 50 patients who had diastolic pressures above 120 were on the average several years younger than those with the lower diastolic pressures, and that the actual time of survival in the two groups was approximately the same.

on their impressions gained in routine practice, but accurate studies in relation to the age of the patient and the type of hypertension present have not, it appears, been made

In still another respect previously reported studies of the prognostic significance of high blood pressure have failed to give the answer that is most needed. This is because the results are stated in terms that are difficult for the person untrained in

TABLE 1 Status, in 1944, of 80 Female and 20 Male Patients with Excessive Hypertension\* of Eight or More Years' Duration

STATUS OF PATIENT	NO OF CASES	AVERAGE PERIOD OF SURVIVAL BELOW EXPECTANCY†
Dead	33	5 7
Living	67	2 5
Disabled		8 0
Active	19	
	48	

\*Systolic pressure of 180 or higher or diastolic pressure of 100 or higher

†Life expectancy exceeded by 10 living and 10 dead patients

dealing with insurance and mortality statistics to interpret. What the physician wishes to know about the hypertensive patient for whose welfare he is responsible is how this condition will affect the length of the patient's life and his health and happiness during the years he has yet to live—in other words, what the relation of this person's probable span of effective life is to that to which, at his age, he is entitled.

The present investigation has been undertaken in an attempt to make a small contribution to the

supervene. In the group of 100 patients here reported retinal hemorrhages were very rare, and renal failure occurred in only 1 case, no case of malignant hypertension developed. For the purpose of the present study a systolic pressure of 180 or a diastolic pressure of 100 was regarded as evidence of excessive hypertension. The records were reviewed and the first hundred patients who were found to have had a recorded pressure of this degree or higher, and who were alive eight years or more afterward, were selected.\* Although many other patients with excessive hypertension of eight years' duration or longer have since been observed, it was recognized that by limiting the study to the patients who were seen earliest, the group would contain only cases in which a long follow-up study has been possible. Of the 100 patients, 90 were found to have had excessive hypertension prior to 1932, the remaining patients having first been observed in 1934, 1935 or 1936. In only 3 cases is the condition of the patient unknown at the present time. These 3 patients are reported as of their last recorded examination.

The average survival time was compared with the average life expectancy of all persons of the same age and sex†. The group then was divided

TABLE 3 Comparison of Actual Duration of Life with Average Expectation of Life (1947)

STATUS OF PATIENTS	AVERAGE EXPECTANCY	ACTUAL DURATION	DEFICIT
	yr	yr	yr
Living	21 6	16 9	4 7
Dead	17 8	14 2	3 6
All patients*	19 8	15 7	4 1

\*The average expectancy of life was exceeded by 28 patients

TABLE 2 Status of Patients in 1947 \*

STATUS OF PATIENT	NO OF CASES
Living	47
In good health	30
Slightly disabled	5
Moderately disabled	3
Markedly disabled	3
Unknown	6
Dead	53
Of cardiac disease	22
Of cerebral disease	9
Of renal disease	2
Of unrelated cause	3
Cause of death unknown	17

\*Thirty-two patients were from twenty-eight to fifty years of age inclusive, 39 from fifty-one to sixty inclusive, 18 from sixty-one to seventy inclusive, and 11 from seventy to seventy-seven, inclusive.

mass of information that will be needed before an adequate answer to this question can be given. It consists entirely of a review of the records of private patients seen since 1914. With a view to finding out what happens to patients with excessive hypertension that is definitely not of the progressive, malignant type, patients were chosen in whom the condition had existed for at least eight years. Eight years without progression was regarded as evidence that malignant hypertension would not

into three parts: the living, the dead, and the physically incapacitated. The patients then were reclassified according to age, sex and degree of hypertension,—both systolic and diastolic pressures being ascertained,—so that the influence of these factors on length of life could be deduced.

The patients in this group were first studied in 1944. The results are recorded in Table 1.

In the three years that have passed since this earlier tabulation, 20 patients have died. At present there are 47 persons still living, and 53 who have died. Tables 2 and 3 give the main facts concerning the whole group. When another ten years have elapsed only a few of the patients will, in the normal course of events, still be alive. At that time a more final judgment regarding ultimate prognosis will be possible.

It is evident from these tables that the average person of the group lives out almost his entire life span. When the various factors that influence the

\*For the initial readings in 1 case I am indebted to Dr. John E. Kenney of Pawtucket, Rhode Island.

†On the basis of tables for males and females presented by Dublin.<sup>11</sup>

Further investigation of this subject should involve the collection of a sufficiently large number of cases to make statistical studies really significant. This could be accomplished by the collaboration of a large number of physicians who have practiced twenty-five years or longer.

It is suggested that when the physician is confronted with a patient who is not over fifty years old and in whom he finds excessive hypertension, frequent examinations should be made for evidence of progression, especially for the signs of retinal, renal or cardiac damage. In the absence of such evidence it is believed that resort to surgery may well be delayed.

454 Angell Street

REFERENCES

1 Janeway T C. Clinical study of hypertensive cardiovascular disease. *Arch Int Med* 12 755-798 1913  
2 Rice L. Arterial hypertension study of 327 patients observed for five to ten years. *South M J* 26 144-150 1933  
3 Paullin J E. Ultimate results of essential hypertension. *J A M A* 87 925-928 1926  
4 Keith N M, Wagener H P and Barker N W. Some different types of essential hypertension: their course and prognosis. *Ar M Sc* 197 332-343 1929  
5 Blackford J M and Wilkinson J N. Hypertension study of two hundred and two cases followed for average of ten years — with remarks on causes and treatment. *Arch Int Med* 6:34-59 1932  
6 Schroeder H A and Steele J M. Studies on "essential" hypertension classification. *Arch Int Med* 64 927-951 1939  
7 Riesman D. High blood pressure and longevity. *J A M A* 96 1105-1111 1931  
8 Yater W M. Fads and fallacies in diagnosis and treatment of hypertension. *M Arr District of Columbia* 9 200-204 1940  
9 King R L, Carline T and Blackford J M. Hypertension, follow-up study of 481 patients. *Northwest Med* 41 298-305 1942  
10 Dublin L I and Lotka A J. *Length of Life. A study of the life table* 400 pp. New York: Ronald Press Co. 1936.

THE ECONOMICS OF INFANT AND CHILD NUTRITION\*

NATHAN B TALBOT, M D,† C C Koo, M D,‡  
WALTER W PICK, M D.§ AND SHIRLEY L WELLS¶

BOSTON

THE recent change in the world food situation from one of apparent relative adequacy to one of obvious deficit invites a brief review of the economics of providing infants and children with an adequate diet. In this connection total calories and protein appear to deserve the most consideration. Moreover, requirements for these two com-

TABLE 1 Recommended Dietary Allowances \*

Age	TOTAL CALORIES	PROTEIN
yr		
Under 1	100†	5-††
1-3	1200	40
4-6	1600	50
7-9	2000	60
10-12	2500	70
13-15	2800-3200	60-85‡
16-20	2400-3600	75-100‡

\*Based on allowances recommended by the National Research Council.  
†Per kilogram of body weight.  
‡The first value is for girls and the second for boys.

ponents must be considered together because the protein needs of the growing child within certain limits are inversely proportional to the total caloric intake. This is due in part to the fact that the amino acids of dietary protein are needed and used for energy when calories from nonprotein sources are insufficient.

Table 1 sets forth the allowances for total calories and for protein recommended by the Food and Nutrition Board of the National Research Council in 1943. Experience in this clinic leads us to believe that these caloric allowances are approximately correct.<sup>2</sup> On the other hand, studies carried out both here and elsewhere<sup>3-8</sup> suggest that the recommended allotments of protein may be appreciably in excess of actual requirements under conditions of ample caloric intake. Assuming, therefore, that the recommendations of Table 1 are ample, the following considerations appear pertinent.

The daily recommended allowances for an average five-year-old child weighing 18 kg are 1600 calories and 50 gm of protein, providing 90 total calories and 2.8 gm of protein per kilogram of body weight. Theoretically, this food can be made up exclusively of vegetable nutrients or can be comprised of a mixture of vegetable and animal substances. When the caloric allotment is provided entirely by a mixture of such vegetable substances as wheat, corn meal, oats, potatoes, beans, peas, soybeans and carrots (Table 2), the protein intake is 75 gm, or 4.2 gm per kilogram of body weight per day. Even if 30 per cent of the calories come from a mixture of oranges, peaches, apples, tomatoes and cabbage and the remaining 70 per cent is derived from the substances mentioned above, the protein intake is about 64 gm, a value in excess of that recommended in Table 1. These data and experience with diets for metabolic ward patients indicate that, quantitatively speaking, it is difficult to feed a child

\*From the Children's Medical Service, Massachusetts General Hospital and the Department of Pediatrics, Harvard Medical School. This work is based in part on studies supported by the Commonwealth Fund of New York.  
†Assistant professor of pediatrics, Harvard Medical School, associate physician, Children's Medical Service, Massachusetts General Hospital.  
‡Graduate student, Harvard Medical School.  
§Clinical assistant, Massachusetts General Hospital.  
¶Research dietitian, Massachusetts General Hospital.

This leads to a comparison of the actual survival time of these patients considered without reference to their life expectancy (Table 7). The deficit—that is, the number of years by which this survival time falls short of normal life expectancy—for each group is also shown in Table 7, which demonstrates that the various factors discussed (age, sex and degree of hypertension) do not cause a marked variation in the actual duration of life. Although older people tend to live up to or beyond their normal life expectancy, this is because their life expectancy is shorter. Their average duration

—findings that are typical of malignant hypertension.

The most frequent cause of death in these patients is cardiac failure. A cerebrovascular lesion is the next most common terminal event.

The younger the patient at the time when the hypertension develops, the less likely he is to live out his full life span. Even in the young group (age fifty and below) the average length of life is over fifteen years (about eleven years below their expectancy). This is the age group in which dorso-lumbar sympathectomy is usually recommended.

TABLE 6 Influence of High Diastolic Blood Pressure

STATUS	DIASTOLIC PRESSURE OVER 120				DIASTOLIC PRESSURE UNDER 120			
	NO. OF PATIENTS	AVERAGE LIFE EXPECTANCY	ACTUAL DURATION OF LIFE	DEFICIT	NO. OF PATIENTS	AVERAGE LIFE EXPECTANCY	ACTUAL DURATION OF LIFE	DEFICIT
		yr	yr	yr		yr	yr	yr
Living	20	24.0	17.8	6.2	27	20.0	16.2	3.8
Dead	30	21.7	14.6	7.1	23	16.6	14.7	1.9

of life is about the same as that of the younger group. It is, of course, true that as the 47 people who are still alive (30 of whom are in apparent good health) continue to live on, the average duration of life for the whole group will lengthen. One may say, then, that the prognosis in hypertensive patients of the type discussed is actually more favorable than the figures indicate. The shortest duration of life recorded in the whole series, after the discovery of the hypertension, is nine years, and the longest twenty-five years.

SUMMARY AND CONCLUSIONS

Hypertension, even of an excessive degree, that has been present eight years or more and is not associated with well established cardiac or renal

For the malignant type of hypertension this operation is certainly of great value in delaying the fatal issue. With fifteen years or more of life ahead of him, however, it is questionable whether a person with the nonprogressive, nonmalignant type of high blood pressure should be subjected to such a radical procedure.

The present study does not indicate that the type of hypertension under discussion carries a poorer prognosis for males than it does for females. The group is too small to make this conclusion definite.

The degree of hypertension is important in relation to the diastolic pressure only. People with very high systolic pressures and relatively low diastolic pressures (the arteriosclerotic type of hypertension) survive appreciably nearer to their

TABLE 7 Actual Duration of Life and Deficit in All Groups

GROUP	LIVING PATIENTS	DURATION OF LIFE	DEFICIT	DEAD PATIENTS	DURATION OF LIFE	DEFICIT
All cases	47	16.9	4.7	53	14.2	3.6
Patients 50 years of age or under	20	18.0	11.4	12	15.0	11.0
Male patients	8	15.9	3.0	12	15.5	4.0
Systolic pressure over 250	9	19.1	3.8	18	16.0	2.5
Diastolic pressure over 120	20	17.8	6.2	30	14.6	7.1
Diastolic pressure under 120	27	16.2	3.8	23	14.7	1.9

disease usually does not indicate a poor prognosis. In fact the patient usually lives to within three or four years of his normal life expectancy.

Such hypertension does not commonly develop into the malignant type. In this series no case of such development was noted. It is not associated with marked arteriolar changes, evidenced by retinal hemorrhages or edema, or with renal damage

normal expectancy, on the average, than those with high diastolic pressures.

Regardless of sex or age or whether or not the diastolic pressure is below 120, this study indicates that these patients will probably live from fourteen to nineteen years. When the 47 patients now living have finished their lives, the figure will probably be considerably more favorable.

Moreover, many vegetables are of relatively low protein and mineral content, and some are deficient in certain essential amino acids. Hence it is only by careful selection and planning that an adequate vegetarian diet can be devised. For practical purposes, therefore, it is usually much easier to provide adequate nutrition with diets containing some animal nutrients. Milk is well suited both economically and nutritionally to this purpose. When only 10 per cent of the total calories are provided by milk, nearly 0.5 gm of protein and 16 mg of

TABLE 4 Approximate Costs To Feed a Five-Year-Old Child 1600 Calories a Day with Diets Made up of Various Proportions of Vegetable-Fruit vs Animal Nutrients \*

TYPE OF DIET	SOURCE OF CALORIES		COST		COST RELATIVE TO DIET A	
	VEGETABLE-FRUIT NUTRIENTS	ANIMAL NUTRIENTS	ACRES OF LAND	100 MAN HR. OF FARM LABOR	LAND	LABOR
	% of total	% of total	$\times 10^{-3}$	$\times 10^{-3}$	%	%
A	100	0	120	36	100	100
B	90	10	183	57	152	158
C	80	20	246	79	205	219
D	70	30	309	100	258	278
E	60	40	372	122	310	340
F	50	50	435	143	362	397
G	40	60	498	164	415	455
H	30	70	561	186	467	515
I	20	80	624	207	520	575
J	10	90	687	229	570	635
K	0	100	750	250	625	695

\*Calculations based on average yield of calories per acre and per 100 man hours given in Tables 2 and 3

calcium per kilogram of body weight are supplied by the milk alone. Because milk is relatively inexpensive to produce, its inclusion to this extent raises the total cost of feeding relatively little (38 per cent) above that calculated for an all-vegetarian regime.

A further illustration of the economics of prescribing diets made up of different proportions of

calories (about 100 per kilogram) of body weight and water (150 cc per kilogram). However, because of variations in the amounts of milk and sugar used, the protein, fat and sugar allowances of each formula are different. For purposes of comparison, values for human milk are given at the bottom of the table.

Formulas A and B correspond closely to those commonly prescribed. When compared to human milk, it is seen that they provide about twice the quantity of protein taken by a breast-fed baby. The same thing is true of such minerals as sodium, potassium, calcium, chloride and phosphorus, the concentrations of which are three or more times greater in cow's than in human milk<sup>12, 13</sup>. Even Formula C, the cow's milk content of which is about half that commonly recommended, yields more protein and minerals than an equivalent volume of human milk. Yet this formula approximates the recommendation of Powers<sup>14</sup> that between 10 and 20 per cent of the total calories come from protein, 15 to 30 per cent from fat and 50 to 70 per cent from carbohydrate and the daily requirement of 2.2 gm of protein per kilogram of body weight reported by Levine<sup>15</sup>.

The relative costs of these formulas are estimated in the right-hand section of the table. It is to be noted that there are two columns under "cents," one of which is computed on the basis of whole milk and the other on the basis of evaporated milk. Formula C costs from one third to one half less than Formulas A and B, whether the measure of cost be monetary, acres of land or man hours of farm labor.

It is possible to make an approximate comparison between the costs of cow's milk vs human milk for infant feeding. It appears that human milk is produced with high efficiency (more than 90 per cent)<sup>16</sup>. If, therefore, a mother derives the

TABLE 5 Comparative Costs of Equicaloric Cow's Milk Formulas and Human Milk

FORMULA	COMPOSITION*			PROTEIN	SOURCE OF CALORIES			DAILY COST†			
	WHOLE MILK	ADDED CARBOHYDRATE	ADDED WATER		PROTEIN	FAT	CARBOHYDRATE	ACRES	100 MAN HR	CENTS	
	cc	gm	cc		gm/kg/day	%	%	$\times 10^{-3}$	$\times 10^{-3}$	whole milk	evaporated milk
A	600	0	0	5.3	22	49	29	120	55	13.2	7.5
B	400	33	200	3.5	15	32	53	82	40	9.9	6.1
C	250	57	350	2.2	9	20	71	53	30	6.6	4.2
Human milk	600	0	0	1.9	7	52	41	35‡	11‡	—	—

\*Based on average values given in the literature.<sup>11, 12</sup>  
†Based on values given in Tables 2 and 3 in addition to chain-store prices in Boston on December 29, 1947 (fresh milk \$0.22, evaporated milk diluted to whole-milk strength \$0.125 per liter and sugar \$0.20 per kilogram).  
‡Assuming that extra food required for milk production is derived entirely from the vegetable nutrients listed in Table 2.

vegetable vs animal nutrients is provided by infant formulas. Table 5 presents information concerning the composition and costs of three arbitrarily selected cow's milk formulas that theoretically might be fed an infant weighing 4 kg. Each of these provides the same allowance of total

extra calories and other nutrients necessary for milk production from appropriate vegetable-fruit nutrients similar to those illustrated in Table 2, the cost in acres and in man hours of farm labor is roughly half that of Formula C. On the other hand, if she obtains these extra calories by drinking cow's

enough calories from a mixed diet without at the same time giving him at least 2 gm of protein per kilogram of body weight daily. Incidentally, cereal-vegetable-fruit diets yielding 1600 calories can also contain over 600 mg of calcium, an ample amount.<sup>2</sup>

So far as is known, there is no objective evidence that mixed cereal-vegetable proteins are quali-

ty is used to raise a mixture of the various animal proteins listed in Table 3, the yields of calories (214,000) and of protein (10 kg) are reduced to approximately 20 per cent of those derived from the mixed vegetables and fruits.

Re-expressed in terms of the productivity of 100 man hours of farm labor, the average yield in the

TABLE 2 *Yield of Vegetable and Fruit Nutrients per Acre and per 100 Man Hours of Farm Labor\**

TYPE OF NUTRIENT	CALORIES		PROTEIN		CALCIUM	
	PER ACRE	PER 100 MAN HR.	PER ACRE	PER 100 MAN HR.	PER ACRE	PER 100 MAN HR.
Sugar†	6 634 000	2 787 000	0	0	0	0
Wheat, whole flour	1 132 000	12 582 000	41	450	167	1,852
Corn meal yellow	1 122 000	4 109 000	26	95	31	114
Oats rolled	987 000	10 963 000	35	390	202	2 245
Potatoes	2 283 000	3 358 000	53	79	348	511
Beans dry	1 081 000	4 159 000	68	260	457	1 756
Peas dry	1 248 000	—	86	—	257	—
Soybeans whole	1 545 000	12 879 000	153	1 238	1 001	8 343
Carrots	2 685 000	829 000	75	23	2 381	735
Cabbage	870 000	799 000	43	40	1,459	1 339
Tomatoes	408 000	242 000	18	11	198	117
Apples	1 073 000	873 000	6	5	98	80
Peaches	939 000	751 000	8	6	150	120
Oranges	1 909 000	1 224 000	31	20	1 264	810
Averages	1 325 000	4 400 000	49	220	615	1 500

\*Adapted from Christenson.<sup>4</sup>

†Excluded from averages.

tatively inadequate. That such regimes are at least compatible with survival is attested by the fact that the poorest peasants in southern Italy have lived on corn meal, green stuffs and olive oil and have done so for generations.<sup>10</sup> Meat in the form of fat pork was taken three or four times a year. There was no milk, cheese or eggs in their dietary. In China the diet is also largely vegetarian. It becomes of interest, therefore, to calculate the relative costs of substituting animal for vegetable

form of the vegetable-fruit nutrients exclusive of sugar is 4,400,000 calories and 220 kg of protein. In the form of animal nutrients, the average yield from the same effort is about 640,000 calories and 28 kg of protein, or but 15 per cent of the productivity described for vegetables and fruit.

These data are reconsidered in Table 4, which presents calculated approximate costs of feeding a five-year-old child for an average day with vegetable-fruit vs animal-nutrient types of diet. It

TABLE 3 *Yield of Animal Nutrients per Acre and per 100 Man Hours of Farm Labor\**

TYPE OF NUTRIENT	CALORIES		PROTEIN		CALCIUM	
	PER ACRE	PER 100 MAN HR.	PER ACRE	PER 100 MAN HR.	PER ACRE	PER 100 MAN HR.
Whole milk	352 000	791 000	18	40	603	1 354
Eggs	144 000	313 000	12	25	49	108
Broilers and chickens	113 000	300 000	12	31	10	25
Hogs (pork and lard)	500 000	1 618 000	8	26	5	17
Steer	57 000	289 000	4	19	2	11
Lambs	115 000	521 000	6	26	4	20
Averages	214	640	10	28	112	256

\*Adapted from Christenson.<sup>4</sup>

nutrients or of adding extra animal-protein-containing foods to the vegetable regime. Tables 2 and 3 provide a basis for comparison.

When an average acre of land is used for raising the mixture of vegetables and fruits mentioned above, the average yield per acre is 1,325,000 calories and 49 kg of protein (Table 2). If an acre of land is used for raising sugar, the yield of calories is relatively much larger (6,600,000), but the protein yield is zero. By contrast, when an average acre

can be seen that the use of animal instead of vegetable-fruit nutrients greatly increases the costs of feeding. Viewed in these lights it seems that to include animal nutrients in the diet of children—and incidentally, of adults—may be more of an economic luxury than a nutritional necessity. Actually, as McCollum<sup>11</sup> has said, it is possible to make a fairly satisfactory diet of foods derived entirely from vegetable sources. But it is not easy to do so because vegetable foods tend to be bulky.

## BOSTON MEDICAL LIBRARY

## Report of the President\*

IN accordance with a long established custom it is my privilege to submit my second annual report as president of the Boston Medical Library.

Since our last annual meeting the active participation of the Massachusetts Medical Society in the affairs of the Library has become a fact. Every member of the Massachusetts Medical Society in good standing is now a Society member of the Library entitled to all the rights and privileges, except the right to vote, which by virtue of our charter is vested solely in the fellows. The Society allots \$5 00 of each member's dues toward the maintenance of the Library.

In view of this response to our appeal it seemed right and proper that the Society should have some voice in the management of the Library. Accordingly a special meeting of the Corporation was called, and the by-laws amended, to increase the membership of the Board of Trustees from twelve to sixteen, the Massachusetts Medical Society being invited to appoint four of that number. This invitation was accepted by the Council, and the president of the Society has appointed four trustees to serve one, two, three and four years respectively. Hereafter one new member will be appointed yearly. The additional income received will enable us to enlarge our personnel and increase our service.

Although we are grateful for this financial aid, we are still more grateful for the increased interest in the Library and hope that it will mean a much greater use of its resources by the members of the Society.

We have continued our efforts to put our house in order. Many volumes have been transferred to the Deposit Library in Cambridge. Many duplicates have been sold. Much remains to be done, but with the increase in our personnel we hope to progress steadily. The trustees have authorized the Librarian and the Director to enlarge our staff and several new members have already been appointed, but the reorganization must necessarily proceed slowly because of the lack of properly qualified persons to fill the positions.

We are greatly hampered by lack of stack room—five tiers of stacks in the fireproof ell have never been installed. The space where the stacks should be is now partially filled with volumes on temporary shelving on temporary scaffolding. This makes proper servicing a difficult if not an almost impossible accomplishment. If we are to give adequate service

these stacks and the service elevator must be installed. This will entail an expense of about \$75,000. How this can be financed is one of the many problems that confront us. It has been suggested that we solicit voluntary contributions, or that we borrow the money and set up a sinking fund to amortize the loan. I request that this be given serious thought.

In considering our financial setup it must be remembered that nearly two thirds of our invested funds are held in trust, the income only to be used for special purposes. Thus, we are committed to purchase rare books, or books on special subjects. We need a much larger unrestricted endowment to purchase current periodicals and volumes. Thanks to the care of the Treasurer, our funds, such as we have, are in excellent condition.

A certain portion of our income must be set aside each year for maintenance and repair of our building. Various repairs are imperative, and much painting needs to be done. The periodical room, which has never been finished, should be put in proper condition as soon as possible.

Very few fellows have resigned, scarcely more than the usual number. This is very gratifying. The fellows constitute the legal corporation of the Library. They are the custodians of its building, its books and its funds. They elect its officers and a majority of its trustees. This corporate body should be larger than it is now, so that the responsibility of this valuable institution may be shared by a large group. The additional income will also help. It may be possible in the future to provide more privileges for the fellows. I hope that each of us will propose one or more fellows during the coming year.

We are again grateful for the devoted services of the Librarian and the Director and our faithful staff. They have accomplished much under trying circumstances.

The Librarian will present a more detailed report on the present condition of the Library and his plans for the future. The number of visitors to the Library is increasing, and much more interest is apparent among the medical profession.

We are far from our goal, but with the hearty co-operation and support of the fellows and the new Society members, we have great hopes for the future.

WALTER G PHIPPEN

\*Presented at the annual meeting of the Boston Medical Library April 26, 1948.

milk, the costs are increased about fivefold and become comparable to those of Formula A

### DISCUSSION

The foregoing analysis sets forth some approximate information concerning average economics of human nutrition. It does not take into account variations in the agricultural potentialities of various geographical areas. Nor does it consider the important though less readily defined factors concerned with the flavor of food, the pleasure of eating and the influence on morale of palatable meals. A consideration of vitamins also has been omitted, though with the exception of vitamin D and possibly of riboflavin, vegetarian diets that are adequate in calories and protein appear to be satisfactory in other respects.

This information is of no moment to peoples who can afford what they want. It is of potential importance only when thrift is a necessity. The data presented provide no basis for recommending that animal be discarded entirely in favor of vegetable nutrients. On the other hand, they suggest that, when survival depends on getting enough to eat, due thought be given to the wastefulness of recommending more than minimal essential allowances of the animal type of nutrient.

Unfortunately, extensive data defining the minimum requirements of normal infants and children for protein, either animal or vegetable, are not available. In most of the published studies of protein requirements, the allowances of total calories were increased or decreased in approximate proportion to the protein allowances. Under these circumstances changes in nitrogen balance could have been due to changes in caloric intake as much as or more than variations in protein intake. Studies carried out in this clinic on healthy children two to ten years old suggest that when the caloric intake is ample, no improvement in the nitrogen balance is obtained by the daily administration of more than 2 gm of mixed protein per kilogram of body weight.<sup>8</sup> More detailed information of this type should be of value especially regarding infant

feeding in areas where cow's milk is scarce. For example, the same quantity of cow's milk dispensed as Formula C (Table 5) would feed one and a half times as many infants as it would dispensed as Formula B and nearly two and a half times as many as it would dispensed as Formula A.

These findings give some scientific substance to the Chinese proverb "20 ounces of chicken costs 20 pounds of rice."

### SUMMARY AND CONCLUSIONS

A brief survey of the approximate, relative costs of feeding infants various types of formula and children cereal-vegetable-fruit diets vs diets of equal caloric and protein content containing animal protein and fat is presented.

When thrift is necessary it is wasteful to feed babies by bottle or to provide more than minimal essential allotments of the animal-protein type of food for older children and adults.

### REFERENCES

- 1 National Research Council. *Recommended Daily Allowances*. Report and Circular Series No. 122, August, 1945. Revised 1946. Washington, D. C.
- 2 Talbot N. B., Sohel E. H., Burke B. S., Lindemann E., and Karlman S. B. Dwarfism in healthy children: its possible relation to emotional, nutritional and endocrine disturbances. *Am. Exp. Med.* 236: 783-793, 1947.
- 3 Siegert, F. Der Nahrungsbedarf des Kindes jenseits des ersten Lebensjahres. *Verhandl. d. Gesellsch. f. Kinderh.* 23: 251, 1906.
- 4 Idem. Der Eiweissbedarf des Kindes nach dem ersten Lebensjahre. *Verhandl. d. Gesellsch. f. Kinderh.* 24: 442-453, 1907.
- 5 Bartlett, W. M. Protein requirement as determined in diabetic children. *Am. J. Dis. Child.* 32: 641-654, 1926.
- 6 Walenta, E. Zur Frage der Eiweissbeschränkung in der Kost erbettischer Kinder. *Monatschr. f. Kinderh.* 41: 450-455, 1928.
- 7 Parsons, J. P. Nitrogen metabolism of children with special reference to protein requirements of children of preschool age. *Am. J. Dis. Child.* 39: 1221-1239, 1930.
- 8 Pick, W. and Talbot, N. B. Unpublished data.
- 9 Christenson, R. P. Cited by Brody.<sup>11</sup>
- 10 Lusk, G. *Elements of the Science of Nutrition*. Fourth edition. 844 pp. Philadelphia: W. B. Saunders Co., 1928.
- 11 McCollum, E. V. and Simmonds, N. *The Newer Knowledge of Nutrition*. Second edition. 675 pp. New York: Macmillan Co., 1925.
- 12 Brody, S. *Bioenergetics and Growth with Special Reference to the Efficiency Complex in Domestic Animals*. 1023 pp. New York: Reinhold Publishing Corp., 1945.
- 13 Shohl, A. T. *Mineral Metabolism*. 384 pp. New York: Reinhold Publishing Corp., 1939.
- 14 Powers, G. F. Infant feeding: historical background and modern practice. *J. A. M. A.* 105: 753-761, 1935.
- 15 Levine, S. Z. Protein nutrition in pediatrics. *J. A. M. A.* 128: 287, 1945.
- 16 Kaucher, M., Moyer, E. Z., Williams, H. H. and Macy, I. G. Adequacy of diet during lactation. *J. Am. Dietet. A.* 22: 594-601, 1945.

men who lived long by using it. The single edition of this work was printed in 1484.

A third book was a treatise on fevers, thrice printed before 1501 and frequently in the sixteenth century. All the incunabula editions are in the Library. Another book is *De pulsibus, urinis et egestionibus*, 1487 and 1497, both editions being in the Library.

His best known work is on baths and mineral springs, printed in Ferrara in 1485. There are three incunabula editions, of which the Library has two (1485 and 1496). The book was probably written before 1450 and later revised before his death in 1462. A work on physiognomy exists only in manuscript. A vernacular text on gout, possibly taken in part from his *Practica* was printed in 1505. Both in the work on physiognomy and in that on baths, Savonarola showed originality, his *Practica* and other medical writings appear to be ordinary treatises of their time.

Three books, illustrating the spirit and practice of medicine in the sixteenth century, were also added in 1947. The first is by a priest from Steinhelm who combined in one volume three of the most popular and widespread beliefs of his time — astrology, physiognomy and chiromancy. The book was published in 1522 in Strassburg and was frequently reprinted for the next one hundred and fifty years. Three Latin printings were needed the first year, and the text was soon set in German, English and French. The *Chiromantia* of John ab Indagine, or von Hagen, was one of the most popular books north of the Alps. John ab Indagine, a humanist who was not afraid to attack scholastic theology, was a friend of a fellow priest, Otto Brunfels, the herbalist. Some even thought him a Lutheran, and he, like Savonarola, sought the greater tranquillity in letters. He was not a great man, but a stern and resolute face stands out on the title page of his book (Fig. 2). His works reached England through the books of Fabian Withers.

The medieval and Renaissance practitioner was fond of one-volume libraries, something he could slip in his saddle-bag and turn to when faced with any occasion — medical, surgical, astrologic or even spiritual. Such is the *Collectanea Medica* manuscript of 1450 in our Library, the *Articella*, mentioned above, and the *Artzneybuch*s of later dates. A good example of the last is the one issued at Nuremberg in 1549 (Fig. 3), consisting of medical treatises of practical interest, including obstetrics and a dental tract.

The third book is on old age and how to prolong life beyond the short span common in the sixteenth century. The most noted book of this type was *De La Vita Sobria* of Luigi Cornaro, first published in Padua in 1558. Cornaro lived to be one hundred years old, but Thomas Philologus of Ravenna, also called Tommaso Rangoni, whose book, *De Vita Hominis Ultra CXX Annos Protrahenda*, the Library acquired in 1947, tried to prolong human life beyond

one hundred and twenty years. Thorndike tells us that Philologus began writing prognostications as early as 1515, taught logic at Padua and then astronomy. He lectured at Bologna, became physician to Cardinal Grimani, a public teacher of astrology at Rome and finally a popular professor at Padua, where "enthusiastic students carried him around town on their shoulders." The town echoed with his name and it was written all over the walls of

Ad diuini Leonidam Marchionem officium libelli  
de aqua ardenti Michaele Savonarola pbrum linc  
fideliter incipit. Utiles quilibet legant.

Um vir grauiſſimus Antonius roſſi  
las utriuſq; uis ſplendor quodam il  
luſtriſſime princeps de ardenti aqua me  
pſiteret idq; ſine intelligere maxime co  
peret cum quoſq; continuo uſu delectaret  
ſi capitis tremore in poſterum allatura  
eſſet in quam opinione multoſq; ſe modere uerebatur  
ego quidem cum ſue benignolentia plurimq; ſeruitus et  
ſemulatioſum nunc bonitatem hanc petitioneſ perſolue  
ret quodam pauca de ea colligere atq; operire conſtitui  
ut per gratum quicq; tibi facerem quo mihi etiam ſanſ  
factum foret. Quam cum ſue uoluntaria quodam reuel  
orem planeq; intelligeret re hanc naturaſ conſideras  
de qua poſt tue ualitudinis uſuſque tue protogatione ſic oc  
cedere poſſet et his cum ſemper dies nocteſq; pugnam  
ſtiam hunc libelluſ ſic edere et plurimuſ laude atq; eſpe  
rentia digniſſima colligere ut tue producende mite no  
mraſq; cum quod nimis cupio per me ſic occaſio dareſ.  
Quam optarem illuſtriſſime princeps cum in me ſacul  
tatem eamq; de re doctrinam cognitam eſſe qua me  
gerrime tibi de hac ſpla re ſuſſicere potuiſſet  
ſues quippe non minus per grauiſſima tibi q; nobi ſra  
croſa erit. Nam cum tamem quoſq; agnitione in me ſen  
tationeſ et quoniam deſcalbeſcam illam ſic digniſſimam ha  
riter aggredi ſicq; u. benentiuſ cum a uentibuſ no  
ſtris nudiſ ſcriptuſ autenticuſq; compenſum. et in no



FIGURE 1 First Page of *De Aqua Ardenti*, by Michele Savonarola (Pisa, 1484)

buildings. In turn Philologus endowed a college at Padua for thirty-two students from his home city of Ravenna and restored churches and other buildings at Venice. In 1575 he published a tract on syphilis. The edition of *De Vita* in the Library was published in Venice in 1550 (Fig. 4).

One other accession is of particular interest. The anatomist, Remmelin, wrote a famous atlas, the *Catoptrum Microcosmicum*, showing the human figure in a series of superimposed plates. The book was first issued with a Latin text in 1613 and was frequently reprinted. The Library has an edition of 1660. The book also appeared in German, and the Library has the 1632 edition, printed at Ulm. In 1947 we acquired an English edition, *A survey of the Microcosme, or the Anatomy of the Bodies of*

## Report of the Librarian\*

IT IS again the privilege of the Librarian to present to the Corporation of the Boston Medical Library his annual report—in this instance, his tenth accounting of the state of the Library. In general the year has been a good one, with a marked increase in use of the Library both by our readers and by those who borrow material from us. The addition of two persons to the staff has provided more and prompter service than we ever were able to offer before. The Library has continued to grow in size as well as in usefulness. In spite of inadequate stacks, poor lighting, unfinished rooms and an untidy duplicate storehouse, our books are still intact and our periodical files in reasonably good shape, and our treasures can be made available to all who knock on our door with scholarly intent and reasonable patience. The Director, whose knowledge of our Library affairs and medical librarianship in general is unexcelled, continued to serve, even on Sundays, those who most needed his help.

### SERVICE TO READERS

Our readers consist of the fellows, members of various classes, including the newly formed Massachusetts Medical Society members, students who are not members and the general public. We serve all, without distinction so far as the use of our collection is concerned in Holmes Hall. Many of the users, over 9000 in 1947, were neither fellows nor members, coming from classes not supporting the Library financially. To this service to the public the Library is dedicated.

The attendance in 1947 was not quite so large as in 1946, but nearly up to the average of the prewar years. Of more importance is the use of the collections, it was larger in 1947 than in any year in our history, with the exception of one year when the Harvard Medical School Library was closed and many of its readers came to the Boston Medical Library for their bookish inspiration. Thus we went ahead in 1947 of our prewar circulation rate, with the use of 42,638 books and periodicals, compared with 38,266 in 1946—a healthy sign in a growing institution. At the same time the interlibrary loans to other institutions doubled, by far the greatest use of our Library in this department ever experienced.

The Library, moreover, increased in size by over 2500 volumes and nearly 4000 pamphlets. Owing to increased personnel we were able to prepare and bind more than 1600 periodical volumes, 1000 greater than in 1946. Thus, the Library furnished more material to its readers in 1947 than ever before, and this service was rendered by our old staff and the two additional and very welcome new members.

\*Read in part at the annual meeting of the Boston Medical Library April 26, 1948.

### ACCESSIONS

Seven incunabula were added to the Library in 1947, bringing our total to 696. They included *De anima* of Alexander of Aphrodisias, three other copies of which were listed by Stillwell as in libraries in the United States. Alexander was a Greek philosopher and commentator on the writings of Aristotle who lived in Athens at the beginning of the third century A.D. Sarton describes him as "the greatest scientific thinker of the time." A general study of Alexander's work in science is badly needed.

Another addition was the second printing of the *Articella*, a popular collection of the writings of Galen, Hippocrates and others, widely used by students in the fifteenth century. The Library has two other incunabula editions of this book, now having three of the six recorded printings before 1501.

The Library has an unusually complete run of the first printings of the works of Michele Savonarola, the physician and grandfather of the Dominican martyr, Girolamo Savonarola. Two further editions were added in 1947, the rare *De aqua ardenti*, published in Pisa in 1484 (Fig. 1), and a copy of *De febris*, issued at Venice in 1496.

Giovanni Michele Savonarola, physician to the famous Este family of Italy, was born at Padua in 1384 and died in 1462, neither date being clearly fixed. All his works were originally circulated in manuscript and only printed posthumously. The most popular was his *Practica de aegritudinibus*, edited by Alexander Sermoneta and Joannes Aquilanus, first published as a printed book at Colle di Valdelsa by Bonus Gallus in 1479, seventeen years after the death of the author. Before that time eager students were forced to use manuscripts, some with faulty copy and all of them both scarce and expensive. With printing, the floodgates of learning were open: two more editions were demanded before 1501, and the book was frequently reprinted in the sixteenth century, filling a need long after the author's death.

The *Practica* is Savonarola's chief medical work and was probably finished by 1440, for a manuscript edition is known of that date. It was written at Padua, where he received his degree of doctor of medicine from the University on August 20, 1413, and later taught and practiced. After 1440 he became physician to Niccolò III, marquis of Este. After the death of Niccolò he served Lionello and then Borso d'Este in the same capacity. The *Practica* deals, according to Lynn Thorndike, with the causes and cure of disease, prognostics, the physician's personality, foods and medicines and their effects, the last being largely taken from Avicenna.

In *De aqua ardenti* Savonarola accepts alcohol as an essential medicine and recounts the lives of noted

voted to the Library as he was to his chosen profession of orthopedic surgery and to Tufts College Medical School, where he served as dean from 1913 to 1922. One of his avocations was the history of medicine, and naturally he turned to the Boston Medical Library as a source of inspiration, believing at

and it was Cushing who wrote in a letter to his father, dated January 31, 1892

Painter I like very much. He is slow, but hangs on to everything he gets. He hails from Great Barrington, Mass. and is a great big solid whole-souled creature such as one likes to meet.

They both went to Massachusetts General Hospital, where Painter was associated with E. H. Bradford, Robert Lovett and the other brilliant orthopedic pioneers of the time. He was surgeon-in-chief at the Carney Hospital for many years.

Even before he was chosen librarian in 1929, Dr. Painter had long been interested in the Boston Medical Library and had served on a number of commit-



FIGURE 3 Title Page of *Arzneibuch* (Nuremberg, 1549)

the same time that he might contribute, at least in his modest way, to the work of the Library.

Dr. Painter was born in Grand Haven, Michigan, May 19, 1869. Coming from an old Virginia family, he enjoyed the reunions of the Painter family held at Pulaski, Virginia, a delightful region between the Blue Ridge and the Allegheny Mountains. He received the degree of A. B. in one of the earlier classes of the newly founded Johns Hopkins University in 1891. After four years of study at Harvard Medical School he received the degree of M. D. in 1895. In his class were many men whose names are well known to the members of the Boston Medical Library. They include Joseph Capps, Arthur Chute, Amory Codman, Harvey Cushing, Elliott Joslin, Timothy Leary, William Robey and Franklin White, many of whom were destined to make their names known not only in this country but also abroad. Harvey Cushing was closely associated with Charles Painter during his four years in the Medical School,

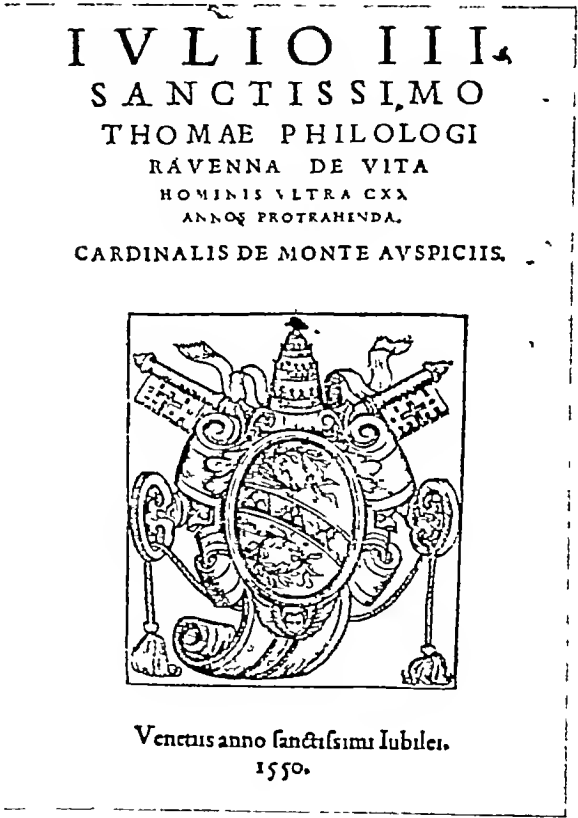


FIGURE 4 Title Page of *De Vita Hominis Ultra CXX Annos Protrahenda*, by Thomas Philologus (Venice, 1550)

tees. His literary endeavors, moreover, led to the creation of a chair of the History of Medicine at Tufts College Medical School, a position occupied by him for a number of years. He edited the *Yearbook of Orthopedic Surgery* and served for a long period on the editorial board and briefly as the editor of the *Journal of Bone and Joint Surgery*. He was president of the American Orthopaedic Association in 1915-1916.

*Man and Woman*, the gift of one of our trustees, 1905 Dr Farlow augmented the work of the first printed in London in 1695 All three books have the librarian, Dr Chadwick, who had started the Li



FIGURE 2 Title Page of *Chiromantia*, by John ab Indagine (Strassburg, 1541)

fine, but fragile, superimposed plates in good condition

#### CHARLES FAIRBANK PAINTER

Dr Charles F Painter died suddenly at his home, January 6, 1947. He served as librarian of the Boston Medical Library from 1929 to 1937, following Dr John W Farlow, who had been librarian since

library on its modest career in 1875 only to see it develop into a medical institution of considerable proportions by 1905. It was Chadwick who saw us into our present house. Dr Painter, in turn, continued the fine standards set by his predecessors. He carried the Library, moreover, through a period of decreasing financial support, without materially reducing the service to its members. He was as de-

a fine account of our first president, with many of the pictures and quite a few of the facts furnished by the Library

### FUTURE

The Librarian plans to fill our space in the Deposit Library with little-used material in 1948. At the end of 1947 about a third of the shelves were in use. As a result some reorganization of our duplicate collection will be possible, but no major change can be considered until our additional stacks are in place. Personnel are to be added as soon as suitable persons can be found. Publishing projects

are under consideration. An addition to Farlow's *History* covering the period from 1918 to 1948 might be a fitting volume or a catalogue of our sixteenth-century books, similar to our published list of incunabula. Our Golden Jubilee, moreover, will occur in 1950, for on Monday, October 18, 1875, in two ground floor rooms at No 5 Hamilton Place, the Boston Medical Library began its reorganized existence, with Dr E H Brigham in charge. At that time Dr O W Holmes was the president, and Dr J R Chadwick the librarian.

HENRY R. VIETS

## MEDICAL PROGRESS

### PHYSIOLOGY\*

HEBBEL E. HOFF, M D,† AND H. J. SCOTT, M D ‡

MONTREAL, CANADA

ON NOVEMBER 22, 1947, the *British Medical Journal*<sup>1-4</sup> celebrated with a special issue the ninetieth birthday of Sir Charles Sherrington, whose *Integrative Action of the Nervous System* had been reprinted earlier in the summer as a feature of the seventeenth International Physiological Congress, the first to be held since the end of the war.<sup>5</sup> Both were gracious tributes to one of the great philosophers of the nervous system, a worthy member of that long and unbroken descent of scientific greatness represented by presidents of the Royal Society. Like that of Boyle, one of the founders of the Society, his philosophy has been anchored in the day-by-day experience of his laboratory, and theories, built on experiment, served to direct the experimentation of the next day, for, as Boyle said, these matters "should not be barely asserted, but explicated and proved."<sup>6</sup> Few neurophysiologists have been a part of so many of the fundamental movements in their field, we can expect only Galen perhaps who was its founding father, for Sherrington saw more clearly than any that the simple reflex, with its afferent and efferent arcs keeping action always under control of environment, furnishes the clue to the operations of the complicated region of the nervous system, where always the basic connection of afferent and efferent, sensory and motor functions is continued. Thus Sherrington was the great master of the reflex, and no one has surpassed him in his description of its nature and in biologic purposiveness, in fact Sher-

ington has brought to a close a whole era in neurophysiology, that of the reflex. Standing thus at the end of one classic development he participated equally importantly in the beginnings of two others: the study of cortical function and the investigation of the intimate physiology of unitary components of biologic patterns—indeed, it was in recognition of his investigation of the "single unit" that he shared with Adrian the Nobel Prize in Medicine in 1932. Finally, when the laboratory could no longer claim him, he has turned his rich experimental background to reflexions of "Man on his Nature,"<sup>7</sup> carrying out to the fullest extent the obligation of the physiologist to attempt always the synthesis of total and unit behavior—to explain the whole in terms of its parts.

So Sherrington has given a philosophy of neurophysiology, but he has furnished too the language and the tools of the work that lies ahead, as witness the happy phrase "synapse" and that inexhaustible source of experimentation, the decerebrate cat. Above all he has had the remarkable faculty of transmitting to others something of his own outlook. In no small measure this has been because of his acute sense of historical perspective, his willingness to learn from Aristotle and Galen, Fernel and Descartes, Marshall Hall and Goltz, and his ability to frame his own work against the background of the past. Few are the centers of neurophysiology where his pupils, or his pupils' pupils, are not to be found, and none where his influence has not reached. It is not inappropriate therefore to review some of the more significant advances in neurophysiology, in which his influence may be seen at work.

\*From the Department of Physiology McGill University Faculty of Medicine.

†Joseph Morley Drake Professor of Physiology McGill University Faculty of Medicine.

‡Research Assistant, Department of Physiology McGill University Faculty of Medicine.

The Library loses a friend of many years' standing. Although heavily engaged in the active practice of surgery he was always ready to devote time to Library activities. His heart, moreover, was truly in the field of literature as well as in the practice of medicine. He was essentially a scholar both of orthopedics and of medical history. Indeed we can truly proclaim with his contemporary, Harvey Cushing, Dr. Painter was a "solid whole-souled creature such as one likes to meet."

### LIBRARY ACTIVITIES

#### Addresses and Meetings

The Librarian addressed the Section of Neurology and Psychiatry of the New York Academy of Medicine on "The History of Neurology in the Last Hundred Years," in New York City on March 11, 1947, the session on the History of Medicine, American Medical Association, on "American Medicine in the Massachusetts Bay Colony," at Atlantic City, June 11, and Massachusetts Historical Society on "Benjamin Waterhouse on Luigi Cornaro's *Long and Healthful Life*," Boston, October 9.

The Director and the Librarian attended a farewell dinner to Dr. Henry E. Sigerist, former professor of medical history at Johns Hopkins University, in May in New York, the meetings of the American Association for the History of Medicine and the annual session of the Medical Library Association, held at Cleveland the same month, and the meeting of honorary consultants to the Army Medical Library in Washington in October. The Librarian also visited the Medical Library of Duke University, the Welch Medical Library in Baltimore and the Medical Library of the New York Academy of Medicine during the year and made numerous visits to the Army Medical Library, both in Cleveland and Washington, as chairman of the Committee on Historical Medicine of the last institution.

In April Miss Genevieve Miller, assistant editor of the *Bulletin of the History of Medicine*, was tendered a dinner before her address to the Boston Medical History Club, and in October Mr. Geoffrey Keynes, the distinguished British surgeon and bibliographer, was a guest of the Librarian in Boston.

#### Book Reviews

About 250 books, received from the *New England Journal of Medicine*, were reviewed in 1947, either by short notes (about 100) or by longer, critical reviews. The short notes were mostly written by Mr. Ballard, and the reviews by some of our 96 devoted reviewers, whose names are listed semiannually in the *Journal*. The Library is indebted to the *Journal* for the books and to the reviewers who carefully evaluate the current literature and, in most cases, courteously deposit the book in the Library for the benefit of our readers.

#### Exhibits

The exhibit of the "Ether Demonstration" was held over for the first half of 1947 and was followed by an exhibit of material relating to the "History of the Boston Medical Library," showing the earliest catalogues of 1807-08, pictures of the various buildings used for the Library on Hamilton Place, Boylston Place and The Fenway, "The Want Book," or "Periodical Deficiency List" of Dr. James Read Chadwick and other memorabilia, arranged by Mr. Ballard.

#### Publications

Recent articles emanating from the Library are as follows:

- Seventy-first Annual Report of the Boston Medical Library for the Year 1946* 42 pp. Boston privately printed, 1947.
- Viets, H. R. Boston Medical Library. Report of the Librarian. *New Eng J Med* 237 14-20, 1947.
- Phippen, W. G. Boston Medical Library. Report of the President. *New Eng J Med* 237 12, 1947.
- Editorial. Fulton's Harvey Cushing. *New Eng J Med* 236 153-155, 1947.
- Viets, H. R. Harvey Cushing by John F. Fulton (book review). *Atlantic Monthly* 179 138, 1947.
- Idem*. Charles Fairbank Painter, 1869-1947. *New Eng J Med* 236 642, 1947.
- Idem*. In honor of Harvey Cushing. *Bull Hist. Med* 21 403, 1947.
- Editorial. Passing era in medical history. *New Eng J Med* 237 106, 1947.
- Viets, H. R. Edward Clark Streeter, 1874-1947. *Bull Hist. Med* 21 843-845, 1947.
- Idem*. Walter Channing (1786-1876). Pioneer in obstetric anesthesia. *North Carolina M J* 8 418, 1947.

#### VARIA

In 1947 the second edition of *A History of Medicine*, by Arturo Castiglioni, edited by Dr. E. B. Krumbhaar, was published. This monumental work, of particular importance for its discussion of the Italian influence on the Renaissance, was brought up to date by the inclusion of events in medicine occurring during the last six years since the first edition. A new history of medicine, also published in 1947, by Cecilia C. Mettler is distinctive, since it is arranged by subjects instead of in the usual chronologic form. Both are fundamentally reference books, although they cannot always be relied upon for bibliographic details. Other books of more than passing interest published in 1947 were *The Development of Modern Medicine*, by Richard Harrison Shryock, an expanded text of a book first issued in 1936, *Studies and Essays in the History of Science and Learning*, issued on the occasion of George Sarton's sixtieth birthday in 1944, but delayed in printing by the war, *Nicolaus Pol Doctor 1494*, by Max H. Fisch, *The Doctor in Oregon*, by O. Larsell, and of particular interest to the Boston Medical Library, *Amiable Autocrat: A biography of Dr. Oliver Wendell Holmes*, by Eleanor M. Tilton,

inhibitory activity must be exerted at the motor neurone or its synapses. The latency of inhibition of the two neurone arcs is, as Lloyd has shown, extremely short, no more perhaps than a millisecond. This demands in turn that the central pathways for such inhibition must be in themselves very short. To cover these requirements Brooks and Eccles have recently brought forward a novel and most ingenious electrical hypothesis of central inhibition that forms a logical counterpart to Eccles's electrical theory of central excitation. According to this hypothesis the inhibitory volley operates by subliminally stimulating an internuncial cell sending a short axon to the motor neurone to be inhibited. On the soma of the internuncial neurone will be created a local synaptic potential that will act as a sink into which current will flow from the axon and inactive areas of the soma and dendrite of that cell. There will therefore be a considerable outflowing current from the synaptic ending of the axon of this cell, which will in large part penetrate the postsynaptic membrane of the motor neurone. There it will produce a localized region of anelectrotonus, and as a result the excitability of the region will be depressed. One may now assume (and there are good histologic grounds for so doing) that the surface of the motor neurone is liberally covered with hundreds of synaptic endings, and postulate that inhibitory endings are more or less uniformly dispersed. If excitatory impulses are alone discharged the local responses will spread and fuse, generating the discharge of an all-or-nothing impulse. If, however, inhibitory impulses arrive simultaneously with or slightly before the excitatory impulses each excitatory focus will be surrounded by a zone of raised excitability, which will as it were isolate the excitatory influences and prevent their growth and fusion into a propagated impulse.

### THE CEREBRAL CORTEX

#### *Somatic Afferent Areas*

Interest in the motor area of the cerebral cortex has been so keen and discussion over it has waxed at times so hot that the equally important function of the cortex as an afferent receiving station has at times been neglected. But those who have thought deeply of the plan of the central nervous system have seen in the development of the higher centers an opportunity for the renewal of the effective association of afferent and efferent fibers that forms the plan of the simple reflex arc. Walshe<sup>14</sup> wrote of this

There we have presented to us a conception of the nervous system in which the entire edifice is reared upon two neurones, the afferent root cell and the efferent root cell. The two form the pillars of the fundamental reflex arc and on the junction between them are superimposed, mediately or immediately, all the other neural arcs, even those of the cerebral cortex itself.

As Adrian<sup>15</sup> stated, "purposive acts, therefore, must be moulded like the movements of walking, by the controlled afferent patterns which are set up as the act progresses." Sherrington<sup>5</sup> wrote

The reactions of receptor organs which respond to stimuli from a distance tend especially to have large cortical representation. These receptors tend more than others to control the skeletal musculature of the creature *as a whole*. The contribution made by the cerebral hemispheres to the solidarity of the motor creature is largely traceable to their bringing to bear on other reflexes the unifying influence of the reactions of the distance receptors. Remembering these conditions it need not surprise us that the distance receptors more and more exert preponderant directive influence over the whole nervous system. To say this is to say no more than that the motile and consolidated individual is driven, guided, and controlled by, above all organs, its cerebrum. The integrating power of the nervous system has in fact in the higher animal, more than in the lower, constructed from a mere collection of organs and segments a functional unity, an individual of more perfected solidarity. We see that the distance-receptors integrate the individual not merely because of the wide ramification of their arcs to the effector organs of the lower centers, they integrate especially because of their great connection in the high cerebral centres. Briefly expressed, their special potency is because they integrate the animal through its brain. The cerebrum itself may be indeed regarded as the ganglion of the distance-receptors.

So too, indeed, thought Descartes, who neglected the spinal cord as a mere bundle of nerve fibers and placed the whole of reflex activity in the cerebrum. Here began all the motor nerves of the body and here were projected all the sensory fibers (according to Descartes a single fiber could, of course, perform both motor and sensory functions, its motor through the flow of animal spirits in its hollow axis cylinder, and the sensory by a fibril running in the core of the fiber). These were so arranged that their spatial pattern within the brain reproduced the spatial distribution of the receptors from which they originated, so that as he wrote of the eye, "if we see any creature come toward us the light reflected from his body paints two images, one in each eye and these two images beget two others by intercourse of the optic nerves in the interior superficies of the brain that look toward its cavity." The demonstration of the histologic basis for such point-to-point projection from retina to cortex constitutes one of the triumphs of neurohistology. Recently, however, the method of physiologic neuronography has been applied to the afferent projection systems, particularly by the group at Johns Hopkins, where Woolsey<sup>16, 17</sup> and a series of collaborators have meticulously traced pathways of action potentials set up by the natural stimulation of some isolated peripheral receptive zone. On the basis of these studies it is now possible to make cortical maps of somatic afferent representation of the body surface and of acoustical representation in the auditory area that show precise point-to-point representation. In 1941 Adrian<sup>18, 19</sup> reported studies of a similar nature that have opened up a completely new aspect of

## THE NATURE OF REFLEX ACTION

Sherrington was one of the first to appreciate the significance of Cajal's first studies with his new modification of the silver-staining technic, the whole of his reflex doctrine is based on the assumption of the validity of the neurone doctrine that Cajal established. This lack of protoplasmic continuity between neurones focused attention on the point at which one axon establishes communication with another neurone, and so important did this region become that he established a name for it—the synapse. To him the fundamental characteristics of reflex behavior stem from the particular physiology of the synapses, and their anatomic pattern. Here there developed states of excitation or inhibition, "CES" and "CIS," whose algebraic sum determined whether the neurone discharged or remained silent, and he determined with care their time courses in several reflexes. But although electrical recording was not neglected at Oxford (the string galvanometer had been enlisted early as an aid in the precise timing of muscular contraction), it has remained for his pupil Eccles to make the most complete study of the intimate nature of synaptic transmission in simple reflexes.

Sherrington<sup>5</sup> described the reflex as follows:

There is the co-ordination which a reflex action introduces when it makes an effector organ responsive to excitement of a receptor, all other parts of the organism being supposed indifferent to and indifferent for that reaction. In this grade of co-ordination the reflex is taken apart, as if separable from all other reflex actions. This is the *simple reflex*. A simple reflex is probably a purely abstract conception, because all parts of the nervous system are connected together and no part of it is probably ever capable of reaction without affecting and being affected by various other parts, and it is a system certainly never absolutely at rest. But the simple reflex is a convenient, if not a probable fiction.

Almost precisely in this sense has Lloyd<sup>8, 9</sup> defined the simplest of all reflexes, the proprioceptive stretch reflex. This reflex has its simplest expression in the knee jerk in the "spinal" man or animal, in a more highly developed form it is the fundamental component of reflex standing. Many earlier physiologists had indeed doubted that the knee jerk was in fact a reflex, its extremely short latency seemed to preclude this possibility.<sup>5</sup> Measuring the central latency of the reflex, Lloyd found that it was in fact so short that impulses entering via dorsal roots must have elicited a response in the ventral-horn cells without the mediation of an internuncial neurone. The stretch reflex is thus the simplest of all reflexes, involving only the direct influence of receptor upon effector neurones. This simple reflex is, however, organized, anatomically and physiologically, in relation to reflexes from other muscles acting at or across the same joint, reinforcing and being reinforced by some, and inhibiting and being inhibited by others, to form a functioning whole, which is the unit of biologic organized activity, the myotatic unit.<sup>9</sup>

Eccles<sup>10-13</sup> has recently summarized the evidence that at a variety of regions of anatomic discontinuity, such as in the synapses of the sympathetic ganglions, at the somatic myoneural junction and at the synapse of the spinal reflex, transmission occurs by virtue of the electrical influence exerted by activity in the presynaptic tissue upon the structure on which it impinges. Studying the electrical behavior of these structures under normal circumstances and when transmission is diminished or suppressed by appropriate drugs, such as curare in the neuromuscular junction and deep anesthesia in the reflex, Eccles has found evidence for the postulate that the passage of the impulse down the terminal portions of the presynaptic fiber causes flows of current in and out of the postsynaptic membranes that act precisely as an externally applied electrical stimulus. As the impulse first approaches the synapse in the presynaptic fiber it creates across the junction a momentary anelectrotonus, or the state produced at the positive pole of an external current applied to the tissue. This anelectrotonic state momentarily depresses the excitability of the postsynaptic tissue and delays its eventual response. It can account almost entirely for the phenomenon of synaptic delay. As the impulse in the presynaptic fiber reaches and occupies the whole of the synaptic expansion, the current is reversed and flows from the immediately adjacent postsynaptic membrane into the activated region of the synapse. This creates in turn at the postsynaptic membrane a catelectrotonic focus, which spreads exponentially over the surface of the neurone, out of its most intense area there grows a local response of the neurone. If by virtue of the concentration of synaptic endings the catelectrotonic focus is large enough in area and intense enough in degree, out of it or out of the local response itself there can develop a full blown action potential that will sweep over the excited cell. If neither the local response nor the exponentially propagated electronic potential is large enough to set up a propagated impulse, the slowly decaying potential will nevertheless alter the threshold of the neurone so that a second impulse arriving at that or nearby synapses and in itself incapable of creating a propagated impulse in a resting neurone might find the threshold now low enough to evoke a response. This is the basis for summation.

In the recent studies on the mechanism of central inhibition that Brooks and Eccles<sup>11, 13</sup> have carried out, one sees "a return to the original concept of Sherrington, that there are converging on motor neurones two sets of impulses, those exciting and so tending to cause the reflex discharge of impulses and those directly opposing this influence." This concept is a necessary consequence of Lloyd's demonstration that the stretch reflex involves only a two-neurone arc, for since this reflex can be inhibited by appropriate afferent stimulation, such

pathologic physiology of the human conditions. Recent studies bring this objective much closer to realization. The first of these is the discovery by Magoun and Rhines<sup>27</sup> of an inhibitory mechanism in the bulbar reticular formation. Stimulation within the reticular substance lying ventromedially in the lower part of the bulb was found to inhibit spinal-cord reflexes and decerebrate rigidity and induced cortical motor responses. Such inhibition was bilateral from either side of the reticulum, although at lower thresholds some ipsilateral inhibition could be identified. A variety of evidence showed that this bulbar-depressor center probably receives activating impulses from a suppressor area (4S) of the cortex, from the cerebellum and from the basal ganglia.<sup>28</sup>

Further work by Bach and Magoun<sup>29</sup> confirms the impression gained by earlier experimenters that much of the facilitation of the stretch reflex that is responsible for decerebrate rigidity descends to the spinal cord via the vestibulospinal tract and originates in the vestibular nuclei. But Rhines and Magoun<sup>30</sup> find that another important source of facilitation descends by a more laterally lying tract from a widespread center for facilitation extending from the thalamus, the sub-hypothalamus, the central gray and tegmentum of the midbrain, the pontine tegmentum and the bulbar reticular formation. Stimulation in these regions facilitates the reflexes of the lower center and augments the effect of cortical stimulation.<sup>30</sup> In the decerebrate animal much of this region has been removed, leaving to the vestibular system the greatest responsibility for maintenance of decerebrate rigidity, but in the intact animal this newly discovered facilitatory center assumes greater importance, particularly in the facilitation of phasic movement. Rhines and Magoun point out that it is essential to recognize that this facilitatory area is the same that on more intense stimulation will yield motion. This motor system, in all probability, maintains the almost normal motor activity of the decorticate cat and permits even the decorticate infant monkey to maintain a simple type of locomotion and muscular activity.

Ward<sup>31</sup> has shown that in the "decerebrate" rigidity resulting from small doses of sodium cyanide or other agents, neuronal activity is suppressed first at the cortical level and then at successively lower levels as the concentration of the agent increases. By implanting electrodes in the bulbar suppressor center he has shown that decerebrate rigidity appeared at the time when failure of nervous activity in centers activating the suppressor region produced a deprivation paralysis of this center and thus permitted the unrestrained activity of the facilitatory center to be expressed in the appearance of decerebrate rigidity.

Taken as a whole these studies form a logical complement to those on stimulation and

ablation of the premotor cortex and serve to establish the concept of a nonpyramidal projection system mediating complex reflex reaching and grasping acts, movements of neck and shoulder-girdle musculature, rhythmic movements of the lips and of the tongue, as in sucking and licking, rhythmic movements of the upper extremities, behavior pattern and patterns of progression as well as inhibition of posture and other reflexes of the spinal cord.<sup>32</sup> Discovery of these brain-stem facilitatory and suppressor regions permits an explanation of many states of atonia and diminution of movements seen in man and in experimental animals, such as the observations of Keller<sup>33</sup> demonstrating atonia rather than decerebrate rigidity after large lesions in the region of the pons, the fixed, immobile and mask-like facies seen in the monkeys with hypothalamic lesions observed by Ranson,<sup>34</sup> the akinesia of cats with large caudal hypothalamic lesions observed by Bard<sup>35</sup> and others and the production of mutism or reduction of facio-vocal activity after damage of the periaqueductal gray matter and tegmentum.<sup>36, 37</sup> All these may be interpreted as resulting from damage to brain-stem centers for facilitation. Most suggestive of the function of the bulbar suppressor center is the observation of Wagley<sup>38</sup> that a section of the reticulospinal fibers in the cord produces spasticity without paralysis.

This view of the function of the extrapyramidal system forms the logical counterpart to the concept of the pyramidal system as a predominantly motor apparatus, developed largely to mediate the control of skilled motion. This surely stems from Descartes, for although Galen recognized that the brain was the source of the spinal cord and the peripheral nerves, his more general concept was of the brain as a pool from which the animal spirit flowed to be distributed by the spinal cord acting more or less as an irrigation-distributing system. Descartes elaborated the hypothesis that the brain was linked to each muscle by isolated nerve fibers originating from the cavities of the brain in a spatial arrangement reconstructing the body. The mind or reflexes generally evoked motor response appropriate to the circumstances by opening these nerve endings to the animal spirits in the manner of an organist manipulating a keyboard. His concept was almost precisely that of Walshe,<sup>14</sup> who, arguing in quite the opposite direction, wrote as follows:

It would seem therefore that we may look upon the pyramidal system as an internuncial, a common pathway by which the sensory system initiates and continuously directs, in willed movements, the activity of the nervous motor mechanisms. The pyramidal system of itself initiates nothing and to speak of it as "responsible for" this or that category of movement is to ignore the force and motor power of its activities. It is simply the channel through which pass the impulse volleys by which willed movement is activated and continuously moulded by controlling cortical afferent patterns of excitation.

the problem of cortical localization. He found that a representation of different parts of the body's surface could be mapped out on the sensory area and that in general the receiving area of the cortex is concerned with parts of the body surface that are most closely related to the outside world. Thus, in the rabbit the mouth parts and in the cat the claws and the dorsal and lateral aspects of the forelimbs are most importantly represented, the face area is large in the dog, and the representation of hand and face important in the monkey.

Most significantly, however, Adrian found that the digits of the cat had a double representation, impulses from the claws and the ventral side of the toes appearing in a second area lying posterior to the face and extending back into the ectosylvian gyrus. A similar double representation has been found in monkey and man.<sup>20</sup> The somatic area I is of course the previously recognized afferent area in the postcentral gyrus of man and its homologue in other mammals. Somatic area II in the monkey lies on the upper back of the sylvian fissure between the auditory areas of the lower sylvian banks and the face subdivision of somatic area I. It is significant that the pattern of representation of body surface in the postcentral gyrus coincides closely with the pattern for distribution of motor points in the precentral gyrus. Representation in the second sensory area is not so precise, the largest responses being produced by stimulation of the extremities of the limbs, the snout and the tail of the monkey. Both contralateral and ipsilateral representation is found, the former being about twice as strong as the latter. There is differentiation of face, arm and leg centers within this area that overlap extensively in the rabbit, less so in the cat and least in the monkey. There are data to suggest that the two areas have separate projections into the cortex although they are apparently interrelated at the cortical level in addition. Rassmussen and Penfield<sup>21</sup> have surveyed over three hundred and fifty stimulation records in man to find 8 patients in whom the presence of a second sensory area would account for unexpected responses for which there was previously no explanation. In these patients subjective evidence of sensation was elicited when the brain was stimulated at the foot of the sensory motor strip just above the sylvian fissure.

Woolsey and Walzl<sup>16</sup> and Ades<sup>22</sup> found a second auditory area lying immediately ventral to the primary auditory cortex in the cat. A point-to-point projection of the cochlea was found in the primary projection area, each cochlea being represented bilaterally in the primary projection area with approximately equal ipsilateral and contralateral representation for each cochlea. The focal area for the basal end of the cochlea was found at the upper end of the anterior ectosylvian sulcus, with the apical end of the cochlea represented just

behind the upper end of the posterior ectosylvian sulcus. The second auditory area lies immediately ventral to the primary auditory cortex, but it is organized in a pattern inverse to that of the primary system with the basal end of the cortex represented caudally and the apex rostrally. Finally, evidence for double representation of vision has also been presented.

Clues to the significance of this re-representation of the three major sensory areas have not yet been found, but Woolsey emphasizes the fact that it appears to be a fundamental principle of organization in other spheres. He points out that there is evidence that the cerebellar receiving areas are also double, that there are apparently slow and fast groups responsible for conduction of pain, that, as Adrian<sup>23</sup> has shown, the electric response of the human eye to the flash of light can be divided into a rapid and a slow component, and that, as pointed out below, a re-representation of the motor area also exists. It is obvious that these studies open up a whole new field for investigation, the detailed analysis of the relations of these areas to each other by direct intercortical communications or through corticothalamic associations has been started<sup>24,25</sup> and gives promise that the future will see an understanding of the association of afferent and motor systems at the cortical level with a degree of completeness that now characterizes the interaction of these two systems at the simple monosynaptic reflex level.

### *Cortical Control of Posture and Movement*

Sherrington's discovery of decerebrate rigidity brought into relief the concept of levels of integration developed by the clinical neurologists, according to which the developmentally higher centers were capable of inhibiting as well as exciting spinal-reflex centers. Damage to higher centers resulted not only in a deprivation paralysis of some functions but also in release-phenomena from discontinuance of the normal braking action. The continued validity of this concept finds expression in modern as well as in the older literature—for example, in the observations of Wang and Lu<sup>26</sup> on the development of the tadpole. These authors observed that the first integrating mechanism to develop in the tadpole is a spinal system for repeated reaction to a single stimulation. Somewhat later there developed in the rostral half of the hind brain a center that inhibits the spinal mechanism, reducing its spontaneous activity and limiting the reaction from external stimulation to a short response instead of the prolonged response of an earlier stage.

The many similarities between decerebrate rigidity and spastic states in man following lesions within the central neuraxis have encouraged the hope that from closer analysis of decerebrate rigidity in animals, clues might be found to the

machinery by which the synthetic powers of that cortex are made possible. The motor cortex seems to possess, or to be in touch with, the small localised movements as separable units, and to supply great numbers of connecting processes between them so as to associate them together in extremely varied combinations."

(To be continued)

REFERENCES

1. Fulton J F Sherrington's impact on neurophysiology *Brit M J* 2 807-810 1947  
2. Brown T G Sherrington — the man *Brit M J* 2 810-812 1947  
3. Ritchie, A. D Sherrington as philosopher *Brit M J* 2 812 1947  
4. Editorial Influence of Sherrington on clinical neurology *Brit M J* 2 825 1947  
5. Sherrington C. S *The Integrative Action of the Nervous System* 434 pp London Cambridge University Press 1947  
6. Patterson, T S John Mayow in contemporary setting contribution to history of respiration and combustion *Isis* 15 47-96 and 504-546 1951  
7. Sherrington C S *Man or His Nature* 413 pp London Cambridge University Press 1940  
8. Lloyd D P C Facilitation and inhibition of spinal motoneurons *J Neurophysiol* 9 421-438 1946  
9. *Idem*. Integrative pattern of excitation and inhibition in two-neuron reflex arcs *J Neurophysiol* 9 439-444 1946  
10. Eccles J C. Electrical hypothesis of synaptic and neuro-muscular transmission *Ann New York Acad Sc* 47 429-455 1946  
11. Brooks C. Mc. and Eccles J C. Electrical hypothesis of central inhibition *Nature* 159 760-764 1947  
12. Eccles J C. Conduction and synaptic transmission in nervous system. *Ann. Rev. Physiol* 10 93-116 1948  
13. Brooks C. Mc., and Eccles J C. Electrical investigation of mono-synaptic pathway through spinal cord *J Neurophysiol* 10 251-274 1947  
14. Walsh F M R. On rôle of pyramidal system in willed movements. *Brain* 70 329-354 1947  
15. Adrian E. D General principles of nervous activity *Brain* 70 1-17 1947  
16. Woolsey C. N and Walzl E. M. Topical projection of nerve fibers from local regions of cochlea to cerebral cortex of cat. *Bull. Johns Hopkins Hosp* 71 315-344 1942  
17. Woolsey C. N Patterns of sensory representation in cerebral cortex. *Federation Proc* 6 437-441 1947  
18. Adrian E D Afferent discharges to cerebral cortex from peripheral sense organs *J Physiol* 100 159 191 1941

19. *Idem* Afferent areas in brain of ungulates *Brain* 66 89-103 1943  
20. Woolsey C N Somatic functions of central nervous system. *Ann. Rev. Physiol* 9 525 552 1947  
21. Rasmussen T and Penfield, W Further studies on sensory and motor cerebral cortex of man *Federation Proc* 6 452-460 1947  
22. Ades H W Secondary acoustic area in cerebral cortex of cat. *J Neurophysiol* 6 59-63 1943  
23. Adrian E. D Rod and cone components in electric response of eye *J Physiol* 105 24-57, 1946  
24. Bailey P von Bonin G Garol H W and McCulloch W S Functional organization of temporal lobe of monkey (*Macaca mulatta*) and chimpanzee (*Pan satyrus*) *J Neurophysiol* 6 121-128 1945  
25. McCulloch W S and Litvin J L Somatic functions of central nervous system *Ann. Rev. Physiol* 10 117-132 1948  
26. Wang G and Lu T Hind brain and early development of behavior in frogs *J Neurophysiol* 7 151-162 1944  
27. Magoun H W and Rhines R. Inhibitory mechanism in bulbar reticular formation *J Neurophysiol* 9 165-171 1946  
28. McCulloch W S Graf C and Magoun H W Cortico-bulbo-reticular pathway from area 4 S *J Neurophysiol* 9 127-132 1946  
29. Bach L M N and Magoun H W Vestibular nuclei as excitatory mechanism for cord. *J Neurophysiol* 10 531-537 1947  
30. Rhines R. and Magoun H. W Brain stem facilitation of cortical motor response *J Neurophysiol* 9 219-229 1946  
31. Ward A H Jr Decerebrate rigidity *J Neurophysiol* 10 89 103 1947  
32. Hines V L Motor areas. *Federation Proc* 6 441-447 1947  
33. Keller A D Generalized atonia and profound dysreflexia following transection of brain stem through cephalic pons *J Neurophysiol* 8 275-288 1945  
34. Ranson S W and Berry C. M. Observations on monkeys with bilateral lesions of globus pallidus. *Arch. Neurol & Psychiat.* 46 504-508 1941  
35. Bard P Hypothalamus and sexual behavior *Res Pub Assn. Nerv Ment Dis* 20:551 579 1940  
36. Kelly, A H Beaton L E and Magoun H W Brain stem mechanism for facio-vocal activity *Federation Proc* 4 40 1945  
37. Bailey P and Davis E. Effects of lesions of periaqueductal gray matter on *Macaca mulatta* *J Neuropath & Exper Neurol* 3 69 72 1944  
38. Wagley P F Study of spasticity and paralysis *Bull Johns Hopkins Hosp* 77 218-274 1945  
39. Willis T *The Remaining Medical Works including Five Treatises* London 192 pp Dring Harper Leigh and Martyn 1681  
40. Sherrington, C. S *Selected Writings* Edited by D Denny-Brown. 532 pp London Hamilton Medical Books 1939

CASE RECORDS OF THE  
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

TRACY B MALLORY, M D, Editor

BENJAMIN CASTLEMAN, M D, Associate Editor

EDITH E PARRIS, Assistant Editor

CASE 34291

PRESENTATION OF CASE

A fifty-eight-year-old woman entered the hospital because of a right-upper-quadrant mass. One week before admission the patient had sudden onset of severe constant pain in the right upper quadrant, which lasted, diminishing somewhat in intensity, for two days and then disappeared only to return again quite suddenly two days before admission. This time the pain was severe enough to require morphine but lasted for only one day. With these attacks there were no chills, fever, nausea, vomiting or jaundice. There were no

genitourinary symptoms or bowel symptoms either with the attacks or during the months before admission. However, during this period the patient noted a small weight loss of undetermined amount. For many years certain articles of diet such as Coca-Cola, ginger ale and sweets caused frequency of urination and burning, and "rich foods" caused indigestion. Seven years before admission, following an attack of right-sided pain, she was told that she had a kidney stone. Two years later, following a period of weakness and nausea of indefinite duration, a parathyroid tumor was removed at another hospital. At about the same time a non-functioning gall bladder was found by x-ray examination. The patient's mother had died of carcinoma of the rectum, and a sister had died of carcinoma of the uterus. Physical examination disclosed a well developed and well nourished woman, the important physical findings being limited to the abdomen. In the right upper quadrant there was a smooth, slightly tender, apparently cystic mass approximately 15 cm in diameter, which appeared attached to the liver. The blood, urine and stool examinations were within normal limits, as were the nonprotein nitrogen, total protein, calcium, phosphorus, alkaline phosphatase, prothrombin time, bromsulfalein test and cephalin-flocculation test. A blood Hinton

Willis<sup>39</sup> adopted much the same view from Regius one of Descartes' students

Moreover, as we have affirmed, that the Instinct for the performing of Motions is brought altogether through the Nerves from the Head to the Muscles, and as every Trunk of the same Nerve, being oftentimes broken into many shoots, variously distributing them, sends it to many destinated Muscles, it may very well be doubted how the animal Spirits, conveying the Symbol of the motion to be performed with a certain choice, do actuate only these or those branches apart from other branches of the same, and do not indifferently enter all the branches or shoots of the same, to wit, as the blood passes through the Trunk of the Artery, and all its ramifications equally. The most Learned Regius, that he might solve this knot, supposes in the Nerves some little doors, like to those which are found in musical Organs, the apertures whereof admit the Spirits to these or those parts especially, the rest being shut up. But he ought to have shewn, if not the little doors themselves, yet at least by what instinct and by whose direction sometimes these, sometimes those are locked up, and others opened. But in truth, this may rather be said, that all the shoots of the Nerves and lesser branches remain distinct and singular among themselves from the part to which they are inserted, even to their beginnings, so that a peculiar tract of Spirits or way of passage lyes open, from the Brain and its medullary Appendix, to every Muscle and nervous part, for in truth, although the Nerves, according to their beginnings, may seem to arise from the greater Trunks, yet it will easily appear, if you shall open the trunk of those branches, that in them many little Nerves, only like hairs, for the sake of a better conduct, are collected together in the same bundle, yea, the coverings being separated, you may follow oftentimes the little Nervulets, and those single to the respective parts and members, to which they are destinated

More than anyone else it has been Sherrington who has been responsible for the development of a modern hypothesis of punctate localization by his repeated demonstration of the response to cortical stimulation and by publication of maps showing a regional representation of the body musculature in the precentral gyrus. It was obvious to Sherrington<sup>40</sup> that "the individual movement, elicited by minutely localized stimulations are, broadly speaking, fractional in the sense that each, though co-ordinately executed, forms, so to say, but a unitary part of some more complex act, that would, to attain its purpose, involve combination of that unitary movement with others to make up a useful whole." Sherrington concluded that the cortex is not merely a selector of patterned movements established at lower levels but a center for the integration of afferent and efferent impulses where both are represented in minute degree and where the possibilities for the interaction of the two are vastly expanded.

The large variety of partial, though discrete and in themselves perfect, movements of separate portions of the bodily framework, evocable by localised point-to-point stimulation of the motor cortex, and the multiform combinations which these assume under cortical reaction and the right mutual associations of the cortical motor points which the physiological phenomena of "facilitation" and "deviation of response" reveal, are suggestive. They lead to the supposition that from movements of locally restricted parts—e.g., movements of a finger or a limb-joint (movements themselves discrete and individually separable in the motor cortex)—the upbuilding of larger combinations varied in character and service

able for purposes of different and varied kind, prehensile, defensive, locomotor, mimetic, masticatory, deglutitional, orientational (in von Monakow's sense), etc., is one of the main offices performed by the motor cortex. The functional properties of this cortex seem specialized for that end. It appears at first sight surprising that a motor nervous organ relatively so high as is the cerebral cortex in the nervous hierarchy, where the power to deal with large integrated complexes of the motor machinery might be expected, exhibits on actual examination a representation, still more or less discrete, of relatively small and "partial" movements. And in the motor cortex this discrete "representation" of small local items of movement, each highly co-ordinated with others yet separably elicitable, instead of becoming less evident with ascent to the higher types of hemisphere, becomes more so. Thus, it is more evident in cat and dog than in rabbit, more evident in the Macaque than in cat or dog, in baboon than in Macaque, in gibbon than in baboon, and in the chimpanzee, orang, and gorilla than in gibbon. It would seem that in order to preserve the possibility of being interchangably compounded in a variety of ways successive or simultaneous, these movements must lie, as more or less discrete and separable elements, within the grasp of the organ which has the varied compounding of them. To draw an analogy merely illustrative, the synthesis of the proteins of the body requires that certain metabolic organs must have, lying at their hand, the numerous amino-acid constituents of proteins, for that purpose the food proteins, split up into constituent chemical subgroups, more or less freed one from another, are presented to the synthetic organs for varied re-grouping in the re-synthesis which follows. The motor cortex appears to be par excellence a synthetic organ for motor acts. How does the motor cortex obtain these fractional and partial movements on which work its powers of varied synthesis? Simpler co-ordinated elements, such as flexion of a single joint—e.g., knee or elbow—can be safely assumed to lie ready to its hand in the bulbo-spinal mechanisms. But the higher of the compounded movements which those mechanisms give tend, if judged from the spinal and decerebrate dog and cat, to be compounds exhibiting total flexion or total extension of a whole limb. In the limb movements evoked from the anthropoid motor cortex, flexion of one joint may go either with flexion or with extension of another. The motor cortex may therefore obtain the partial and fractional movements it so variously weaves together by, to a certain extent, breaking up compounds already constructed by lower centres. Such analytic power may be a property of its own, or of some other, perhaps subcortical, organ with which it keeps close touch. Such synthesis involves time adjustments as well as spatial adjustments. The bulbo-spinal axis also, of course, synthesizes motor acts. But the difference between the constructive planes of the two is considerable. Bulbo-spinal synthesis constructs in the main those locally restricted but co-ordinate movements which the cortical synthesis finds ready to hand as elements for it to work with. The bulbo-spinal organ taken as a whole does, even in types so high as dog and cat, synthesize in addition to the local elementary movements a not inconsiderable number of more complex ones, such as respiratory, defensive, and even locomotory. But comparison of the synthetic capacity of the bulbo-spinal organ with that of the motor cortex reveals a great excess of synthetic capacity in the latter, as evidenced by the variety and multiform scope of the motor acts and sequences it builds up. Especially is this so when it is borne in mind that many acts which, when naturally performed, are bilateral, are, when excited by stimulation of one motor cortex, essentially unilateral, indicating that the two motor cortices have to be regarded as in many respects a single organ when in natural operation. Together they form, in such an animal type as the anthropoid ape, an organ for synthesis of movements—and of postures—on a vast scale. Phenomena, such as "reversal of response," "facilitation," and "deviation of response," prominent in cortical responses, and accounting for the functional instability of cortical motor points, are indicative of the enormous wealth of mutual associations existing between the separable motor cortical points, and those associations must be a characteristic part of the

## DR MCKITTRICK'S DIAGNOSIS

Hydrops of gall bladder

## ANATOMICAL DIAGNOSES

*Carcinoma of gall bladder*

*Cholelithiasis*

## PATHOLOGICAL DISCUSSION

DR CASTLEMAN Perhaps the reason why the surgeon waited eight days was that the patient was sent in to Dr G G Smith as a urologic problem and it took a few days to have the general surgeons see her. Dr Richard H Sweet examined her. The mass was smooth and tender and felt to him like a hydrops of the gall bladder. He did not believe it was kidney. At operation he found that the mass was a large gall bladder adherent to the omentum and also to the transverse colon, where one could see it pressing against the hepatic flexure. It was inflamed, had a red, thick wall and extended down into the bed. In removal a good deal of grumous material came out, and when the mass was opened, it was found to contain large numbers of stones. In freeing up some of the adhesions it was discovered that there were several nodular areas in a portion of the fundus, which to Dr Sweet, looked suspicious of carcinoma. When finally examined, there were large, papillary-like masses projecting into the lumen of the gall bladder, which on microscopic examination proved to be an undifferentiated carcinoma. Several stones were present as well.

This case is interesting because seven years previously a Graham test had been positive. Had the gall bladder been removed at that time, I suppose that the cancer would have been prevented. Dr Joel Goldthwait of our laboratory looked up the cases of carcinoma of the gall bladder that were found at autopsy, and out of 12,000 autopsies in adults, he found stones in 12 per cent, and 3 per cent of the cases with stones had carcinoma of the gall bladder. The usual statistics are between 3 and 5 per cent.

DR JACOB LERMAN What correlation was there between stones and cancer?

DR CASTLEMAN Ninety-five to 98 per cent of cases of carcinoma of the gall bladder occurred in patients with gallstones. The incidence is very high and one wonders whether, if a patient shows a stone on x-ray study, the gall bladder should be removed. What is the experience of the surgeons? Do they always remove it?

DR MCKITTRICK That depends on the surgeon and the patient. I would have advised cholecystectomy in a patient with a pathologically obstructed gall bladder, which I assume she had seven years before admission. I should like to ask how many gall bladders are pathologic without

stones. If stones are demonstrated, I think the gall bladder should be removed.

DR CASTLEMAN The stones are not visible on the films in this case.

DR MCKITTRICK That is not unusual, even in a carefully done cholecystogram one may not see the pigment stones. That is why I wondered how often one sees a pathologic gall bladder without some form of concretion in it.

DR CASTLEMAN I should say that most of the really diseased gall bladders have stones.

DR MCKITTRICK That is the clinical impression that most surgeons have.

## CASE 34292

## PRESENTATION OF CASE

An eleven-year-old schoolboy was admitted to the hospital following attacks of acute spasmodic abdominal pain.

Five months previously he experienced a one-day episode of severe pain just below the umbilicus, coming in spasms and causing him to double up in bed. There was no nausea, vomiting or change in bowel habits. There were no chills, fever or bloody or tarry stools. Following this he resumed his normal activity with good appetite and no weight loss. Eleven days prior to admission the pain returned, and he was operated upon at another hospital. According to his mother, the appendix was not involved, but a "tumor of the cecum" was found and the operation was terminated without an attempt at resection. He convalesced uneventfully and was admitted to this hospital for diagnosis and treatment.

Physical examination was negative except for a recent right pararectus scar. No abdominal tenderness or masses were noted.

Examination of the blood showed 14.6 gm of hemoglobin and a white-cell count of 8700, with 57 per cent neutrophils. A urinalysis was negative. A stool specimen was guaiac negative. A barium enema filled the colon readily from rectum to cecum. The terminal ileum was not demonstrated. The appendix was not adequately visualized in the pre-evacuation study but was well filled in the post-evacuation films. It was movable and not remarkable in appearance. Along the medial aspect of the cecum at about the level of the ileocecal valve there was an extrinsic pressure deformity about 2.5 cm in diameter. This was best demonstrated with the patient prone.

On the fifth hospital day an operation was performed.

## DIFFERENTIAL DIAGNOSIS

DR LEO BURGIN By virtue of the previous laparotomy a good deal of the wind has been taken out of my sails. Such every-day possibilities as an

test was negative. An intravenous pyelogram showed a soft-tissue mass, 8 cm in diameter, on the right side of the abdomen with apparently no connection to the kidney. There was good renal function, and no stones were seen. A barium enema showed the same mass in relation to the superior aspect of the transverse colon but not intrinsic in the colon.

On the eighth hospital day an operation was performed.

### DIFFERENTIAL DIAGNOSIS

DR JOHN B MCKITTRICK: May we see the x-ray films?

DR JAMES J McCORT: The mass is present on the right side. Following a barium enema it is seen to cause a slight pressure defect in the region of the hepatic flexure. There is also a small diverticulum in this region, which is well demonstrated on the spot film. On the pyelogram one can see the mass extending below the inferior pole of the kidney and through the mass one can see the outline of the kidney clearly. There is no distortion or displacement of the calyces or pelvis. The mass itself is smooth and shows no calcification.

DR MCKITTRICK: The pain is characteristic of gallstone colic. It was severe, recurrent and in one instance required morphine. The patient did not have chills, fever or jaundice, and we have no evidence from the history that there was any inflammatory process going on. Indigestion is mentioned, but the history does not tell us how severe it was. This is significant in view of a later statement regarding a slight weight loss.

I believe that the urinary frequency attributed to Coca-Cola, ginger ale and so forth had nothing to do with the present episode. One cannot tell what the frequency means. The frequent passage of large amounts of urine after the ingestion of sugar should make one investigate the patient from the point of view of diabetes. In the past, she had renal stones, and five years later the removal of a parathyroid tumor. It would be interesting to know what prompted the search for the parathyroid tumor.

DR BENJAMIN CASTLEMAN: There is a letter from her doctor saying that he saw her because of a toxic thyroid gland. She was sent to the Peter Bent Brigham Hospital and seen by the late Drs Elliott Cutler and Soma Weiss. Apparently, the parathyroid tumor was discovered in the process of thyroidectomy, so that I do not believe that she had symptoms of hyperparathyroidism.

DR MCKITTRICK: I wondered if the history of kidney stones had stimulated the search.

DR CASTLEMAN: Dr Soma Weiss thought that the vomiting was due to the toxic goiter.

DR MCKITTRICK: The mass in the right upper quadrant was slightly tender, smooth and 15 cm in diameter, and appeared to be attached to the liver. This means gall-bladder disease until proved

otherwise. We are not given one item of important information about this mass. I would like to know whether it was fixed or movable and how long it had been present. The laboratory studies reported are negative. There is no bilirubin report, but I would anticipate this determination to be normal.

The only diagnosis that I can make is hydrops of the gall bladder. I am a little skeptical of this diagnosis because it appears too simple. Such a condition may develop painlessly, in fact, it usually does. It is due to obstruction by a stone in the lower end of the gall bladder or cystic duct, with distention of the gall bladder without infection. That is one reason why I wanted to know whether it was movable. The average hydrops is movable and may attain considerable size. In this case, there was enough tone left in the wall of the gall bladder to cause pain.

What should one consider in the way of differential diagnosis? There is always the question of carcinoma. I do not see how one can rule it in or out. The association of stones and carcinoma of the gall bladder is high, carcinoma of the gall bladder being almost always associated with gallstones. We have insufficient evidence, even with the weight loss, to make a diagnosis of carcinoma. Also, the diagnosis of carcinoma of the gall bladder is usually not made preoperatively, although at times one can legitimately suspect it. There are various lesions of the kidney that could present this picture, but they are fairly well ruled out by the preoperative examination. Apparently, in the mind of the attending physician, a lesion in the colon was also considered since a barium enema was done. It is entirely possible for lesions of the hepatic flexure to present themselves in this location and to appear to be fixed to the liver. We cannot rule out a lesion in the head of the pancreas. A cyst in the head of the pancreas can attain a large size and give the physical character of the mass described in this patient. I do not see how we can rule that in or out, but I do not believe the history is consistent with cyst of the pancreas.

Should we consider the common duct in our diagnosis? It is true that a large, distended gall bladder can occur in a patient with obstruction to the common duct in the absence of much or any jaundice. Usually, however, these patients have other symptoms that suggest common-duct disease, such as chills, fever and jaundice. A determination of the blood bilirubin would have helped in this regard.

The surgical service waited eight days to operate upon this woman. If my diagnosis is correct, she could have been operated upon much sooner. My diagnosis is stone impacted in the lower end of the gall bladder, with hydrops.

### CLINICAL DIAGNOSIS

Hydrops of gall bladder

terminal ileum in a nine-year-old child operated on for appendicitis

In the present case we have evidence of a lesion intimately associated with the cecum in a boy of eleven who appeared to be well otherwise. The lesion was responsible for colicky pain on at least two occasions. In the course of laparotomy it is described as a tumor of the cecum. I believe this lad had a duplication of the cecum.

May we see the x-ray films?

DR STANLEY M. WYMAN: The barium-filled colon on the large film fails to reveal the lesion described, but after evacuation there is a faint suggestion of irregularity of the cecum medially. The films taken during examination show a continual demonstration of a filling defect on the medial wall of the cecum. The fluoroscopist believed that this changed somewhat in contour during examination. This spot film taken after barium shows a faint suggestion of lobulation in that area. The ileocecal valve is not filled on any film so that one cannot say whether this is the ileocecal valve or the region adjacent to it. The well filled appendix is seen in this film and appears normal. The fluoroscopist's impression was that the mass was entirely extrinsic, but I think it is hard to exclude the possibility of an intramural lesion pressing on the lumen of the bowel.

DR BURGIN: The note said in effect that the deformity was better visualized when the patient was prone, suggesting that the weight of the lesion itself gave rise to it. That would be more evidence for a lesion outside rather than inside the bowel.

DR WYMAN: I was not sure about that statement, and I asked the fluoroscopist about it. He was not entirely certain in retrospect that that was so.

DR BURGIN: Since the patient had very little in the way of symptoms referable to disturbed function within the gastrointestinal tract, I am going to stick to my original diagnosis of enterogenous cyst of the cecum.

#### CLINICAL DIAGNOSIS

Benign tumor of cecum

#### DR BURGIN'S DIAGNOSIS

Duplication of intestinal tract.

#### ANATOMICAL DIAGNOSIS

*Duplication of intestinal tract (terminal ileum)*

#### PATHOLOGICAL DISCUSSION

DR RICHARD H. SWEET: I was called upon to perform the second operation in this case. The surgeon who performed the first operation is a competent surgeon in western Massachusetts but a close relative of the patient who decided against doing radical surgery on a member of his own family. When I talked with him and reviewed

the history the picture seemed most suggestive of intussusception of a transitory nature that relieved itself spontaneously. The surgeon described the tumor quite accurately as being very soft and having little substance. When I felt it, it was obviously not mesenteric adenitis. One could see normal lymph nodes. The appendix was free and uninvolved. The tumor felt as though it were part of the wall of the cecum, although it was very soft. Only when I removed it and had a chance to dissect the mesentery off a little bit and looked more carefully was I certain of its nature. I thought it was a soft, polypoid lesion of the bowel itself, but we performed a rather limited resection, removing the cecum and a portion of the terminal ileum.

DR TRACY B. MALLORY: The specimen removed showed a cyst, lying within the wall of the terminal ileum in immediate apposition to the ileocecal valve, with a relatively small internal diameter (7 mm), which was included in the muscular layers of the ileal wall. The content of the cyst was a pure mucous fluid, and the lining was quite smooth and looked like intestinal mucosa. That was confirmed microscopically. This is, I think, a very clear example of a so-called duplication of the intestinal tract. It was a small lesion that produced symptoms rather later in life than usual, probably because it remained so small. We thought at the time of examination that there was a slight degree of intussusception through the ileocecal valve. Dr Sweet perhaps had a better chance of determining that than we had.

DR SWEET: I could not be sure. It was obvious that it lay somewhat above and posterior to the ileum. I was surprised to learn that it was part of the ileum. It seemed to me that it was part of the cecum. There was no intussusception at the time of operation or at the time of the previous operation.

DR MALLORY: An intraluminal tumor is a very common cause of intussusception. A tumor exterior to the lumen of the bowel causes intussusception less frequently, but nevertheless could be a primary basis for intussusception or volvulus.

DR BENJAMIN CASTLEMAN: How else would you account for the colic, Dr Sweet, unless there was a degree of intussusception in the past?

DR SWEET: I am sure that is what this patient had. There is no other way to explain it—no inflammatory reaction and no narrowing of the bowel. The only way I could explain the obvious small bowel colic was that the bowel had become intussuscepted.

DR CASTLEMAN: Is that what Ladd and Gross say?

DR BURGIN: They mention distention of the cyst as a cause of pain. Of course these cysts are usually larger than the one described here. One in a lad seven or eight years of age, who I remember never to have had symptoms, was 1.5 cm

acute appendicitis, with or without abscess, Meckel's diverticulum and mesenteric adenitis are tossed out. One is led at once to the site of the lesion—the vicinity of the cecum. Our possibilities are still further narrowed by the demonstration of "an extrinsic pressure deformity about 2.5 cm in diameter." Rather than have some of our ideas dispelled at once by the roentgenologist, perhaps it might be better to proceed with the discussion and be refuted later by the x-ray films and Dr Mallory.

The first episode of pain is not particularly helpful. It sounds like colic. Many a youngster has had such a bout of colic owing to functional rather than organic difficulty. I presume that this episode was elicited by whoever took the history and may or may not be referable to the existing disease.

The attack of pain eleven days before admission must have simulated appendicitis. A laparotomy was performed, and a "tumor of the cecum" was found. That the appendix continued to be normal is attested to by the subsequent x-ray films, which revealed a freely movable organ, well filled with barium. Certainly the deformity described, the absence of fever, the normal white-cell count and the negative physical findings are against infection in the sense of an abscess, or other inflammatory process.

Could a mesenteric lymph node be large enough and close enough to the cecum to give such a picture? Certainly nonspecific mesenteric adenitis occurs without fever or elevated white-cell count. The findings at the previous laparotomy are against such a hypothesis. I doubt that lymph nodes ever reach such a size. Perhaps the surgeons can enlighten us on this point. I suppose one ought to consider lymphoma—of the Hodgkin's type with enlarged lymph nodes. The absence of a prolonged history of nodes elsewhere, of anemia and of intermittent fever seems to rule out this possibility. A tuberculous adenitis (tuberc mesenterica), especially if a number of lymph nodes were fused together, might give rise to a mass large enough to give the deformity shown by x-ray study. Pain is perhaps the most consistent complaint but need not be present. We have no information regarding the tuberculin test, nor is there anything to suggest tuberculosis elsewhere.

What of malignant tumors? Those inside the bowel would be associated with melena of varying degrees, anemia, loss of weight, nausea, vomiting and so forth. Cancer of the gastrointestinal tract is quite rare in childhood and when present is more likely to be in the rectosigmoid area. This patient presumably remained in good health after the first episodes of pain, cancer seems unlikely. The evidence offered is for a lesion outside the bowel. We may likewise rule out benign tumors of the gastrointestinal tract, adenoma, fibroma and so forth for those lesions would be expected to give rise to disturbed gastrointestinal function.

What about abdominal tumors outside the bowel? The most common malignant abdominal tumors in children are those connected with the kidney, such as embryoma, and those arising from sympathetic nervous tissue in the retroperitoneal space. These tumors occur earlier in life and are associated with an enlarged abdomen and palpable mass, usually in the flank in cases of embryoma, nodular masses are generally palpable in cases of neuroblastoma. The latter metastasizes early to liver, lung and bone. Signs of debility are generally present.

What other structures should we consider? Changes in the tissue adjacent to the cecum—the mesentery—might well be responsible for this picture. Bits of lymphatic tissue may become displaced in the mesentery and proliferate, and since no communication is available with the lymphatic system, cysts (so-called mesenteric cysts) are the result. These may occur anywhere in the mesentery either at the base or at the enteric border. Since they are not usually tensely filled, they tend to be flabby and, until they become large, may escape notice on abdominal palpation. In the typical case a painless, slowly enlarging abdomen is the only complaint. Symptoms of obstruction or abdominal pain may occur intermittently. Generally the cysts are large and freely movable. I can visualize such a cyst giving rise to this x-ray picture. However, because of its very flabby nature, one would expect an inconstant picture, which we assume was not present in the case under discussion.

There is another lesion that can arise in tissues adjacent to the cecum—or for that matter anywhere in the gastrointestinal tract. This is the so-called enterogenous cyst or, as such lesions are often called, duplication of the alimentary tract. Small outpocketings of intestinal mucosa occur regularly in the fetal alimentary tract. Some of these may fail to regress and become pinched off and give rise to an adjacent duplication. These duplications then secrete to a varying degree, sometimes to the point of pressure necrosis. In contradistinction to mesenteric cysts, these duplications are firmly adherent to the intestine and usually have a smooth-muscle coat of more than one layer. They may be large enough to be felt by palpation and often give rise to symptoms of colicky pain, partial obstruction and visible peristalsis. The pain may arise from distention secondary to excessive secretion within the cyst. Occasionally they press upon mesenteric vessels as they lie within the leaves of the mesentery and give rise to sloughing or bleeding of adjacent bowel. On the other hand, they may not give any symptoms for long periods. In fact Ladd and Gross\* report the incidental finding of a 12-cm duplication of the

\* Ladd, W. E. and Gross, R. E. *Abdominal Surgery of Infancy and Childhood*. 455 pp. Philadelphia and London: W. B. Saunders Co., 1941. P. 83.

by a few horses in rounding him up and branding him, and then putting him into a weaning pen in the fall. Cowboys think they work hard, but most of us would gladly trade jobs with them—the horse donates most of the foot pounds. During the ensuing winter some man energy is expended in feeding the steer hay while the snow is deep. The following summer his own legs carry him up into the mountain ranges, where he stores away all the  $\text{NH}_2$  groups and peptide linkages that are later recognized as beefsteak. Finally, a horse carrying a rider gathers him and his fellows together and takes them to the railroad, where the oxidation of carbon as coal (or oil) carries them to the stockyards. The energy of transforming him from a steer to a beefsteak is a complicated problem of industrial work, but it probably finds its analogue in Aroostook County through the sorting, grading, cleaning and sacking of the potato.

Furthermore the steer has availed himself of grass growing on land that generally cannot be used for anything else. If the steer does not eat the grass it is eaten by wild animals or else it goes to seed. If the steer eats it after it is ripe many of the seeds go through him unchanged and undigested but will grow new grass on the same pasture. In essence, although the steer meat requires 17 acres for 1,000,000 calories as opposed to the 0.44 acres for 1,000,000 calories of potatoes, that is not the whole story. There is in addition a difference in the energy expenditure required to produce the food in edible form and a wide discrepancy in the types of land that must be used to produce the two foods. Even though it requires 17 acres to produce 1,000,000 calories of beef it is quite conceivable that this amount of beef is produced with the expenditure of fewer calories than the 1,000,000 calories of potatoes and with considerably less depletion of the earth's resources. It thus becomes apparent that the gross figure of acres required to produce food does not wholly cover the subject of planning the economy of the United States or, indeed, that of the world. If 1,000,000 calories of good protein is to be obtained in the most efficient way all the other energy input factors must be measured, weighed and carefully accounted for.

## SHERINGTON'S CLASSIC CONTRIBUTION TO NEUROPHYSIOLOGY

LAST November 27, Sir Charles Scott Sherrington, dean of the world's physiologists, Nobel Laureate and author of *The Integrative Action of the Nervous System* (1906) quietly celebrated his ninetieth birthday. Sir Charles was very much alive, and the Physiological Society of Great Britain even more so, for they republished his famous monograph<sup>1</sup>—referred to by the author as “my rather elderly book”—and saw to it that appropriate notices appeared in the *British Medical Journal* and the *Lancet*. Best of all, Sir Charles wrote a “Foreword to 1947 Edition,” as brilliant a piece of writing as ever came from his pen—thoughtful, meaty, with a meticulousness of style long familiar to his devoted followers, whose contact with him in recent years has been largely through *Man on his Nature* (1940) and *The Endeavour of Jean Fernel* (1946). In crisp sentences he deals with some ambiguities that have arisen since 1906 and turns from the simpler forms of reflex behavior

The field of the psyche is entered. An old adage has it that to the trodden worm its own trodden self is the world's greater half. That anthropomorphic worm may typify ourselves to us, the “self” of each of us goes far to epitomize the integration we are now to look at. We can retain the scheme of spatial nervous arrangement we used before, this time, however, not mutilating the central organ, but keeping the animal—the human animal if you will—intact. The receptors at the starting-points of the nerve-thread we find now to be, by conspiracy with a psyche in the central organ, sense-organs. The full panel of the “five-senses” is in session, and by further collaboration with the psyche, a world of subject and object for the individual is in being. The individual has attained a psychological existence. Phases and moods of mental life accrue. Each waking day is a stage dominated for good or ill, in comedy, farce or tragedy, by a *dramatis persona*, the “self.” And so it will be until the curtain drops. This self is a unity. The continuity of its presence in time, sometimes hardly broken by sleep, its inalienable “interiority” in (sensual) space, its consistency of view-point, the privacy of its experience, combine to give it status as a unique existence. Although multiple aspects characterize it it has self-cohesion. It regards itself as one, others treat it as one. It is addressed as one, by a name to which it answers. The Law and the State schedule it as one. It and they identify it with a body which is considered by it and them to belong to it integrally. In short, unchallenged and unargued conviction assumes it to be one. The logic of grammar endorses this by a pronoun in the singular. All its diversity is merged in oneness.

Furthermore, “the body-mind liaison provides in a largely physical world the physical means of giving

# The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established 1828

Official Organ of

THE MASSACHUSETTS MEDICAL SOCIETY

and

THE NEW HAMPSHIRE MEDICAL SOCIETY

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND

PUBLISHED WEEKLY UNDER THE JURISDICTION OF THE  
COMMITTEE ON PUBLICATIONS

James P. O'Hare, M.D. Richard M. Smith, M.D., *Chairman*  
Oliver Cope, M.D. Conrad Wesselhoeft, M.D.  
John Fallon, M.D.

Joseph Garland, M.D., *Editor*

*Associate Editors*

Thomas H. Lanman, M.D. Donald Munro, M.D.

Henry Jackson, Jr., M.D.

Clara D. Davies, *Executive Editor*

Robert O. Leary, *Assistant Editor*

*Editorial Board*

C. Guy Lane, M.D.	Maxwell Finland, M.D.
Henry R. Viets, M.D.	James M. Faulkner, M.D.
Robert M. Green, M.D.	Carroll B. Larson, M.D.
Dwight O'Hara, M.D.	Francis D. Moore, M.D.
Fletcher H. Colby, M.D.	C. Stuart Welch, M.D.
Robert L. Goodale, M.D.	Vernon P. Williams, M.D.
Chester M. Jones, M.D.	Benjamin Castleman, M.D.
Harvey R. Morrison, M.D.	Hugh R. Leavell, M.D.

**SUBSCRIPTION TERMS** \$7.00 per year in advance, postage paid, for the United States (medical students, \$4.00 per year) Canada, \$8.00 per year (Boston funds), \$9.50 per year for all foreign countries belonging to the Postal Union.

**MATERIAL** should be received not later than noon on Thursday, three weeks before date of publication.

**THE JOURNAL** does not hold itself responsible for statements made by any contributor.

**COMMUNICATIONS** should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts. Telephone KE 6-2094.

**NEW ENGLAND ADVERTISING REPRESENTATIVE** Edwin B. Tyler, 89 State Street, Boston, Massachusetts. Telephone LA 3-5516.

## ACRES, MEN AND NUTRITION

A broader view of nutrition appears to be just around the corner. Although the Citizen's Food Committee long since abandoned the eggless Thursday and the meatless Tuesday, there is beginning awareness of a broader exchange of energy than that which exists between the A & P and the kitchen stove.

Dr. Fredrick J. Stare, in a recent issue of the *Atlantic Monthly*, calls attention to the fact that both meat and eggs must trace their energy origins to botanical processes, and that growing things in turn receive their energy from the sun, storing it in a convenient system based on the reversible oxidation of carbon.

Dr. Stare provides a table showing the number of acres of fertile land required to produce 1,000,000

calories of various foods. We see, for instance, that 1,000,000 calories of sugar requires 0.15 acres, as contrasted with 1,000,000 calories of beef, which requires 170 acres, of "fertile land." These figures are valuable, the concept is fundamental, and we are further indebted to Dr. Stare for the important work in nutrition that is being conducted at the Harvard Nutrition Laboratories under his able direction. Similar comparisons are to be found in the paper by Talbot and his associates published elsewhere in this issue of the *Journal*.

But are we not further forgetting the already forgotten man? The system of energy exchange that starts at the sun and ends with photosynthetic products on our tables (or in the mouths of Europe) involves another energy investment besides that of the sun's rays and the raw materials contained in the acres of fertile land. It is the energy of the working man who produces the food.

A contrast between the potato at 0.44 acres per 1,000,000 calories and the steer at 17 acres per 1,000,000 calories is instructive. Aroostook County farmers can tell a good deal about the energy required to raise an acre of potatoes. Each potato must be planted individually, cultivated, hoed, weeded and finally harvested by back-breaking effort. There may be machines that do this in 1948, but this argument considers the energy put into the potato patch by the men who work it rather than the energy from gasoline (even admitting that the products of the gasoline station also trace their origins back to plant life and solar energy). In the transport of the food energy of that potato from the seed to the table there is an expenditure of energy on the part of men — energy that the men in turn have received from other botanical products. In Aroostook County this manpower probably traces itself back to potatoes in large part, and it has been re-expended to harvest more potatoes.

A shift of attention to the steer reveals that the steer's mother, the cow, does most of the hard work. The bull, it is true, plays a brief but important role, thereafter disporting himself about the pastures in a carefree manner. After the calf is born he lives on his mother's milk for a few months, and the only other energy from animate sources that goes into raising him further comes from the energy expended

ges Radiological Society, succeeded in achieving a degree of publicity that, while it reflected no credit on a considerable number of physicians who perhaps had not heard of the Hippocratic Oath, nevertheless waked the "organized profession" into action

Let us hope that clean glasses will aid in a clearer view of all manner of rebates, kickbacks and other fee-splitting devices

## MASSACHUSETTS MEDICAL SOCIETY

### DEATHS

**DOUCETT** — Frederick L. Doucett, M.D., of East Weymouth, died on June 19. He was in his seventy-ninth year. Dr. Doucett received his degree from Tufts College Medical School in 1900. He was formerly a member of the Weymouth Board of Health.

A daughter, two brothers and a sister survive.

**FELCH** — Carrie I. Felch, M.D., of Boston, died on June 11. She was in her eighty-sixth year.

Dr. Felch received her degree from Tufts College Medical School in 1906.

A nephew survives.

**HOUGHTON** — Henry L. Houghton, M.D., of Boston, died on June 17. He was in his eighty-first year.

Dr. Houghton received his degree from Harvard Medical School in 1894. He was formerly president of Hahnemann Hospital, Boston.

His widow and a daughter survive.

**LINDSAY** — Joseph I. Lindsay, M.D., of Grafton, died on June 6. He was in his eighty-fifth year.

Dr. Lindsay received his degree from University of Vermont College of Medicine in 1888. He was formerly a member of the staff of Worcester Memorial Hospital and was a fellow of the American Medical Association.

A son, two grandchildren and a sister survive.

**MACCORISON** — Carl C. MacCorison, M.D., of North Berwick, Maine, died on June 4. He was in his seventy-first year.

Dr. MacCorison received his degree from Dartmouth Medical School in 1906. He was formerly medical superintendent of the North Reading State Sanatorium and was a member of the Massachusetts Medical Society and a fellow of the American Medical Association.

A brother and two sisters survive.

**PARE** — Francis M. Pare, M.D., of Worcester, died on January 28. He was in his forty-sixth year.

Dr. Pare received his degree from Georgetown University School of Medicine in 1931. He was a member of the staff of St. Vincent's Hospital and a member of the New England Obstetrical and Gynecological Society.

His widow, mother, father, two sons, a brother and two sisters survive.

**TORNEY** — George H. Torney, M.D., of Brookline, died on June 1. He was in his seventy-sixth year.

Dr. Torney received his degree from University of Pennsylvania School of Medicine in 1894. He was a member of the American Psychiatric Association and the New England Society of Psychiatry and a fellow of the American Medical Association.

His widow and two sons survive.

## MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

### THERAPY OF ROCKY MOUNTAIN SPOTTED FEVER

Therapy for Rocky Mountain spotted fever is still in the developmental stage. The following is a résumé of information received from Dr. John W. Oliphant, of the Rocky Mountain Laboratory, Hamilton, Montana.

#### *Para-aminobenzoic Acid (Paba)*

Since 1945, published and unpublished reports of 135 cases treated with para-aminobenzoic acid have been collected at the Rocky Mountain Laboratory of the United States Public Health Service. The average mortality for the United States for Rocky Mountain spotted fever is 20 per cent, of the patients treated with paba, 14 died — a mortality of 10.3 per cent. In 4 of these cases treatment was stated to have been begun too late. In 8 of the remaining cases, no beneficial results were observed. In 78 cases, some physicians thought the paba had been quite beneficial whereas others considered it of value but not to such a great extent. In 35 cases, no opinion was expressed. Statistical analysis of these 135 cases was not possible because complete information was lacking from many of the reports.

Flinn et al.<sup>1</sup> recommended a blood concentration of 30 to 60 mg. per 100 cc. Para-aminobenzoic acid in an initial dose of 4 gm. and 2 gm. every two hours results in blood levels of 5 to 10 mg. per 100 cc. Some patients respond well to this dose. The two-hour interval of medication is necessary because of the rapid excretion of the drug in the urine. Continued administration for at least two days after the temperature has returned to normal is recommended to prevent relapse.

Para-aminobenzoic acid is relatively insoluble in water but has a solubility of about 1 gm. per 20 cc. in 5 per cent sodium bicarbonate solution. The bicarbonate may be useful in preventing nausea and acidosis. Paba is available in powder or tablet form. The sodium salt is soluble and may be used orally or intravenously. It comes in 0.5-gm. tablets, in sterile vials containing 4 gm. of salt and in ampoules containing 1 gm. of salt in aqueous solution.

Leukopenia has been reported during paba therapy. Agranulocytosis might result.

#### *Supportive Therapy and Para-aminobenzoic Acid*

The clinical studies of Harrell and his co-workers<sup>2</sup> and of Ravenel<sup>3</sup> have emphasized that with the development of Rocky Mountain spotted fever, dehydration, loss of serum protein and blood chlorides, acidosis and in some cases anemia occur. The treatment according to Ravenel<sup>4</sup> is as follows: the fluid

expression to the psychical" and "each of the two achieves its aim only by reason of a *contact utile* between them"

And this liaison can rank as the final and supreme integration completing its individual. But the problem of *how* that liaison is effected remains unsolved, it remains where Aristotle left it more than 2000 years ago

As Fulton<sup>2</sup> notes "To the most profound student of the nervous system the world has yet known, the mind of man remains still unexplained"

Many will believe with Fulton that the problem is not quite where it was two thousand years ago, thanks to the researches of the former Waynflete Professor of Physiology at Oxford. Sherrington has at least pointed the road that will one day lead to an answer to this age-old question. Others,<sup>3-7</sup> moreover, took advantage of Sherrington's birthday to express similar sentiments

#### REFERENCES

- 1 Sherrington C. *The Integrative Action of the Nervous System* 433 pp New Haven Yale University Press 1947
- 2 Fulton, J. F. Sherrington's impact on neurophysiology *Brit. M. J.* 2 807-810 1947
- 3 Brain W. R. To Sir Charles Sherrington, O. M. on his 90th birthday, November 27, 1947 *Lancet* 2 803 1947
- 4 Editorial. Brain and mind *Lancet* 2 357, 1947
- 5 Brown, T. G. Sherrington — the man *Brit. M. J.* 2 810 812, 1947
- 6 Ritchie A. D. Sherrington as philosopher *Brit. M. J.* 2 812 1947
- 7 Editorial. Influence of Sherrington on clinical neurology *Brit. M. J.* 2 825 1947

#### CONGRESS LOOKS AT HEALTH

It was perhaps inevitable that in anticipation of a national election there emerged a small avalanche of legislation related to matters that might be issues in the campaign

There seemed to be no profit for any political party in the forwarding of such major projects as the Wagner-Murray-Dingell Bill or the Taft Bill, both of which were killed. The National Science Foundation Bill (S 2385) finally failed of adoption, although in principle this seemed to be the proper approach toward solution of the part Washington should play in helping the earlier realization of actual and potential values made available by the several groups in the field of science

The medical parts of the program—for example, those relating to research and control in diseases of the heart and circulation—will be less well forwarded by such a bill as S 2215 (the National Heart Bill), and scientific advance will not be as

well integrated by it. This bill, introduced by Senators Bridges, Pepper, Ives and Murray, as specialized legislation aimed at meeting needs only in a single field, important as they are, was finally adopted with amendments

Many people believe that infantile paralysis has absorbed too large a proportion of public funds for the needs or accomplishments, when comparison is made with the much higher morbidity and mortality of circulatory diseases. Perhaps it is not surprising that some of the cardiologists who felt this disproportion keenly were strongly behind specialized legislation for their own interests, whereas other wise cardiologists, perhaps with larger perspective, preferred to take their chances with a much more comprehensive kind of legislation like the National Science Bill. Some there are who believe that there is no need for federal legislation in these matters. There seems, however, to be general agreement that all-over co-ordinated scientific investigation would accelerate the finding of needed truths that seem just beyond the horizon

Scientific research under governmental organization was performed so successfully in wartime that we may hope to see the thread picked up again. Compromise is necessary in legislation, but compromise with loss of larger obtainable values represents a shortsighted policy

#### KICKBACKS KICK BACK

BLINDED, no doubt, by the bright sunshine of the brilliant land in which they practice their art, an impressive number of the physicians of Los Angeles County seem unable to have read with understanding the Principles of Medical Ethics of the American Medical Association. Ironically, this visual incapacity has had to do with the receiving of rebates or "kickbacks" on eyeglass prescriptions from the local purveyors of these optical adjuncts

For eight years efforts from within the medical profession were of no avail in putting to an end this lucrative by-product of a professional activity otherwise not without honor. Eventually, however, the Los Angeles Better Business Bureau, aided by the *Reader's Digest* and the backing of the Los An-

## CORRESPONDENCE

## SUSPENSION OF REGISTRATIONS

To the Editor It has come to my attention that through a clerical oversight in this office, you were not notified that the registrations of several physicians were suspended because of their failure to comply with our statutory requirement concerning United States citizenship.

Under Chapter 415, Section 3, of the Acts of 1939, all physicians registered by the Board must satisfy the Board that they are American citizens. An attempt was made to communicate with such physicians whose applications indicated that they were born outside the United States. As a result of the information received, on July 12, 1946, the Board voted to suspend the registrations of the following physicians because they have stated they are not citizens of the United States or do not intend to become citizens.

Walter Bergwell	Lund, Sweden
John R. Corbett	Summerside, P. E. I.
Arthur G. Corea	Boston, Mass.
Derek Denny-Brown	Boston, Mass.
Robert H. Ellis	Ottawa, Ontario
Hubert Giovannetti	Sidney, Nova Scotia
Arthur M. Goulding	Toronto, Ontario
Marion Hook	Hastings, England
William M. Lynch	Sherbrooke, Quebec
Sidney H. McPherson	West Hartford, Conn.
Geraldine Oakley	Calgary, Alberta
Margaret Parks	St. John, New Brunswick
Elizabeth Ross	Meadowville, Nova Scotia
John R. Ross	Poughkeepsie, New York
Howard H. Smith	Charlottetown, P. E. I.
Edward V. Sullivan	Fairville, New Brunswick
Everett O. Thomas	St. Stephen, New Brunswick
Stephen B. Thorson	Winnipeg, Manitoba
Edmund Eugene Walker	Springfield, Mass.

H. QUINBY GALLUPE, M.D., Secretary  
Board of Registration in Medicine

State House  
Boston

## BOOK REVIEW

*Congenital Malformations of the Heart* By Helen B. Taussig, M.D. 4<sup>th</sup> ed., cloth, 618 pp., with 177 illustrations. New York: The Commonwealth Fund, 1947. \$10.00.

This volume has long been awaited by the pediatrician and the specialist in cardiovascular disease. Ten years have elapsed since Gross first successfully ligated a ductus arteriosus. This decade has witnessed the emergence of congenital heart disease from its obscurity as the academic diversion of the ultraspecialist to a position of importance in the consciousness of the practitioner and even of the layman. This evolution has been in large measure the result of a series of brilliant surgical procedures and the development of improved methods of study (notably angiography and cardiac catheterization). For the past twenty years Dr. Taussig has been intimately concerned with this progress, and she is responsible for the fundamental clinical observation upon which the now well-known Blalock-Taussig operation is based. This timely volume reflects the author's wide experience in this field.

The book is divided into four parts. The first deals with basic principles, methods of diagnosis and the physiology of the malformed heart. The second concerns malformations of the heart in which there is difficulty in supplying the body with adequate oxygenated blood. The third involves malformations compatible with life for many years, and the fourth is devoted to therapy.

The arrangement of the book is logical. The style is readable and direct, and frequent diagrams of the altered circulation are most helpful in elucidating the more complicated defects. The text is further strengthened by a summary at the end of each important discussion. Perhaps in some instances these summaries would have been more forceful

bad they been shorter. The illustrations are generous and effective.

This volume is destined to take its place beside the important studies of Maude Abbott as a standard reference for those concerned with this special field.

## BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

*Andreas Vesalius Bruxellensis. The bloodletting letter of 1539. An annotated translation and study of the evolution of Vesalius's scientific development.* By John B. de C. M. Saunders, F.R.C.S. (Ed.) and Charles D. O'Malley. 8<sup>th</sup> ed., cloth, 94 pp. New York: Henry Schuman, 1947. \$5.00. Limited to 500 copies.

It is noteworthy that this is the first published translation into English of a complete work of Vesalius. Professor Charles U. Clark, of Toronto, had previously made an unpublished translation of the venesection letter, which was made available to the authors, who checked it with their manuscript. The authors in their introduction trace the scientific development of Vesalius, placing the letter on venesection midway between his pure Galenic anatomy, as shown in his recension of Gunter's *Institutiones anatomicae* (1538) and his scientific treatise on anatomy, the *Fabrica* (1543). They point out that Vesalius not only was an anatomist but also was greatly interested in the whole field of medicine. The venesection problem is considered in all its aspects, beginning with the writings of Hippocrates, Galen and other classic writers and ending with the controversy of the contemporaries of Vesalius. The scholarly annotations to the introduction and the text are invaluable. The publishing is excellent in every way. The monograph should be in all medical-history collections.

*Private Enterprise or Government in Medicine.* By Louis H. Bauer, M.D. 8<sup>th</sup> ed., cloth, 201 pp. Springfield, Illinois: Charles C. Thomas, 1948. \$5.00.

Dr. Bauer, a trustee of the American Medical Association and currently president of the Medical Society of the State of New York, in this monograph presents a study of the proposed socialization of medicine by the federal Government and the counterproposals by the American Medical Association and the proponents of voluntary sickness insurance. The preliminary chapters discuss the state of medical care in the United States, the growth of Government in medicine and public health and foreign medical systems and their comparison with American systems. The following chapters consider the compulsory-sickness-insurance movement through 1944 and the legislation before Congress in 1945 to 1947. The various bills, including the Sheppard-Towner Act, the first Wagner bill of 1939, the Wagner-Murray-Dingell bill of 1943, the second bill of 1945 by the same group of senators, the third bill by the same group introduced in 1945 and providing for a national health program, the Fulbright-Taft bill of 1947 and the Taft-Smith-Ball-Donnell bill (S. 545) of 1947, are analyzed and discussed in relation to the problem of adequate medical care for the people of the United States. Also are considered and analyzed the voluntary insurance system and the ten-point plan of the American Medical Association. Included is the famous message to Congress of President Truman, dated November 19, 1945, requesting legislation for adoption of a national health program, and discussion of the work of the Committee on the Costs of Medical Care, the National Health Survey of 1935 and the National Health Conference of 1938. A chapter is devoted to the development of the voluntary insurance system in the United States. A bibliography of pertinent references is appended to the text. The book is well published in the characteristic good style of the publisher. It should be in all medical and general libraries and read by all physicians interested in the problem of the socialization of medicine.

and electrolyte balance should be restored to normal by means of intravenous injections of glucose in physiologic saline, lactate or Ringer's solution and should be maintained at a normal level by oral intake of fluid and added sodium chloride. Intravenous injections of electrolytes in solution in a patient whose serum protein is too low will serve only to produce more edema and possibly circulatory failure with pulmonary edema. Acidosis may be corrected by intravenous or subcutaneous injections of sixth molar solution of sodium lactate in appropriate dosage. The serum protein level of the blood depleted in the disease by starvation, vascular damage and liver failure should be restored to normal by intravenous injection of plasma and, in emergencies, serum albumin. This level should be maintained by plasma and a high-protein diet. If anemia develops blood should be given freely. Blood from patients convalescing from Rocky Mountain spotted fever is of no particular value. A high intake of vitamins should be furnished. Thiamin is given to help prevent shock. Ascorbic acid is given to obviate blood-vessel endothelial damage, and vitamins B complex and K for liver damage and to reduce increased prothrombin time. Depending on the size of the patient 0.5 to 1 gm of para-aminobenzoic acid per pound of body weight per day is given. Small children receive 1 gm per pound, very large children, half that amount, and the intermediate, about 0.75 gm. This is partially buffered with 10 cc of a 5 per cent solution of sodium bicarbonate per gram to prevent acidosis and nausea, and is given at two-hour intervals. The blood level of the drug should be estimated each day, in each case the same length of time after a dose of the drug. A level of 30 to 60 mg per 100 cc is desirable, 60 to 80 mg may be hazardous. Administration is continued four or five days after the temperature has reached normal.

The toxic effects of para-aminobenzoic acid to be watched for are acidosis, leukopenia, abdominal distention and delirium. If the white-cell count falls to 3000, the paba should be discontinued. Tympanites and delirium occur fairly frequently but are probably of little importance.

The complications of Rocky Mountain spotted fever are congestive heart failure (for which oxygen and digitalis in full dosage are helpful), pneumonia (usually lobar and rickettsial, ordinarily not helped by penicillin), encephalitis and thrombophlebitis. The heart failure is usually reversible, and when recovery occurs it is complete. It is possible but extremely difficult to treat these patients without laboratory control. Frequent determinations of the carbon dioxide combining power, serum protein and para-aminobenzoic acid levels of the blood are virtually a necessity, and determinations of the nonprotein nitrogen and chloride blood levels and prothrombin time may be a valuable aid.

Rocky Mountain spotted fever causes extreme vascular damage. Intravenous fluids used in therapy should be given cautiously to guard against unfavorable reactions.

### Serum

Hyperimmune rabbit serum has been shown to have a definitely protective and therapeutic effect in experimental animals if used early during the infection. It has been employed in numerous human beings and appears to be beneficial, particularly if administered before or shortly after the rash appears. It is available commercially from Lederle and Sharp and Dohme. The recommended dose is 1 cc per kilogram of body weight. Directions for testing the patient's sensitivity to rabbit protein and dosage accompany the antiserum.

Neoarsphenamine in metaphen solution, penicillin and sulfonamide drugs have been tried with no evidence of any beneficial results.

### REFERENCES

1. Flinn L. B., Howard J. W., Todd C. W. and Scott, E. G. Para-aminobenzoic acid treatment of Rocky Mountain spotted fever. *J A M A* 132 911-915 1946
2. Harrell, G. T., Venning W., and Wolff W. A. Treatment of Rocky Mountain spotted fever with particular reference to intravenous fluids: new approach to basic supportive therapy. *J A M A* 126 929-934 1944
3. Ravenel S. F. Para-aminobenzoic acid therapy of Rocky Mountain spotted fever: outline of comprehensive plan of treatment with report of five cases. *J A M A* 133 989-994 1947
4. Idem. Treatment of Rocky Mountain spotted fever with para-aminobenzoic acid: comprehensive plan. *South M J* 40 801-814 1947

### MISCELLANY

#### DR DEWITT C. ROMAINE FELLOWSHIP

Columbia University College of Physicians and Surgeons has received a bequest, amounting to approximately \$140,000, from the estate of the late C. Evaretta Romaine, it was recently announced. The fund, which will be set up as the Dr. DeWitt C. Romaine Fellowship, will be used to investigate diseases of the blood system and other medical problems.

#### VETERANS ADMINISTRATION

Dr. Augustus Thorndike, of Boston, has been appointed director of Veterans Administration Prosthetic and Sensory Aids Service. Dr. Thorndike, who graduated from Harvard Medical School in 1921 and served overseas with the 103rd General Hospital, developed and directed the Army's reconditioning program for disabled soldiers. He was awarded the Legion of Merit for this work.

#### WHO PROGRAM

The Interim Commission of the World Health Organization, which now consists of 43 nations — 33 UN members and 10 nonmembers — has declared its program for 1949. It is proposed to concentrate on four international problems — malaria, maternal and child health, tuberculosis and venereal disease. Forty-four other medical and related fields will also be included in the Commission's activities. Work on an international pharmacopoeia is also progressing under the aegis of the Expert Committee on the Unification of Pharmacopoeias.

## NOTICES

### BIOLOGY CONFERENCE, BROOKHAVEN NATIONAL LABORATORY

The Biology Department of Brookhaven National Laboratory announces a conference to be held at Brookhaven from July 26-30 on the subject, "Biologic Applications of Nuclear Physics." The program will include sessions on health physics, isotope techniques and applications of radiocarbon, radioiron and radiophosphorus. The last three days will be devoted to a symposium on radioiodine. Reservations for attendance at the conference will be filled in the order in which they are received.

Applications for registration and inquiries should be addressed to Miss Ellen Matteson, Brookhaven National Laboratory, Upton, New York (telephone, Patchogue 2600, Extension 114).

### SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINING THURSDAY, JULY 22

FRIDAY JULY 23

\*10:00 a.m.-12:00 m Medical Staff Rounds Peter Bent Brigham Hospital

TUESDAY JULY 27

\*12:15-1:15 p.m. Clinicorontogenological Conference Peter Bent Brigham Hospital

\*1:30-2:30 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children Massachusetts General Hospital

WEDNESDAY JULY 28

\*12:00 m.-1:00 p.m. Clinical Conference (Children's Hospital) Amphitheater Peter Bent Brigham Hospital

\*Open to the medical profession

JUNE 28-JULY 23 Harvard Seminar on Health Education Page 866 issue of June 10

JULY 6-24 Students International Clinical Congress Page 455 issue of March 25

JULY 12-17 First International Poliomyelitis Conference Page 36 issue of January 1

JULY 26-30 Biology Conference Brookhaven National Laboratory Notice above.

AUGUST 11-21 International Congress on Mental Health Page 344 issue of March 4

AUGUST 23-26 International Society of Hematology Page 419 issue of March 18

AUGUST 26-28 American Association of Blood Banks Page 420 issue of March 18

SEPTEMBER 7-11 American Congress of Physical Medicine Page 562 issue of April 15

SEPTEMBER 7-11 American Occupational Therapy Association Page 21 issue of July 8

SEPTEMBER 9 Some of the Advances in Surgery Dr. Frank H. Lahey, Fentucket Association of Physicians 8:30 p.m. Haverhill.

SEPTEMBER 13-15 American Academy of Pediatrics Olympic Hotel Seattle Washington

SEPTEMBER 16-18 Vermont State Medical Society Annual Meeting Burlington

SEPTEMBER 20-23 American Hospital Association Page 310 issue of February 26

SEPTEMBER 29 Mississippi Valley Medical Editors Association Page 170 issue of January 29

OCTOBER 6-9 American Board of Ophthalmology Page 170 issue of January 29

OCTOBER 18-22 American College of Surgeons Page 34 issue of July 1

OCTOBER 27 New England Obstetrical and Gynecological Society Annual Meeting Hotel Somerset Boston

NOVEMBER 1-3 American Clinical and Climatological Association Page 382 issue of April 15

NOVEMBER 8-12 American Public Health Association Page 420 issue of March 18

NOVEMBER 10-13 Association of Military Surgeons of the United States Page 722 issue of May 13

NOVEMBER 20-23 American Academy of Pediatrics Annual Meeting Chalfonte Haddon Hall Hotel Atlantic City New Jersey

DECEMBER 7-9 Southern Surgical Association Annual Meeting Page 343 issue of April 8

DECEMBER 9 and 10 New York State Society of Anesthesiologists Page 34 issue of July 1

## Washingtonian Hospital

41-43 WALTHAM STREET, BOSTON, MASS

Incorporated 1859

Conditioned Reflex, Psychotherapy, Semi-Hospitalization For Rehabilitation of Male Alcoholics

Treatment of Acute Intoxication and Alcoholic Psychoses Included

Outpatient Clinic and Social-Service Department for Male and Female Patients

JOSEPH THIMANN, M.D., Medical Director

Visiting Psychiatric and Neurologic Staff  
Consultants in Medicine, Surgery and the Other Specialties  
Telephone HA 6-1750

## Valleyhead Hospital

CONCORD, MASSACHUSETTS

For the treatment of psychoneuroses, alcoholism, mild mental disorders and chronic diseases. Pleasant pastoral setting near historic Concord. Accepted modern therapies used. Complete occupational and recreational facilities available including outdoor swimming pool and tennis court.

S GAGNON, M.D.  
Superintendent

J BUTLER TOMPKINS, M.D.  
Director of Clinical Psychiatry

J P THORNTON, M.D.  
Consultant in Neuro-psychiatry

IRVING KATZMAN, M.D.  
Psychiatrist

Post Office Box 151 Concord Mass Tel Concord 1600

## THE CHANNING HOME

For the MEDICAL and SURGICAL treatment of Pulmonary Tuberculosis in Women

Established 1857

198 PILGRIM ROAD BOSTON 15, MASS

Our endowment permits variations in charges for patients board. There are no physicians fees.

Those patients suitable for treatment with STREPTOMYCIN will receive the drug without cost, out of funds supplied by the Research Grants Division of United States Public Health Service.

Good nursing care and food are emphasized.

Address all applications to

ELIZABETH H. PELTON, Superintendent

## Tablets Ferglate-B with C

High in vitamin B complex content to quicken hemoglobin response to iron therapy

### EACH TABLET CONTAINS

Ferrous Gluconate (5 grains)	0.375 gm	Pyridoxine HCl	0.15 mg
Thiamin HCl	3 mg	Calcium Pantothenate	0.5 mg
Riboflavin	2 mg	Ascorbic Acid	30 mg
Niacinamide	20 mg	Yeast-Liver Base	q.s.

### INDICATIONS

Iron deficiency and nutritional anemias as a source of iron and B complex factors

Write Department N12 for Professional Sample and Literature

**KENMORE PHARMACAL CO.**

500 COMMONWEALTH AVENUE  
BOSTON 15, MASS

*Endocrine Therapy in General Practice* By Elmer L. Sevringhaus, M.D., director, Endocrine and Nutritional Clinics, Gouverneur Hospital, New York City. Sixth edition. 8°, cloth, 264 pp., with 49 illustrations. Chicago: The Year Book Publishers, Incorporated, 1948. \$4.00.

This book, first published in 1938, has passed through six editions and seven printings, speaking well for its soundness and popularity. This new edition has been carefully revised to keep it abreast of current knowledge in its field. Although no major changes have been made in the text, about a third of the pages have been altered. The printing is well done with a good, large type that is easy to read. The book is recommended for all medical libraries and should prove valuable to physicians interested in the subject.

*Illustrative Electrocardiography* By Julius Burstein, M.D., visiting electrocardiographer and chief of the Cardiac Clinic, Morrisania City Hospital, New York City, and associate cardiologist and chief of the Cardiac Clinic, Jewish Memorial Hospital, New York City, and Nathan Bloom, M.D., associate professor of medicine and chief of the Department of Electrocardiography, Medical College of Virginia, Richmond. Third edition. 8°, cloth, 309 pp., with 99 plates. New York: D. Appleton-Century Company, Incorporated, 1948. \$6.00.

This work, first published in 1935, has been thoroughly revised to bring it up to date with the significant advances in its field. All but two of the ninety-nine plates are new. A chapter on radiology of the heart by Dr. Philip Slater has been added. A good index concludes the volume. The publishing is excellent.

*The Case of Rudolf Hess: A problem of diagnosis and forensic psychiatry* By the following psychiatrists in the Services who have been concerned with him from 1941 to 1946: Henry V. Dicks, M.D., J. Gibson Graham, M.D., M. K. Johnston, M.D., D. Ellis Jones, M.D., Douglas McG. Kelley, M.D., N. R. Phillips, M.D., and G. M. Gilbert, Ph.D. Edited by J. R. Rees, M.D. 8°, cloth, 224 pp. New York: W. W. Norton and Company, Incorporated. \$3.00.

This monograph constitutes a case history of Rudolf Hess by the eight British and American psychiatrists who were concerned with him from 1941 to 1946. The case is studied from the time Hess parachuted into England, in May, 1941, until his appearance before the Nuremberg tribunal in 1946. The last chapter is a general review of the case, and the considered opinion of the psychiatrists favors a diagnosis of schizophrenia of a paranoid type. An appendix contains the documents presented to the Nuremberg court. The book is well published and reasonably priced. This unusual case history should be in all psychiatric collections.

*An Introduction to Gastro-Enterology: A clinical study of the structure and functions of the human alimentary tube* By James D. Lickley, M.D. 12°, cloth, 143 pp., with 21 illustrations. Baltimore: The Williams and Wilkins Company, 1947. \$3.00.

This small manual was written for senior medical students and beginning practitioners in the field of gastroenterology. The text is well written and well organized, and the volume well published. The printing was done in Great Britain.

*A Manual of Clinical Therapeutics: A guide for students and practitioners* By Windsor C. Cutting, M.D., professor of therapeutics, Stanford University School of Medicine, San Francisco, California. Second edition. 12°, cloth, 712 pp., with 30 illustrations. Philadelphia: W. B. Saunders Company, 1948. \$5.00.

This manual, first published in 1934, has been revised to bring it up to date. Material has been added, especially on the antibiotics, antimalarials, antihistamines, antithyroid drugs, anticonvulsants, folic acid and plasma fractions. Exact dosages for children have been inserted in an appendix. Diet lists and a number of illustrations have been added to the text. The various appendices of special procedures, diet therapy, symptoms and treatment of poisoning, diet lists, metric and English equivalents, tables and charts for weight, height and age, prescription abbreviations and for weight, height and age, prescription abbreviations and other data, clinical and physiologic data and a list of prescrip-

tions, drugs and doses add much to the value of the work. Especially valuable is the list of therapeutic agents and dosages. The volume is well published and should prove useful as a ready reference source to all medical librarians and physicians.

*Advances in Military Medicine Made by American Inventors working under the sponsorship of The Committee on Medical Research* Edited by E. C. Andrus, D. W. Brook, G. A. Carden, Jr., C. S. Keefer, J. S. Lockwood, J. T. Wearn and M. C. Winternitz. Associate editor: Tuckerman Day. With a foreword by Alfred N. Richards. In two volumes. 8°, cloth. Volume I, 472 pp., and 62 illustrations. Volume II, 900 pp., and 94 illustrations. Science in World War II. Office of Scientific Research and Development. Boston: Little, Brown and Company (An Atlantic Monthly Press Book), 1948. \$12.50 for the two volumes.

The work describes the activities of the Committee for Medical Research of the Office of Scientific Research and Development and constitutes a history of medical progress during World War II. The Committee was established in June, 1941, by presidential order, and nearly 1700 physicians and 3800 scientifically trained research workers were associated with the Committee. Its staff was divided into six sections: medicine, surgery, physiology, chemistry, aviation medicine and malaria. The material in the two-volume set is arranged in the same divisions, with supplementary chapters on penicillin and sensory devices. In the section on chemistry there are a number of papers on chemical-warfare agents and antipest agents. In physiology are discussed shock, plasma, blood substitutes and whole blood, problems of nutrition, water disinfection, acclimatization to heat and cold and protective clothing. In medicine the principal topics are infections and venereal and tropical diseases. Aviation medicine includes the study of crash injuries, effects of acceleration, visual problems, motion sickness, anoxia and altitude-decompression sickness. Surgery includes papers on infection, wound healing, orthopedics, gas gangrene, burns, peripheral nerve lesions, concussion, frostbite and trenchfoot and surgical plastics and hemostatics. Malaria is considered in five chapters. A good index concludes the text, which is paginated continuously through the two volumes. There is a large bibliography of the writings of persons working on contracts with the Committee and a list of the contracts. The publishing is good in every way. The work is recommended for all medical and general libraries.

*Experimental Air-Borne Infection* By Theodor Rosebury. With the co-authorship and assistance of the staff of the Laboratories of Camp Detrick, Maryland. 8°, cloth, 222 pp., with 75 tables. Baltimore: The Williams and Wilkins Company, 1947. \$4.00. *Microbiological Monographs*. Official Publication of The Society of American Bacteriologists.

This report presents the major results of a co-operative wartime project carried out at Camp Detrick, beginning in December, 1943, and ending after the cessation of World War II. A special blood chamber was constructed and after safety tests had been made and found satisfactory, work with infective agents was begun March 21, 1945, and continued until the project was terminated. The text is divided into five sections, the first four considering the history of the subject, equipments and methods, the selection of an atomizer and basic data. Section five discusses the stability and infectivity of a group of special bacteria and viruses. A summary concludes the text. The material is well arranged, and the text well written. The volume is well published in every way. It forms the first volume of a new series of microbiologic monographs and is an official publication of the Society of American Bacteriologists. It is recommended for all medical libraries and public-health collections.

*Fundacion Lucas Sierra: Hospital de Viña del Mar. Journales Clinicas de Ferano*, 1947. 4°, paper, 304 pp., with 46 illustrations. Viña del Mar, Chile: Fundacion Lucas Sierra, 1947.

This volume constitutes the proceedings of a three-day clinical conference held at Verano, Chile. Papers were read by specialists on special anesthesia, salivary lithiasis, diabetes, cholecystitis, allergy, diseases of the biliary tract, leukemia, surgery of the thorax, heart and hypertension, the biliary tract, and hospital organization. The volume is well published and should be in all large medical libraries.

(Notices on page xi)

# The New England Journal of Medicine

Copyright © 1948 by the Massachusetts Medical Society

Volume 239

JULY 22 1948

Number 4

## THE VALUE OF ANTIBIOTICS IN DIABETIC SURGERY\*

M J KUFFEL, MD † L N IRVIN, MD † D H HOOKER, MD † AND D P FOSTER, MD §

DETROIT, MICHIGAN

IF A diabetic patient must submit to major surgery, what is his prognosis? Or if a person has inherited the recessive genes of diabetes where should his interest be directed to prevent a frank diabetic state and the inevitable associated surgery? According to Root,<sup>1</sup> practically every diabetic patient at some time in his life is operated on and the prognosis is materially affected by the efficiency of diabetic control during the years preceding the emergency.

The reduction of the mortality in diabetic surgery over the years has been striking. Before the discovery of insulin in 1922 the surgical mortality stood at the appalling figure of 40 to 80 per cent.<sup>2</sup> In contrast, Joslin<sup>3</sup> reports a mortality of 11.5 per cent at the New England Deaconess Hospital for the period 1923 to August 1, 1926. From 1923 to 1941 the rate at the same institution was 7.3 per cent. Finally, from 1942 to January, 1946 the mortality dipped to a new low of 2.2 per cent. Joslin believes that this last improvement has been due in a large measure to the use of antibiotics. It is the purpose of this paper to draw a comparison between the management and surgical results in diabetes before and after the introduction of penicillin.

It is well known that the most prominent and universal pathologic change in diabetes is arteriosclerosis. Root et al.<sup>4</sup> have shown that coronary occlusion occurs three to eight times more frequently in diabetic patients over fifty years of age than in nondiabetic persons. McLaughlin<sup>5</sup> has stated that calcification in the peripheral vessels is demonstrable in 91 per cent of all patients who have had diabetes ten years and that pulsations in the arteries of the lower extremities tend to disappear ten to twenty years earlier than in nondiabetic persons. Root<sup>1</sup> claims that some degree of vascular nephritis can be demonstrated in almost all diabetic patients beyond fifty years of age. This generalized arteriosclerotic state in addition to producing grave circulatory changes may contribute to frequent and dan-

gerous skin infections. Boyd<sup>6</sup> considers the presence of large amounts of sugar in the tissues together with the hypemia resulting from faulty metabolism to be an important factor. We believe that hyperglycemia alone does not necessarily promote infection provided sufficient amounts of sugar are being metabolized.

The pathologic changes in diabetic tissue are the result of a vicious circle, which involves faulty circulation and anoxia and also tissue degeneration, often complicated by infection, fever and local edema. General toxemia leads to a diminished tolerance for carbohydrates. One method of attacking this circle is by decreasing or eradicating the infection. This can be accomplished more often and more quickly with antibiotics.

The recuperative power of the pancreas is normally very great when infection is controlled. Eisele<sup>7</sup> reported a diabetic patient with a diseased gall bladder requiring 1000 units per day preoperatively, who became insulin resistant. Two years after cholecystectomy the patient was asymptomatic and required no insulin.

### TREATMENT BEFORE AND AFTER OPERATION

The diabetic patients operated on at the Henry Ford Hospital are generally prepared as follows. On the day before the operation blood sugar, carbon dioxide combining power and blood chloride are taken. If these are within normal range, the diet is withheld on the morning of surgery and in its place 300 cc. of 20 per cent glucose is given intravenously with 10 units of regular insulin. Immediately on return from the operating room the patient is given another 300 cc. of 20 per cent glucose intravenously with 10 units of regular insulin followed by a clivsis of 1000 cc. of physiologic saline solution. The blood pressure is taken every two hours (for a period dependent on the condition of the patient) and 500 cc. of whole blood or plasma is given if the systolic pressure drops below 100. Excessive loss of fluids by profuse sweating or vomiting or drainage is replaced by additional clivses.

Food by mouth is offered on the evening of the first postoperative day in the form of fruit juices.

\*From the Department of Medicine, Division of Metabolism, Henry Ford Hospital.

†Resident in Medicine, Henry Ford Hospital.

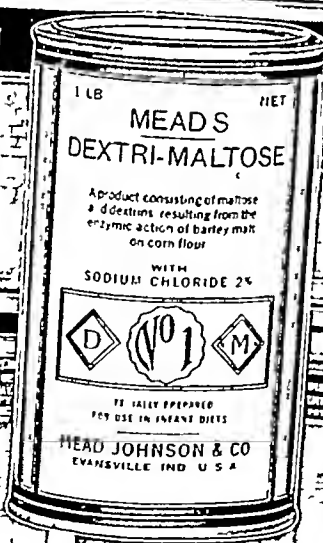
‡Resident, Henry Ford Hospital.

§Physician-in-Charge, Division of Metabolism, Department of Medicine, Henry Ford Hospital.

# BACKGROUND

The use of cow's milk, water and carbohydrate mixtures represents the one system of

infant feeding that consistently, for over three decades, has received universal pediatric



recognition. No carbohydrate employed in this system of infant feeding enjoys so rich and enduring a background of authoritative clinical experience as Dextri Maltose

The types of anesthetics and their combinations are illustrated in Table 6. The selection depends on the type of case, and the judgment and experience of the surgeon. Joslin<sup>9</sup> believes that with the aid of insulin, any type of anesthetic may be used. All observers agree that some have certain advantages over others. Root,<sup>1</sup> in studies using carbon dioxide levels as an indicator, has shown that the anesthetics of choice in order of value are spinal, ethylene, nitrous oxide and ether, and cyclopropane, the last being excellent for patients presenting cardiac complications. Other writers give different preferences. McKim and Fowler<sup>10</sup> favor cyclopropane. Where it can be used, all agree that local anesthesia is by far the safest. Hale and Tovell<sup>11</sup> point

blood sugar values are increased. Avertin is to be condemned because it is more toxic to the liver cells and the liver is slower in recovering than with other anesthetics.<sup>16</sup> Anoxia, which is a side effect of any general anesthetic and is of grave concern to the

TABLE 5 Operations

OPERATION	PATIENTS IN FIRST GROUP	PATIENTS IN SECOND GROUP
Amputations		
Major	21	24
Minor	4	6
Laparotomies	54	24
Pelvic and rectal	29	17
Ocular	24	9
Incision and drainage (for abscesses)	57	9
Lobectomy and thoracoplasty	6	1
Orthopedic	20	0
Ear, nose and throat	16	7
Thyroidectomies	0	4
Miscellaneous	24	10

TABLE 4 Diets Prescribed for Patients with Diabetes

FOOD	PATIENTS IN FIRST GROUP		PATIENTS IN SECOND GROUP	
	ON ADMISSION	ON DISCHARGE	ON ADMISSION	ON DISCHARGE
Protein				
30-39	1	1		
40-49	4	5		
50-59	30	35		
60-69	96	119	19	15
70-79	29	34	56	56
80-89	2	34	15	17
90-99	0	0	7	6
100—	0	0	9	10
Intravenous	5	7	5	5
Special	48	15	2	4
Fat				
40-39	5	4	2	1
60-79	15	16	16	16
80-99	11	18	11	12
100-119	48	50	57	28
120-139	28	58	18	24
140-159	36	32	8	9
160-179	9	13	4	1
180-189	6	11	0	2
200-219	3	10	7	8
220—	1	7	1	1
Intravenous	5	5	5	5
Special	48	15	2	4
Carbohydrate				
0-99	34	43	9	5
100-119	32	35	3	2
120-139	8	12	51	51
140-159	36	44	2	2
160-179	0	2	2	2
180-199	1	0	50	52
200-219	48	53	7	8
220—	3	6	0	0
Intravenous	5	7	5	5
Special	48	15	2	4

diabetic patient, is increased by deep and prolonged anesthesia as well as by excessive narcosis.

Table 7 demonstrates an interesting comparison in the causes of death during the two eras. Prior to

TABLE 6 Types of Anesthetic

ANESTHETIC	PATIENTS IN FIRST GROUP	PATIENTS IN SECOND GROUP
Ethylene	82	15
Local	59	31
Spinal	18	16
Ether and ethylene	26	10
Sodium pentothal	0	1
Nitrous oxide	7	6
Ethylene and avertin	1	2
Ether and nitrous oxide	6	1
Ether	4	0
Cyclopropane	0	6
Refrigeration	0	5
Ethylene and cyclopropane	0	3
Nitrous oxide and cyclopropane	0	1
Avertin and cyclopropane	0	1
Nitrous oxide (spinal)	0	1
Avertin	1	0
Unrecorded	11	0

the current use of penicillin, septicemia represented the greatest single cause of death. There were no deaths from septicemia among the more recent cases. This is consistent with Joslin's<sup>3</sup> statement that

TABLE 7 Causes of Death

CAUSE	PATIENT IN FIRST GROUP	PATIENTS IN SECOND GROUP
Myocardial insufficiency	4	2
Coronary occlusion	2	1
Diabetes	5	0
Septicemia	5	0
Pulmonary embolus	1	1
Portal thrombosis	0	1
Multiple metastases	2	0
Tuberculosis	2	0
Gangrene (gas bacillus)	1	0
Uremia	1	0
Cerebral embolus	1	0
Sudden death (no autopsy)	1	0
Totals	23 (10.7%)	5 (4.5%)

"deaths from septicemia have ceased, thanks to penicillin."

We believe that the marked improvement in mortality in recent years is due for the most part to the

out the inadvisability of its use in areas deficient in circulation. There is much to be said of the advantages of refrigeration anesthesia. Many commonly used agents have been shown to have extremely undesirable and dangerous side effects. In animal experiments with ether, Bloor<sup>12</sup> has reported an increase in blood fat from 40 to 100 per cent, the rate of rise being greatest during the first hour. Brown and Long,<sup>13</sup> after two and a half hours' administration of ether to cats, found an 87 per cent reduction of glycogen in the cardiac musculature. It is well known, as cited by Wilcox and Tovell,<sup>14</sup> that even in normal subjects ether produces an acidotic condition proved by recovery of acetone bodies in the urine. Foster<sup>15</sup> believes that ether probably interferes with the utilization of carbohydrate since

gingerale, milk and buttermilk as tolerated, or up to 6 ounces every two hours. In addition, sufficient 5 per cent glucose is given intravenously to total an intake of 100 gm of carbohydrate per twenty-four hours. During that time, the urine is examined for sugar every two hours. If the reaction is ++ or more, 10 units of regular insulin is given. From this point the oral consumption of food is gradually increased as tolerated until the patient is again on his regular diabetic diet. During this convalescent period the urine is tested four times daily (before meals and at bedtime), and regular insulin given as described above. From these values together with a daily fasting blood sugar determination, the proper dosage of protamine zinc insulin is calculated. In certain cases it may be necessary to use supplementary regular insulin before meals and at bedtime.

The diabetic patient in acidosis, requiring surgery, presents a more complex problem. Except in cases of dire necessity, no patient should be subjected to operation whose carbon dioxide combining power is below 30 vol per cent or with a blood sugar above 350 mg per 100 cc. Much can be accomplished to correct these conditions within the first four to six hours after admission. An outline of the treatment of acidosis is tedious and detailed and seems to have no place in this report. For a comprehensive outline of our views of that subject, the reader is referred to the work of Foster et al.<sup>8</sup>

### DISCUSSION

The series of cases herein reported consists of two groups, each representing a different era of management. The first group includes 215 diabetic patients operated upon prior to 1940—that is, be-

TABLE 1 Sex Incidence

PERIOD	MALE PATIENTS		FEMALE PATIENTS	
	NO	PER CENTAGE	NO	PER CENTAGE
Before 1940	85	39.5	130	60.5
January 1, 1945 to January 1, 1947	51	46.0	60	54.0
Totals	136		190	
Averages		41.7		58.3

fore penicillin was available. The second comprises 111 operations performed between January 1, 1945, and January 1, 1947, selected from 825 diabetic cases excluding fractures, dental procedures and all pediatric surgery, the antibiotics, particularly penicillin, were used freely with telling effect in this group.

The sex incidence shows a 7 per cent increase in surgical intervention for male patients in the second group (Table 1). Although the variance is not great, it suggests a tendency toward self-neglect during the war years.

The age incidence in both groups indicates that approximately 90 per cent of the patients were over

forty years of age (Table 2). This figure obviously illustrates the importance of adequate management of uncomplicated diabetes after middle age. Our results seem to parallel those of others in that the

TABLE 2 Age Incidence

AGE	PATIENTS IN FIRST GROUP		PATIENTS IN SECOND GROUP		ALL PATIENTS	
	NO	PER CENTAGE	NO	PER CENTAGE	NO	PER CENTAGE
50+						
0-9	3	1.4	—	—	3	0.91
10-19	4	1.9	2	1.8	6	1.69
20-29	3	1.4	4	3.6	7	1.7
30-39	11	5.1	6	5.4	17	5.50
40-49	45	21.0	23	20.7	68	20.82
50-59	67	31.1	33	29.7	100	40.67
60-69	55	25.5	28	25.3	83	25.42
70-79	23	10.7	14	12.6	37	11.35
80-89	4	1.9	1	0.9	5	1.52

greatest incidence of diabetic surgery was in the fifth decade of life.

On discharge approximately 73 per cent of cases in the second group showed a blood sugar level of less than 150 mg per 100 cc (Table 3). Three cases exhibited 250 mg per 100 cc or more. This excellent control can be attributed in a large measure to the efficacy of protamine-zinc insulin and penicillin, particularly in view of the fact that many of these patients were discharged prior to the complete healing of their wounds.

An analysis of the diet indicates a trend toward increasing the carbohydrate allowance (Table 4). This is also true, in a lesser degree, of the protein prescribed, whereas the fat intake remains fairly constant.

The miscellaneous operations in Table 5 include simple procedures such as removal of cysts and wens, venous ligation, skin grafts and the extraction of foreign bodies. Amputations and skin infections constituted approximately a third of the cases. These conditions are given careful consideration because they are, in a large degree, preventable through early education and proper management of

TABLE 3 Blood Sugar\*

BLOOD SUGAR	PATIENTS IN FIRST GROUP		PATIENTS IN SECOND GROUP	
	ON ADMISSION	ON DISCHARGE	ON ADMISSION	ON DISCHARGE
mg/100 cc				
50-149	70	130	50	81
150-249	95	47	51	7
250-349	30	6	6	0
350-449	7	2	2	0
450-549	1	2	2	0
Unrecorded	12	28	0	

\*In the patients who died, the last blood sugar prior to death is recorded.

the patient. The patients in the second group showed a 50 per cent reduction in skin infection requiring surgery, again owing, we believe, to the use of penicillin.

It is rather striking that not a single case of glomerulonephritis is reported by the investigators<sup>11, 12</sup> mentioned above.

So far as animal experimentation is concerned, Bersh and Grollman,<sup>8</sup> Marshall and Davis,<sup>9</sup> Swingle<sup>10</sup> and Harrison and Darrow<sup>11</sup> found no significant diffuse renal damage in their adrenalectomized animals. On the other hand, Marine,<sup>12</sup> MacMahon and Zwemer,<sup>13</sup> Simpson and Korenhevsky,<sup>14</sup> Banting and Gairns<sup>15</sup> and Hartman et al.<sup>16</sup> observed rather extensive renal disease in their adrenalectomized animals.

Thorn, Koepf and Clinton,<sup>17</sup> in 1944, described 2 cases of renal failure with a syndrome simulating adrenocortical insufficiency. They ascribed this syndrome to the loss of sodium and chloride secondary to renal disease rather than disease of the adrenal cortex. They demonstrated that in these cases relief was not afforded by treatment with adrenocortical substances but was attained by treatment with sodium chloride. The authors implied that the renal tubule is the end-organ for the adrenocortical hormones concerned with the balance of sodium and potassium in the plasma and the urine. To maintain a normal electrolyte balance the organism requires a normally functioning adrenal cortex as well as an intact renal tubule.

The following case is presented as one in which the disturbed physiology leading to death resulted from the worst possible combination—that of a diseased adrenal cortex and a diseased end-organ. It is possible that these two organs, the adrenal cortex and the kidney, suffered damage from a common etiologic agent. Since the renal lesion in this case was of a rather specific character, it is more probable that this was a case of two major coexistent diseases, each a result of a different etiologic mechanism.

### CASE REPORT

A. Y., a 55-year-old married man, was admitted to the hospital on April 10, 1947. He complained of generalized itching of 9 weeks' duration. A rash, which had started on the thighs, had spread rapidly to the trunk, neck, arms, buttocks and lower legs. The lesions had become vesiculated and weeping over both lower legs. The patient had noticed marked darkening of the skin over all areas involved by the rash.

His occupation had brought him in daily contact with raw camel and alpaca wool.

Seven years before admission, he had begun to suffer from episodes of diarrhea occurring off and on at irregular intervals. One of those episodes was so severe that it lasted "nearly a year." No cause for this condition was found at the time. The attacks of diarrhea were interspersed with attacks of constipation of such severity that it necessitated frequent recourse to "laxatives." The patient had noticed a recent increase in nervousness and fatigability.

For 3½ years previous to admission, he suffered from mild "bronchial asthma," for which he was treated by desensitization to kapok and "dusts."

There was a history of nocturia and albuminuria of at least 4 years' duration, and about 4 years before admission a physician had made a diagnosis of "chronic nephritis." X-ray study of the chest in 1942 had shown "old calcified tuberculosis," inactive. There were no significant data in the family and past histories, except that the patient's father had died of pulmonary tuberculosis at the age of 57.

Physical examination revealed a thin, apprehensive man in marked discomfort from a generalized itching rash. There was a mild seborrheic dermatitis of the scalp and an erythematous, papular excoriated rash over the thighs, buttocks, legs, trunk, neck and upper arms. Over the lower legs this had become vesiculated, weeping and impetiginous. In all areas involved by the rash, a blotchy, tan pigmentation of the skin had become confluent over the genitalia, thighs, neck and lower legs. There were large, tender femoral and inguinal lymph nodes bilaterally. There were a few small patches of brownish pigmentation on the hard palate and a few small irregular spots of blue-brown pigmentation of the buccal mucosa and the soft palate. Breath sounds were of the asthmatic type, and there were numerous musical expiratory rales throughout the chest. The heart was not enlarged and no murmurs were heard. The abdomen was essentially normal. The prostate was slightly enlarged, smooth and firm.

The blood pressure was 150/100, and the pulse 100. Examination of the blood disclosed a hemoglobin of 10.5 gm per 100 cc (photoelectric-cell technic), a white-cell count of 12,000 and a blood chloride (as sodium chloride) of 411.

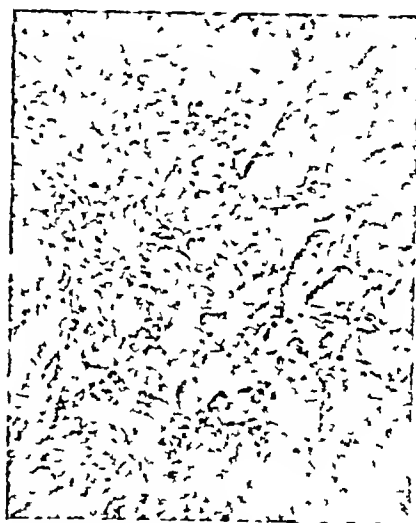


FIGURE 1. Hematoxylin and Eosin Stain of Suprarenal Glands, Showing Nodular Acute Accumulations of Cortical Cells, Fibrosis and Lymphocytic Infiltrations (x150).

mg and a blood urea nitrogen of 27 mg per 100 cc. Four morning urine specimens showed a maximum specific gravity of 1.012, two specimens contained a trace of albumin and a moderate number of finely granular casts. A film of the chest demonstrated healed apical tuberculosis on the left and a heart of normal size.

The patient was treated symptomatically for his dermatitis, receiving moist compresses to his lower legs, and calamine lotion to the rest of his body. During the first 10 hospital days he remained afebrile, ate well and felt relatively comfortable. There was some improvement of his dermatitis and marked relief from the pruritus. The pigmentation remained unchanged. On the 9th hospital day, repeated checking showed a blood pressure of 145/95 to 150/100.

On the 11th hospital day the patient became drowsy, but stated that otherwise he felt fine. His blood pressure dropped to 70/45, the pulse rose to 120, and his temperature to 105°F by rectum. He vomited once during the day but thereafter took some fluids and soft food by mouth without nausea, vomiting or diarrhea. The white-cell count was 17,400, with 50 per cent neutrophils, a blood culture showed no growth, the nonprotein nitrogen was 75 mg, the creatinine 4.5 mg, the chloride (as sodium chloride) 444 mg, and the fasting blood sugar 114 mg per 100 cc.

Addisonian crisis was suspected. Despite vigorous treatment with physiologic saline solution, glucose and adrenocortical hormones, the patient became progressively worse and died on the twelfth hospital day.

use of penicillin, but credit must also be given to the better understanding of the management of his case by the diabetic patient. In the 111 cases in the second group 52 per cent of patients were given penicillin. The dosage ranged from 100,000 to 400,000 units per day and covered a time range from two to forty-two days. The maximum total dosage used in a single case was 7,300,000 units.

### SUMMARY AND CONCLUSIONS

A survey of 326 cases of diabetic surgery is presented, one group, of 215 patients, operated on prior to 1940 without benefit of penicillin and the other, comprising 111 cases, treated surgically between January 1, 1945, and January 1, 1947, with the liberal use of penicillin. The results are compared.

Approximately 90 per cent of patients came to surgery after the age of forty years. There was moderate variation in the sex incidence.

The practice of increased carbohydrate and protein allowance is substantiated.

A comparison of various anesthetics is made, the use of local anesthesia being preferable when possible. The dangers of anoxia are stressed.

A reduction in mortality from 10.7 to 4.5 per cent has been obtained. The use of penicillin in diabetes has removed septicemia as a cause of death and has become a major contribution in the management of diabetic surgery.

The diabetic patient facing surgery has, in recent years, entered an era promising much greater chances not only of survival but also of rehabilitation. Medical and surgical teamwork cannot be overemphasized. Penicillin has proved to be a formidable weapon.

### REFERENCES

1. Root, H. F. Medical aspects of diabetic surgery. *New York State J. Med.* 42:2296-2302, 1942.
2. Van Alstyne, G. S. Diabetes from surgical standpoint. *Illinois M. J.* 80:376-380, 1941.
3. Joslin, E. P., Root, H. F., White, P., Marble, A. and Bailey, C. C. *The Treatment of Diabetes Mellitus*. Eighth edition, 861 pp. Philadelphia: Lea & Febiger, 1946.
4. Root, H. F., Bland, E. F., Gordon, W. H. and White, P. D. Coronary atherosclerosis in diabetes mellitus: postmortem study. *J. A. M. A.* 113:27-30, 1939.
5. McLaughlin, C. W., Jr. Problems on surgical management of diabetic gangrene. *Surgery* 13:423-433, 1943.
6. Boyd, W. *The Pathology of Internal Diseases*. Fourth edition, 837 pp. Philadelphia: Lea & Febiger, 1944.
7. Eisele, H. E. Results of gallbladder surgery in diabetes mellitus. *Ann. Surg.* 118:107-115, 1943.
8. Foster, D. P., Lowrie, W. L. and MacMillan, J. Plan of treatment for diabetic acidosis. *Am. J. Digest. Dis.* 10:371-379, 1943.
9. Joslin, E. P. *The Treatment of Diabetes Mellitus*. Fifth edition, 670 pp. Philadelphia: Lea & Febiger, 1935.
10. McKim, L. H. and Fowler, A. F. Surgery and diabetes mellitus. *S. Clin. North America* 25:1027-1032, 1945.
11. Hale, D. E. and Tovell, R. M. Choice of anesthetic agents and methods of their administration for diabetic patients. *Surgery* 3:100-110, 1938.
12. Bloor, W. R. Studies on blood fat. I. Variations in fat content of blood under approximately normal conditions. *J. Biol. Chem.* 19:1-24, 1914.
13. Brow, G. R. and Long, C. N. H. Biochemical changes in heart during anesthesia. *Anesth. & Analg.* 9:193-197, 1930.
14. Wilcox, F. C. and Tovell, R. M. Anesthesia in relation to diabetes. *Anesth. & Analg.* 18:94-101, 1939.
15. Foster, N. B. Surgical aspects of diabetes. *J. A. M. A.* 84:512-516, 1925.
16. Coleman, F. P. Effect of anesthesia on hepatic function. *Surgery* 3:87-99, 1938.

## ADDISON'S DISEASE COMPLICATED BY CHRONIC GLOMERULONEPHRITIS\*

LOUIS RAVREBY, M.D.,† AND WILBUR H. SAWYER, M.D.‡

IN THE classic description of the disease that bears his name, Addison presented no significant clinical evidence of renal disease in any of the 11 cases he reported. Of those cases, all of which were autopsied, only one is reported to have been diffusely pathologic. He describes the kidneys of this case as "contracted and granular."<sup>1</sup>

### REVIEW OF THE RECENT LITERATURE

Regarding the effect of adrenocortical insufficiency on renal function, it is fair to state that very little of anything happens to renal function in the intercritical phases of Addison's disease. On the other hand, nearly all investigators find rather marked renal dysfunction during crisis, characterized chiefly by an elevated blood urea, nonprotein nitrogen and hyperproteinemia. This is attributed to the dehydration, hypotension, reduced blood volume and shock accompanying Addisonian crisis.<sup>1-4</sup>

This picture is reversed by treatment with salt and desoxycorticosterone acetate.<sup>1-3</sup> Soffer<sup>1</sup> regards this dysfunction as nonspecific and as similar to the renal dysfunction resulting from dehydration and shock from any cause.

The question of whether or not adrenocortical insufficiency results in any specific diffuse morphologic lesion in the kidney has not been satisfactorily answered. On the basis of human patients at autopsy, no renal lesion was found by at least two groups of investigators.<sup>4, 5</sup>

Rowntree and Snell<sup>1</sup> found cases of severe renal disease in about a third of their 31 autopsied cases, and only 1 with hypertension.

Of 566 cases selected from the literature, Guttman<sup>6</sup> observed anatomic changes in the kidney sufficient to render a diagnosis in only 10 per cent. The nature of the lesion in the involved kidneys is not described adequately enough to make any positive statement.

Only one author, Barker,<sup>7</sup> reported significant renal disease in 11 of a total of 28 cases of Addison's disease.

\*From the Department of Medicine, Veterans Administration Hospital, Togus, Maine.

†Chief of medicine, Veterans Administration Hospital, Bedford, Massachusetts.

‡Assigned to Medical Department by United States Navy Veterans Administration Hospital, Togus, Maine.

It is rather striking that not a single case of glomerulonephritis is reported by the investigators<sup>1, 4-7</sup> mentioned above.

So far as animal experimentation is concerned, Gersh and Grollman,<sup>8</sup> Marshall and Davis,<sup>9</sup> Swingle<sup>10</sup> and Harrison and Darrow<sup>11</sup> found no significant diffuse renal damage in their adrenalectomized animals. On the other hand, Marine,<sup>12</sup> MacMahon and Zwemer,<sup>13</sup> Simpson and Korenchevsky,<sup>14</sup> Banting and Cairns<sup>15</sup> and Hartman et al<sup>16</sup> observed rather extensive renal disease in their adrenalectomized animals.

Thorn, Koepf and Clinton,<sup>17</sup> in 1944, described 2 cases of renal failure with a syndrome simulating adrenocortical insufficiency. They ascribed this syndrome to the loss of sodium and chloride secondary to renal disease rather than disease of the adrenal cortex. They demonstrated that in these cases relief was not afforded by treatment with adrenocortical substances but was attained by treatment with sodium chloride. The authors implied that the renal tubule is the end-organ for the adrenocortical hormones concerned with the balance of sodium and potassium in the plasma and the urine. To maintain a normal electrolyte balance the organism requires a normally functioning adrenal cortex as well as an intact renal tubule.

The following case is presented as one in which the disturbed physiology leading to death resulted from the worst possible combination—that of a diseased adrenal cortex and a diseased end-organ. It is possible that these two organs, the adrenal cortex and the kidney, suffered damage from a common etiologic agent. Since the renal lesion in this case was of a rather specific character, it is more probable that this was a case of two major coexistent diseases, each a result of a different etiologic mechanism.

### CASE REPORT

A. Y., a 55-year-old married man, was admitted to the hospital on April 10, 1947. He complained of generalized itching of 9 weeks' duration. A rash, which had started on the thighs, had spread rapidly to the trunk, neck, arms, buttocks and lower legs. The lesions had become vesiculated and weeping over both lower legs. The patient had noticed marked darkening of the skin over all areas involved by the rash.

His occupation had brought him in daily contact with raw camel and alpaca wool.

Seven years before admission, he had begun to suffer from episodes of diarrhea occurring off and on at irregular intervals. One of those episodes was so severe that it lasted "nearly a year." No cause for this condition was found at the time. The attacks of diarrhea were interspersed with attacks of constipation of such severity that it necessitated frequent recourse to "laxatives." The patient had noticed a recent increase in nervousness and fatigability.

For 3½ years previous to admission, he suffered from mild "bronchial asthma," for which he was treated by desensitization to kapok and "dusts."

There was a history of nocturia and albuminuria of at least 4 years' duration, and about 4 years before admission a physician had made a diagnosis of "chronic nephritis." X-ray study of the chest in 1942 had shown "old calcified tuberculosis," inactive. There were no significant data in the family and past histories, except that the patient's father had died of pulmonary tuberculosis at the age of 37.

Physical examination revealed a thin, apprehensive man in marked discomfort from a generalized itching rash. There was a mild seborrheic dermatitis of the scalp and an erythematous, papular excoriated rash over the thighs, buttocks, legs, trunk, neck and upper arms. Over the lower legs this had become vesiculated, weeping and impetiginous. In all areas involved by the rash, a blotchy, tan pigmentation of the skin had become confluent over the genitalia, thighs, neck and lower legs. There were large, tender femoral and inguinal lymph nodes bilaterally. There were a few small patches of brownish pigmentation on the hard palate and a few small irregular spots of blue-brown pigmentation of the buccal mucosa and the soft palate. Breath sounds were of the asthmatic type, and there were numerous musical expiratory rales throughout the chest. The heart was not enlarged and no murmurs were heard. The abdomen was essentially normal. The prostate was slightly enlarged, smooth and firm.

The blood pressure was 150/100, and the pulse 100. Examination of the blood disclosed a hemoglobin of 10.5 gm per 100 cc (photoelectric-cell technic), a white-cell count of 12,000 and a blood chloride (as sodium chloride) of 411.

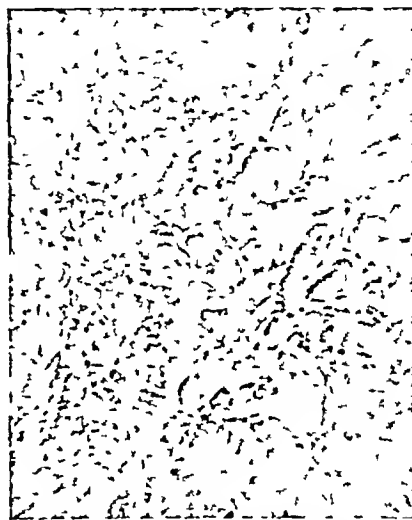


FIGURE 1 Hematoxylin and Eosin Stain of Suprarenal Glands, Showing Nodular Acute Accumulations of Cortical Cells, Fibrosis and Lymphocytic Infiltrations (x150)

mg and a blood urea nitrogen of 27 mg per 100 cc. Four morning urine specimens showed a maximum specific gravity of 1.012, two specimens contained a trace of albumin and a moderate number of finely granular casts. A film of the chest demonstrated healed apical tuberculosis on the left and a heart of normal size.

The patient was treated symptomatically for his dermatitis, receiving moist compresses to his lower legs, and calamine lotion to the rest of his body. During the first 10 hospital days he remained afebrile, ate well and felt relatively comfortable. There was some improvement of his dermatitis and marked relief from the pruritus. The pigmentation remained unchanged. On the 9th hospital day, repeated checking showed a blood pressure of 145/95 to 150/100.

On the 11th hospital day the patient became drowsy, but stated that otherwise he felt fine. His blood pressure dropped to 70/45, the pulse rose to 120, and his temperature to 105°F by rectum. He vomited once during the day but thereafter took some fluids and soft food by mouth without nausea, vomiting or diarrhea. The white-cell count was 17,400, with 50 per cent neutrophils, a blood culture showed no growth, the nonprotein nitrogen was 75 mg, the creatinine 4.5 mg, the chloride (as sodium chloride) 444 mg, and the fasting blood sugar 114 mg per 100 cc.

Addisonian crisis was suspected. Despite vigorous treatment with physiologic saline solution, glucose and adrenocortical hormones, the patient became progressively worse and died on the twelfth hospital day.

At autopsy\* the skin of the face, chest, abdomen and extremities was tannish brown. The anterior aspects of the lower extremities showed the skin to be scaly and desquamating. The serous cavities were not remarkable.

The heart weighed 250 gm. Except for brown atrophy of the myocardium, a thickening fibrosis and retraction of the mitral leaflets there were no gross abnormalities. The chordae tendineae were thickened, fused and shortened.

The lungs showed early acute bronchopneumonia at the bases of the lower lobes, and firm bilateral apical scars were present. The tracheobronchial lymph nodes were calcified.

The liver and gall bladder and extrahepatic bile ducts revealed no gross abnormalities. The spleen was not remarkable.

The right suprarenal gland measured 1 by 0.1 cm and weighed 1.2 gm. It was extremely soft in consistence, and the cortex was determined with difficulty. It was absent in some areas and when present was thin and tan. The medulla was a deep purple gray. The left suprarenal gland measured 1.2

increased in amount, and there were infiltrations of lymphoid cells. The small arteries and arterioles showed slight arteriosclerosis (Fig 2).

The pathological diagnoses were idiopathic cytotoxic atrophy of the suprarenal glands, chronic glomerulonephritis, mitral stenosis and insufficiency, healed apical tuberculosis and healed calcified tuberculosis of the mediastinal lymph nodes, brown atrophy of the myocardium, and bilateral, basal, acute bronchopneumonia.

## DISCUSSION

The combination of chronic glomerulonephritis and adrenal insufficiency is not common. In this case, it made the diagnosis of Addison's disease uncertain until crisis, as manifested by collapse, hypotension, hyperthermia and death, occurred. The addition of a severe contact dermatitis served further to obscure the underlying adrenal disease.

Asthenia, fatigue and nervousness had been present but only since the onset of the generalized itching dermatitis. Weight loss was absent. Typical pigmentation of the oral mucosa was present. The true significance of the widely distributed skin pigmentation was not at first appreciated, but was attributed to the long-standing dermatitis. Anorexia, nausea and vomiting were almost completely absent—the patient vomited only once after going into crisis. Until the onset of crisis he maintained a high blood pressure. This is not unusual in patients who have had a pre-existent hypertension,<sup>1-3, 18</sup> which this patient may well have had, on the basis of chronic glomerulonephritis.

Hypoglycemia was not present and the blood chloride was a low normal. The elevated blood urea nitrogen could be explained on the basis of chronic renal disease. A Kepler-Power water-diuresis test<sup>19</sup> would have been of no diagnostic value, since the presence of impaired concentrating power of the kidney would in itself cause a positive reaction. 17-ketosteroid excretion<sup>20</sup> could not be measured, since sufficient laboratory resources were not immediately available.

As the diagnosis of adrenal insufficiency was obscured by the presence of renal disease and a severe dermatitis, this combination presented definite therapeutic problems. The reason for the final hospitalization and the most pressing complaints was the severe dermatitis, and our first therapeutic efforts were directed against this problem. When full-blown Addisonian crisis did occur, the presence of renal disease probably contributed to the ineffectiveness of hormone therapy. Thorn, Dorrance and Day<sup>2</sup> imply that desoxycorticosterone acetate is contraindicated in cases of Addison's disease associated with hypertension. They found, in fact, resultant hypertension in some of the patients treated with desoxycorticosterone acetate, even in the absence of pre-existent hypertension. The action of adrenocortical hormones on the retention of sodium is dependent on an intact, functioning end-organ, the renal tubule. The presence of the tubular insufficiency as evidenced by a low urinary specific



FIGURE 2 Hematoxylin and Eosin Stain of Kidneys, Showing Chronic Glomerulonephritis (x350)

by 0.1 cm and weighed 1.3 gm. Grossly it was similar to the right, with the addition of small, pinhead-sized, nodular areas of yellow-tan cortex.

The kidneys together weighed 120 gm. They were equal in size, the right kidney was firm in consistence, and the capsule stripped with difficulty, tearing the gray tan granular cortex. The granules were irregular. On section the cortex measured 3 mm in diameter and was yellow gray, and the markings were indistinct. The medulla was purple gray, and the corticomedullary demarcation was indistinct. The mucosa of the renal pelvis was gray white and smooth. The left kidney was similar in appearance.

The remainder of the organs showed no gross lesions. The central nervous system was not examined.

On microscopical examination the important lesions were found in the suprarenal glands and the kidneys. The former showed the cortex to be present as nodular clusters of enlarged cells. Many of the cells contained a brown granular pigment in their cytoplasm. Cortical cells were seen, showing retrogressive changes as evidenced by remnants of cells and fragmented nuclei. Both cortex and medulla showed some fibrosis and lymphocytic infiltration (Fig 1).

The glomeruli of the kidneys were not uniformly affected. Many showed fibrosis of the glomerular tufts and fibrous adhesions between the lobules of the tufts and capsule. Rarely, glomeruli were converted into balls of fibrous tissue. Normal glomeruli were seen. The tubules in the region of the fibrosis showed atrophy. The interstitial and connective tissue was

\*Performed by Dr. Benjamin Newman, pathologist, Veterans Administration Hospital, Togus, Maine.

gravity may well have hastened the death of this patient.

It appears that even a small amount of adrenocortical tissue is adequate for body needs under ordinary circumstances.

The marked renal disease, by impairing over-all sodium chloride loss, may have modified to some extent the sodium chloride deficit that frequently precipitates Addisonian crisis.

In the presence of combined Addison's disease and kidney disease in which salt and water-hormone studies fail to distinguish between the two diseases, the levels of carbohydrate in the blood become very important as a diagnostic measure. In the case reported above the only recorded blood sugar determination was normal, which leads us to believe that even a small amount of adrenal cortex was adequate to maintain a normal fasting blood sugar.

Specific diffuse renal disease is no more common in Addison's disease due to idiopathic atrophy than one might expect on a basis of coincidence. When it is present, as in this patient, it poses problems regarding both early correct diagnosis and the effectiveness of specific therapy.

#### SUMMARY

A fatal case of idiopathic adrenal atrophy complicated by chronic glomerulonephritis is presented.

Specific diffuse renal disease is an unusual complication of Addison's disease. Its presence may make diagnosis and treatment more difficult.

#### REFERENCES

- 1 Rowntree L. G. and Snell A. M. *A Clinical Study of Addison's Disease* 317 pp Philadelphia W. B. Saunders Co. 1931
- 2 Thorn G. W., Dorrance, S. S. and Day E. Addison's disease: evaluation of synthetic desoxycorticosterone acetate therapy in 158 patients. *Ann. Int. Med.* 16:103-109 1942
- 3 Soifer L. J. *Diseases of the Adrenals* 304 pp Philadelphia Lea & Febiger 1946
- 4 Talbott J. H., Pecora, L. J., Melville R. S. and Consolazio W. V. Renal function in patients with Addison's disease and in patients with adrenal insufficiency secondary to pituitary panhypofunction. *J. Clin. Investigation* 21:107-119 1942
- 5 Conybeare, J. J. and Mills G. C. Observation on twenty-nine cases of Addison's disease treated in Guy's Hospital between 1904 and 1920. *Guy's Hosp. Rep.* 4:369-375 1924
- 6 Guttman P. H. Addison's disease: statistical analysis of five hundred and sixty-six cases and study of pathology. *Arch. Path.* 10:742-785 and 895-935 1930
- 7 Barker V. W. Pathologic anatomy in 28 cases of Addison's disease. *Arch. Path.* 8:432-450 1929
- 8 Gersh I. and Grollman A. Kidney function in adrenal cortical insufficiency. *Am. J. Physiol.* 125:66-74 1939
- 9 Marshall E. K., Jr. and Davis D. M. Influence of adrenals on kidneys. *J. Pharmacol. & Exper. Therap.* 8:325-350 1916
- 10 Swingle W. W. Studies on functional significance of suprarenal cortex. I. Blood changes following bilateral epinephrectomy in cats. *Am. J. Physiol.* 79:666-678 1927
- 11 Harrison H. E. and Darrow D. C. Renal function in experimental adrenal insufficiency. *Am. J. Physiol.* 125:631-643 1939
- 12 Marine D. Evidence of kidney-suprarenal interrelationship. *Arch. Path.* 6:169 1928
- 13 MacMahon H. E. and Zwemer R. L. Pathologic histology of adrenalectomized cats. *Am. J. Path.* 5:491-498 1929
- 14 Simpson S. L. and Korenchevsky V. Histological changes in kidneys of adrenalectomized rats. *J. Path. & Bact.* 40:483-488 1935
- 15 Banuing F. G. and Gairns S. Suprarenal insufficiency. *Am. J. Physiol.* 77:100-113 1926
- 16 Hartman F. A., MacArthur C. G., Gunn F. D., Hartman W. E. and MacDonald J. J. Kidney function in adrenal insufficiency. *Am. J. Physiol.* 81:244-254 1927
- 17 Thorn G. W., Koepf G. F. and Clinton M. Renal failure simulating adrenocortical insufficiency. *New Eng. J. Med.* 231:76-85 1944
- 18 Peters G. A. Relationship of adrenal cortex to hypertension: observation on effect of hypoadrenalism on patient with hypertensive vascular disease. *J. A. M. A.* 129:537 1945
- 19 Reforzo-Membrives J., Power M. H. and Kepler E. J. Studies on renal excretion of water and electrolytes in cases of Addison's disease. *J. Clin. Endocrinol.* 5:76-85 1945
- 20 Fraser R. W., Forbes A. P., Albright F., Sulkowitch H., and Reifenshien E. C., Jr. Colorimetric assay of 17-ketosteroids in urine: survey of use of this test in endocrine investigation: diagnosis, and therapy. *J. Clin. Endocrinol.* 1:254-256 1941

## SPASM AND FIBROSIS OF THE SPHINCTER ANI DUE TO REFLEX ACTION\*

FRANCIS C. NEWTON, M.D.,† AND CHARLES A. MACGREGOR, M.D.‡

BOSTON

SPASM and fibrosis of the anal sphincter associated with a long history of marked constipation, tenesmus, mild intermittent abdominal cramps and an almost daily intake of cathartics is a rather frequently observed clinical entity about which little has been written, but which is important enough on occasions to suggest major but unnecessary surgery.<sup>1-3</sup>

Twenty-one cases are reviewed in the present study. These patients were first seen because of variable complaints. Some sought advice because of constipation alone. Others complained of tenesmus. The majority, however, complained of vague abdominal discomfort, intermittent mild abdominal cramps, a sense of pelvic fullness, anorexia, flatus and marked constipation. All the symptoms at first are of such mild character that the progress

of the disease is very insidious. And because it is so insidious and gradual, it is allowed to establish itself as a part of the patient's life before he is aware that it requires medical advice; it is considered a minor problem in hygiene, requiring only home remedies.

It is much more prevalent among women than men. Of the 21 patients, 19 were women. Possibly this is because women lead a less active and more sedentary life in general than men and thus are more prone to constipation. The average age was fifty-five years, the youngest patient being twenty-nine and the oldest eighty-seven. All but 2 gave a history of marked constipation needing almost daily cathartics for many years. All but 1 had some tenesmus. A few had had minimal or moderate rectal bleeding on occasions. Not one of the women had had any degree of prolapse, which is of interest in that constipation played a predominant part in the syndrome. Three patients stated that borborygmus was an annoying symp-

\*From the Surgical Clinic, Peter Bent Brigham Hospital.  
†Clinical professor of surgery, Harvard Medical School, surgeon, Peter Bent Brigham Hospital.

‡Assistant and Arthur Tracy Cabot Fellow in Surgery, Harvard Medical School, junior associate in surgery, Peter Bent Brigham Hospital.

tom Eight stated that flatus was prominent Eight also complained of a sense of fullness in the pelvis Twelve had intermittent mild or moderately severe low abdominal cramps Six of the 21 patients also had anorexia or mild nausea, or both

The self-medication varied considerably but in general consisted of the taking of various forms

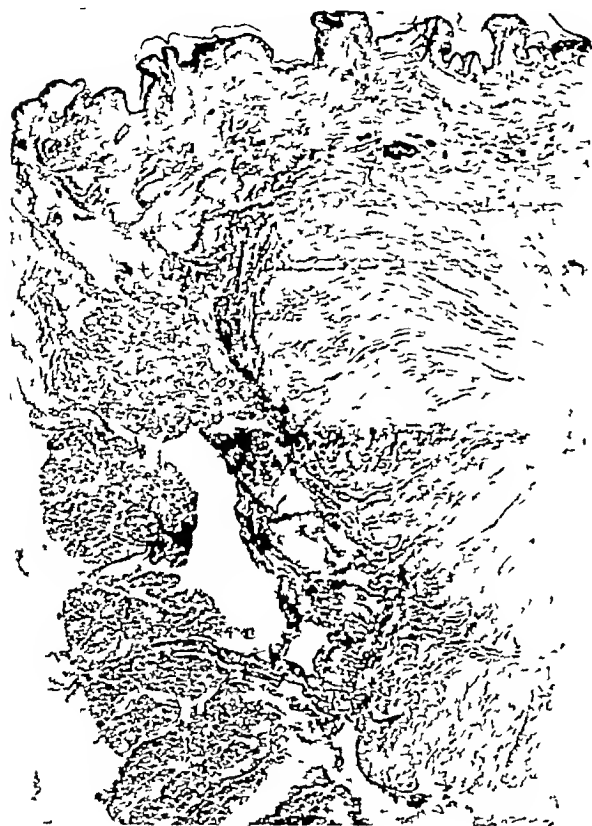


FIGURE 1 Longitudinal Section of a Normal Anal Canal at the Level of the Junction of the Internal and External Sphincters The internal sphincter consists of smooth muscle and is on the right A moderate amount of fatty subcutaneous tissue can be seen overlying the striated muscle of the external sphincter

of mild cathartics For example, 1 patient had taken approximately  $\frac{1}{2}$  pint of mineral oil daily for fourteen years She had started it fourteen years previously on her doctor's advice after a hemorrhoidectomy The vicious circle that was established is all too familiar to most proctologists<sup>1, 4, 5</sup> A second patient had moved her bowels only with the aid of enemas for seventeen years A third had been on a peptic-ulcer regimen for about five years with various constipating antacids and alkalis In all but 1 case there was a long history of frequent catharsis averaging ten to fifteen years

Physical examination always revealed a marked degree of spasm of the anal sphincter In many cases the examiner was unable to introduce even

the tip of his finger without causing considerable pain<sup>3</sup> Both the internal and external sphincters were found to be spastic, hypertrophied, hard and hyperirritable Moreover, in most cases, the internal sphincter was definitely smaller in diameter than the external

In 6 cases no other rectal or anal disease was found In 4, hypertrophied papillae or small anal polyps were present An additional 4 patients had very small external and internal hemorrhoids Five showed either a small established fissure in ano or areas of abrasion of the anal canal These associated pathologic conditions in no case seemed severe enough to have been the cause of the patient's symptoms Rather, they merely acted as an aggravating factor in the vicious circle of constipation, catharsis, spasm and fibrosis of the sphincter

A recent patient (P B B H L8421), with a history of excessive use of mineral oil daily for over twenty years, received dilatation and partial division of the external sphincter under general anesthesia Sigmoidoscopy was carried out at the same time, revealing two small polyps 12 and 18 cm from the anal canal These were excised and



FIGURE 2 Longitudinal Section of the Anal Canal in Case 5A327, Showing the Muscle Fibers of the External Sphincter Ten Days after Partial Division

on microscopical examination one proved to be malignant Accordingly, after suitable preparation, a combined abdominoperineal resection was carried out, thus giving an unusual opportunity for microscopical examination of the tissues in the region of the anus

Figure 1 demonstrates a longitudinal section of the anal canal at the junction of the external and internal sphincters The internal sphincter, which is smooth muscle (involuntary), is seen on the right, and the external sphincter, which is striated muscle

(voluntary), is on the left, separated by only a small amount of fibrous tissue. It is important to note the character of each muscle group and also of the small amount of fibrous and fatty tissue making up the subcutaneous layers.

Figure 2 presents a longitudinal section of the anal canal in the case mentioned above, demonstrating the effect of the partial division of the external sphincter. The striated muscle fibers show fatty degeneration and atrophy. There is only a moderate amount of fibrosis of the subcutaneous tissue, and this is most apparent overlying the internal sphincter.

One patient refused operation, but all others had a dilatation of the anal sphincters and partial division of the external sphincter.

In the following case, illustrating the need for accurate recognition of this diagnostic problem,

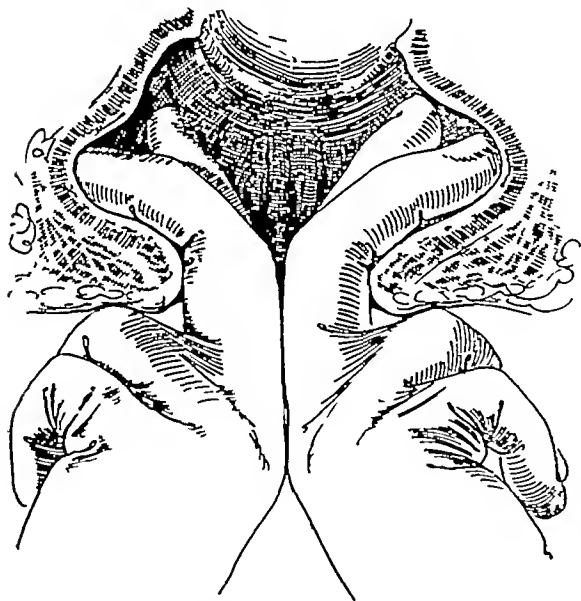


FIGURE 3 Procedure for Dilatation of the Anus

The gloved hands of the surgeon are covered with vaseline, and, with the dorsum of the hands approximated, the index fingers are inserted into the anus. The fingers are introduced full depth, moderately flexed, and then pulled outward as the hands are rotated slowly from side to side, increasing constantly a firm, persistent tension on the sphincter muscles. (Reproduced from Cutler and Zollinger<sup>8</sup> by permission of the publisher.)

the patient gave such a vague yet incapacitating history that abdominal exploration was carried out to rule out a chronic obstruction thought possibly due to adhesions or a slowly growing tumor.

L. M. (PBBH S45291), a 66-year-old single woman, was admitted to the hospital complaining of intermittent lower abdominal pain and occasional episodes of nausea. The pain was frequently relieved by the passage of flatus. She had also been troubled with severe persistent constipation requiring frequent catharsis and enemas. Mineral oil two or three times a day, followed by a cathartic in the evening had been her routine for many years. She stated

that her stools were usually partially fluid and that solid movements were very painful. There had been no bloody stools or protrusion of any rectal masses. No previous surgery had been carried out.

Physical examination of the abdomen was negative. Rectal examination revealed a firm stricture about 1.5 cm within the anal rim. This stricture appeared to be a contraction of the whole anal canal rather than a thin diaphragm.

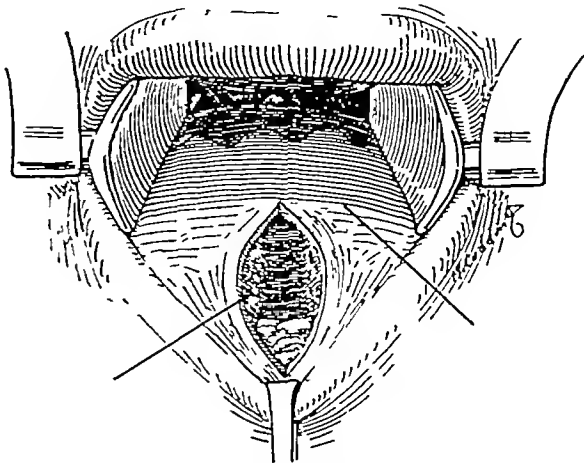


FIGURE 4 Incision of the Spastic External Sphincter

When necessary, the incision is made in the midline posteriorly and is carried only as deep as is necessary to obtain definite relaxation of the sphincter. Complete division is obviously to be avoided to avoid incontinence. Usually, however, the danger of this is minimal since the ridge of spastic tissue generally does not involve the entire sphincter.

The tip of the forefinger only could penetrate it, and attempts to dilate it were extremely painful. There was no blood on the examining finger.

Preoperatively, the diagnosis seemed obscure. It was difficult to see how the stricture of the anal canal could be the causative factor, because it was not tight enough to interfere at all with the passage of gas and the patient always had had loose stools.

Urinalysis and blood studies were negative.

A barium enema was normal. Exploratory laparotomy was carried out on the 4th hospital day under avertin and ether anesthesia, and very careful and thorough exploration revealed no disease. The appendix was removed as an incidental procedure and was later reported as normal by the pathologist. Immediately after the laparotomy, anal dilatation was performed, and an incidental small anal polyp noted. Two weeks later, excision of the small anal polyp was carried out. Further examination at that time revealed nothing additional. The polyp presumably played no part in the basic disease. The patient was discharged with bowel movements normal and free from tenesmus for the first time in 20 years.

Four years later the patient was seen and examined by the surgeon. She had been on a normal diet without laxatives or catharsis and had had normal bowel movements with only occasional tenesmus.

The treatment advocated consists of anal dilatation under a general anesthetic (Fig. 3). This should be carried out slowly (to avoid tearing of the muscle fibers, with resultant hematoma and fibrosis) over a period of ten minutes, until one is able to insert a total of four or five fingers to their full depth with ease. Frequently, one is forced partially to incise the external sphincter in the midline posteriorly because of a shelf-like hyperplasia

or even fibrosis of the tissue (Fig 4) This will be felt as a firm, unyielding ring just below (caudad to) the mucocutaneous junction Such incision is occasionally erroneously referred to as a pectinotomy It is well to carry out sigmoidoscopy or proctoscopy now if one has been unable because of the spasm to do so previously Also, hemorrhoidectomy, excision of polyp or curettage of a fissure, if indicated, should then be done

Local injections of an anesthetic to control points of discomfort are considered unnecessary since

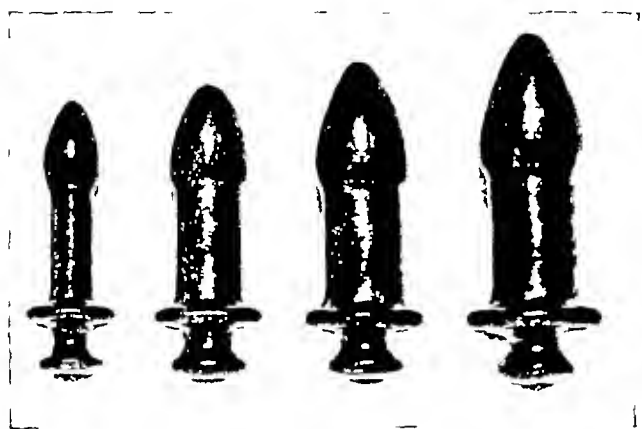


FIGURE 5 Young's Dilators

the dilatation itself prevents any painful spasm of the sphincter If the external sphincter requires partial division or other disease, such as hemorrhoids, polyps or fissures, has been present, the postoperative treatment should consist of clear fluids without milk for four days, followed by a gradual return to a normal high-residue diet without catharsis for the next two or three days If no abnormality other than spasm is found, a high-residue diet without catharsis may be resumed immediately Beginning on the fourth day in the uncomplicated case, rectal dilatation should be performed daily, either digitally or by the use of

Young's dilators (Fig 5) These consist of a series of graduated dilators, which may be passed by the patient with the aid of a small amount of lubricating jelly, beginning with the smallest and working up to the largest size each time The daily dilatation should be continued as long as is required to re-establish normal bowel habits Periodic rectal examinations should be made by the physician to detect any tendency to recurrence of the anal spasm

In the 21 cases in the present series, follow up reports varying from six months to five years give consistently good results Only 1 case required readmission for a second dilatation It is of interest that 2 cases showed extensive diverticulosis; quite possibly a result of the constipation and straining

### SUMMARY

A clinical entity of spasm and fibrosis of the sphincter ani, with marked constipation, chronic excessive use of cathartics and vague symptoms of abdominal discomfort, anorexia, cramps, tenesmus and flatus, is described and 21 cases reviewed

The incidence is far greater in women than in men

The average age when the disease is recognized is fifty-five years

The average duration of symptoms is ten to fifteen years

Treatment consists of anal dilatation with or without partial division of the external sphincter

Postoperative care should include a high-residue diet (unless diverticulosis is present) without catharsis and with anal dilatation by the patient and follow-up examinations by the physician

### REFERENCES

- 1 Gabriel W B *The Principles and Practice of Rectal Surgery* Second edition 363 pp London H K Lewis & Co Ltd., 1937
- 2 Hullsiek H E Section of anal sphincter *Minnesota Med* 24:756-758 1941
- 3 Bacon H E Anorectal operative procedures with special reference to avoidance of pain, based on series of one thousand cases *J A M A* 116:363-367 1941
- 4 Rankin F W, Bergen J A, and Buie, L A *The Colon, Rectum and Anus* 846 pp Philadelphia W B Saunders Co. 1935
- 5 Bacon H E *Anus, Rectum, Sigmoid Colon: Diagnosis and treatment* Second edition 857 pp Philadelphia J B Lippincott Co., 1941
- 6 Cutler E C and Zollinger R *Atlas of Surgical Operations* 181 pp New York Macmillan Co 1939

## SUCCINATE THERAPY IN ACUTE RHEUMATIC FEVER\*

RENÉ WÉGRIA, M D,<sup>†</sup> EDWARD E. FISCHEL, M D,<sup>‡</sup> AND PAUL E. WILSON, M D<sup>§</sup>

NEW YORK CITY

IN 1945, Gubner and Szucs<sup>1</sup> compared the efficacy of several drugs in the treatment of acute rheumatic fever. They reported that a group of patients treated with ascorbic acid and a succinate compound, subenon (calcium double salt of benzoic acid and succinic acid benzyl esters), introduced in 1936,<sup>2,3</sup> responded more favorably than a group of patients treated with ascorbic acid and salicylate. They stated that fever, leukocytosis and elevation of the erythrocyte sedimentation rate subsided more promptly, that carditis developed in fewer patients, that "relapses" of rheumatic activity were less frequent and that the average duration of the period of hospitalization was shorter in the patients treated with succinate. The purpose of this paper is to report the observations made on a small group of 10 patients treated with subenon.

## METHOD

Cases were selected in which a definite diagnosis of acute rheumatic fever could be established. To reach the diagnosis and to follow the course of the disease, the following clinical and laboratory data were used: history, physical examination, temperature, blood counts, erythrocyte sedimentation rate,<sup>4</sup> throat culture, antistreptolysin titer<sup>5</sup> and electrocardiogram. In most cases, therapy was instituted within forty-eight hours after admission, this time being used to establish the diagnosis and collect the necessary data. All the patients were given slightly larger doses of subenon (5.4 to 7.2 gm daily) than those in the studies of Gubner and Szucs<sup>1</sup> (4.0 to 5.3 gm daily), except 2 patients, five and nine years old, who received 3.6 gm every day. Two patients received some ascorbic acid. As Gubner and Szucs reported that the erythrocyte sedimentation rate returned to normal values within the first twenty-four days of subenon therapy in all their cases, we attempted to keep our patients on succinate therapy exclusively for at least three weeks. The results observed in a group of patients receiving either small or large doses of salicylate, reported in a previous study,<sup>6</sup> were used as a background to evaluate the course of the disease during subenon therapy.

## CASE REPORTS

**CASE 1** A 40-year-old Irish housewife, who had had a sore throat 4 weeks before admission, developed a temperature of 101°F and had pain in both hips and heels 4 days before admission. She was admitted to the hospital with the diagnosis of acute rheumatic fever. She was observed for 2½ days, during which the temperature ranged between 101 and 102°F, and the heart rate between 100 and 130. The sedimentation rate was 107 mm in 1 hour, and the white-cell count 13,000. Subenon (18 gm every 6 hours, day and night) was started on the 3rd day and continued for 12 days. Ascorbic acid 100 mg every day was also given from the beginning of the 2nd week. During the first 2 days of subenon administration, acute arthritis of both knees, elbows, wrists and all fingers, which required up to 500 mg of demerol a day, developed. Signs and symptoms of the rheumatic polyarthritis persisted until the administration of aspirin. On the fourth day of subenon administration, pericarditis developed, and a gallop rhythm was heard. The temperature ranged between 99 and 101°F, the heart rate remained unchanged. The white-cell count rose to 19,000, and the sedimentation rate to 119 mm in 1 hour, remaining above 110 until the 18th hospital day. On the 15th hospital day the sedimentation rate was still 113 mm in 1 hour. Signs and symptoms of the rheumatic polyarthritis had persisted. Subenon was stopped, and acetylsalicylic acid was given. The sedimentation rate began to fall steadily 4 days later, and the polyarthritis improved immediately.

During the administration of subenon, this patient with acute rheumatic polyarthritis showed no objective or subjective signs of improvement and developed myocarditis and pericarditis.

**CASE 2** A 5-year-old Negress who had had a sore throat 2 weeks before admission complained, 1 week before admission, of pain in both knee joints followed within 3 days by pain in the elbows and wrists. She was admitted to the hospital with a diagnosis of acute rheumatic polyarthritis. The temperature was normal. She had a sinus tachycardia (rate of about 120 per minute) and a normal PR interval. The sedimentation rate was 68 mm in 1 hour. Nose and throat culture revealed beta-hemolytic streptococci. The antistreptolysin titer was 832 units. Subenon (0.6 gm every 4 hours, day and night) was administered from the 2nd hospital day for 6½ weeks. Ascorbic acid (0.1 gm every day) was also given. The patient remained asymptomatic but kept having a marked sinus tachycardia (rate up to 160 per minute). At the end of the 4th week, she developed subcutaneous nodules. Her temperature remained normal except for an occasional day when it rose to 101.6°F. The sedimentation rate fell slowly from 68 to 46 mm in 1 hour at the beginning of the 3rd week, rose within 1 week to 83 mm and fell slowly to 53 mm by the middle of the 7th week. At that time a gallop rhythm developed, and subenon was discontinued.

During six weeks of subenon therapy, this patient developed subcutaneous nodules and gallop rhythm and kept having febrile episodes. The sedimentation rate after an initial slight decrease, rose to higher levels than on admission and was still markedly elevated at the end of the period of subenon administration.

**CASE 3** A 9-year-old girl had had a sore throat, acute catarrhal otitis media and migratory polyarthritis 2 weeks

\*From the departments of Medicine and Pediatrics, Presbyterian Hospital and Columbia University College of Physicians and Surgeons. This study was aided by a grant from the Life Insurance Medical Research Fund.

<sup>†</sup>Associate in medicine, Columbia University College of Physicians and Surgeons, assistant physician, Presbyterian Hospital.

<sup>‡</sup>Fellow in medicine, Columbia University College of Physicians and Surgeons, assistant physician, Presbyterian Hospital.

<sup>§</sup>Assistant in pediatrics, Columbia University College of Physicians and Surgeons, assistant pediatrician, Presbyterian Hospital.

before admission. One week before admission, she was given sulfadiazine and aspirin. She was admitted to the hospital with a diagnosis of acute rheumatic polyarthritis. During 2 days of observation, her temperature ranged between 101 and 104°F, and her heart rate between 100 and 120. The sedimentation rate was 110 mm in 1 hour. Rough systolic and diastolic murmurs heard at the apex were thought to be due to a previous subclinical attack of rheumatic valvulitis. On her 2nd hospital day the administration of subenon (0.9 gm every 6 hours) was begun. Her temperature remained between 101 and 104°F. There was an increase in symptoms and signs of the polyarthritis, and several additional joints became involved. The sedimentation rate rose from 110 to 132 mm in 1 hour on the 6th day of subenon therapy and varied between 100 and 110 mm for the next 2 weeks. An electrocardiogram taken on the 14th day of subenon therapy revealed that, with the same heart rate as before, the PR interval had risen from 0.14 to 0.24 second. Because 18 days of subenon therapy had not brought about any improvement in symptoms or signs, it was discontinued. The institution of salicylate therapy was followed by a rapid drop of the temperature and a return of the PR interval to normal (0.16 second) within 4 days.

In this case of acute rheumatic polyarthritis subenon did not produce any subjective or objective improvement and did not prevent the involvement of other joints and the appearance of a marked prolongation of the PR interval.

**CASE 4** A 49-year-old Negro with hypertensive and arteriosclerotic heart disease had had acute rheumatic polyarthritis 7 years before admission. Three weeks before admission, the patient had an upper respiratory infection followed 1 week later by acute migratory polyarthritis. He was admitted to the hospital with a diagnosis of acute rheumatic polyarthritis. On the 2nd hospital day, the administration of subenon (12 gm every 4 hours) was begun and continued for 36 days. The temperature ranged between 100 and 102°F and became normal after 1 week. The sedimentation rate, which was 70 mm in 1 hour on admission, rose to 100 mm within 10 days and remained between 100 and 110 mm for another 3 weeks. After 37 days of hospitalization (36 days of subenon therapy), it was still 90 mm. Demerol and codeine were used to control the joint pain, which persisted throughout the 5 weeks of subenon therapy. Additional joints became involved during the same period. Digoxin and mercurial diuretics, which the patient had been receiving for 2 years because of cardiac failure due to arteriosclerotic heart disease, were continued. On admission, a throat culture yielded a hemolytic streptococcus. Penicillin (10,000 units by intramuscular injection every 4 hours) was also given from the 3rd to the 22nd hospital day. Subenon was discontinued after 36 days of administration. The patient then received acetyl salicylic acid, which was promptly followed by the usual subjective and objective signs of improvement of the arthritis. The sedimentation rate fell to 22 mm in 1 hour after 25 days of salicylate therapy.

In this case of acute rheumatic polyarthritis the temperature became normal after twelve days of subenon administration. The patient, however, kept having signs and symptoms of acute polyarthritis and developed arthritis in joints previously not involved. The sedimentation rate rose markedly during subenon administration, remained elevated and was still 90 mm in 1 hour—that is, higher than on admission—after five weeks of subenon therapy.

**CASE 5** A 16-year-old boy, who had had chills and fever 3 weeks before admission and a sore throat 2 weeks before admission, developed acute migratory polyarthritis of the knees, ankles and toes 1 week before admission. He was admitted to the hospital with a diagnosis of acute rheumatic polyarthritis. From the 2nd hospital day, he received 12 gm of subenon every 4 hours, day and night, for 32 days.

His temperature, which ranged between 102 and 103°F for 6 days, returned to normal within 10 days and remained normal thereafter. The signs and symptoms of arthritis persisted for 9 days, and during that period, additional joints became involved. Large amounts of demerol and codeine had to be used to control the pain. The sedimentation rate, which was 108 mm in 1 hour on admission, was 118 and 103 mm respectively on the 7th and the 12th hospital day. By the 16th hospital day it was 57 mm, and it then came down progressively to normal (20 mm or less) by the end of the 4th hospital week. The PR interval, which was 0.18 second on admission, with a heart rate of 87 per minute, was 0.20 second on the 6th hospital day, with a heart rate of 80, on the 25th hospital day, it was 0.16 second, with a heart rate of 70. Subenon therapy was discontinued after 32 days. The patient was discharged home well after a period of 49 days in the hospital.

In this case of acute rheumatic polyarthritis, probably with mild rheumatic myocarditis, there was clinical improvement with subenon, and the sedimentation rate came down to normal on the twenty-sixth day of subenon administration.

**CASE 6** A 42-year-old Negress who had had a sore throat 4 weeks before admission developed acute arthritis of the left knee 1 week before admission and 2 days later had pain in the right hip. She was admitted to the hospital with a diagnosis of acute rheumatic polyarthritis. Her temperature was 102°F, the sedimentation rate 88 mm in 1 hour, and the antistreptolysin titer 712 units. The administration of subenon (12 gm every 4 hours) was begun on her 3rd hospital day and continued for 18 days. Until the end of this period, heavy doses of demerol and codeine had to be used for the arthralgia, and the patient developed arthritis of the elbows, shoulders and wrists. Her temperature ranged between 100 and 104°F throughout the period of subenon administration. The sedimentation rate, which rose to 130 mm in 1 hour on the 4th day, was 127 mm on the 14th day and 110 mm on the 18th and last day of subenon administration. The PR interval, which was 0.18 second on admission, rose to 0.24 second with a slightly higher heart rate on the last day of subenon therapy. The administration of subenon was stopped after 18 days. The patient was then given sodium salicylate and improved.

Although treated with subenon, this patient continued to have fever and migratory polyarthritis, the sedimentation rate rose, remaining markedly elevated. The PR interval became prolonged after eighteen days of subenon therapy.

**CASE 7** A 7-year-old girl who had had a severe sore throat 3½ weeks before admission had fever and a mild knee ache 3 days before admission. She was admitted to the hospital with a diagnosis of acute rheumatic arthritis and rheumatic myocarditis. Her temperature was 103°F, the sedimentation rate 106 mm in 1 hour, and the PR interval 0.20 second, with a heart rate of 130 per minute. The administration of subenon (0.9 gm every 4 hours) was begun on the 3rd hospital day and continued for 21 days. The symptoms of arthritis were very mild and transient before any therapy and could not be used to evaluate the course of the disease. The patient's temperature, ranging between 100 and 103°F during the control period, fell gradually to normal within 1 week of hospitalization. The sedimentation rate, which was 106 mm in 1 hour on admission, was 102, 67 and 62 mm after 4, 10 and 17 days of subenon administration, respectively. The heart rate and the PR interval decreased progressively. The PR interval, which was 0.20 second with a heart rate of 130 on admission, was 0.20, 0.17 and 0.16 second with a heart rate of 90 per minute after 4, 10 and 17 days of subenon therapy, respectively. The patient was discharged home on the same regimen after 21 days of subenon therapy. Fourteen days later, when seen in the clinic, she was well, but her sedimentation rate was still 55 mm in 1 hour.

In this case of acute rheumatic fever with mild monoarthritis and myocarditis, the patient improved clinically, but the sedimentation rate was still markedly elevated after twenty-one days of subenon therapy. After another fourteen days of subenon therapy at home, the sedimentation rate was still 55 mm in 1 hour.

**CASE 8** A 14-year-old girl, who had had chorea at the age of 10, had a sore throat 1 month before admission and intermittent fever with a mild ache in the left foot for the 10 days preceding admission. She was admitted to the hospital with a diagnosis of acute mild rheumatic polyarthritis and myocarditis. On admission she had a mild ache in the left knee and both hips. Her temperature was 100.4°F and never rose above 101°F. The sedimentation rate was 55 mm in 1 hour. The administration of subenon (12 gm every 4 hours) was begun on the 3rd hospital day and continued for 32 days. The joint pains, which were mild even during the control period, subsided gradually although she kept having an occasional pain in other joints than those involved on admission. The sedimentation rate rose from 55 to 86 mm in 1 hour by the sixth day of subenon therapy and was 70, 50, 55 and 50 mm after 13, 20, 22 and 29 days of subenon administration respectively. The electrocardiogram taken on admission showed nodal tachycardia, when the next electrocardiogram was taken 2 weeks later, the patient had converted to regular sinus rhythm with a heart rate of 80 and a PR interval of 0.20 second. The PR interval was still 0.20 second after 25 days of subenon therapy. After a 32-day period of subenon administration the sedimentation rate was still 50 mm, and sodium salicylate therapy was begun. After 21 days of salicylate administration, the sedimentation rate became normal, and the PR interval was 0.18 second with a heart rate of 65.

In this case of mild acute rheumatic fever no obvious effect of subenon was noted on the sedimentation rate or the electrocardiogram, the only criteria available in the study of this case.

**CASE 9** A 17-year-old boy, who had had acute rheumatic polyarthritis at the age of 8, had a pharyngitis 1 month before admission, and joint pains during the week preceding admission. He was admitted to the hospital with a diagnosis of acute rheumatic polyarthritis, involving both knees and ankles, with acute myocarditis. On the first hospital day, his temperature ranged between 101 and 102°F, and his heart rate between 100 and 130. The sedimentation rate was 55 mm in 1 hour. An electrocardiogram showed a PR interval of 0.26 second, with a ventricular rate of 100. On the 2nd hospital day the administration of subenon (12 gm every 4 hours day and night) was started, and it was continued for 34 days. Large amounts of demerol were required for analgesia. The patient's temperature remained above 101°F for the first 6 days of subenon administration, and dropped to between 100 and 101°F during the following week, after which it became and remained normal until the end of the 6th week of hospitalization. On the 2nd hospital day the patient developed acute pericarditis. The sedimentation rate rose to 118 mm in 1 hour on the 5th day of subenon administration, decreasing gradually to 45 mm by the end of the 5th week. At that time, the joint pains had progressively subsided, the PR interval had gradually decreased to 0.20 second with a ventricular rate of 84, and subenon was discontinued. One week later, the patient's temperature rose to 101°F, and the sedimentation rate to 61 mm in 1 hour. The joint pains reappeared, and the PR interval increased to 0.24 second. The administration of subenon was resumed for another 29 days. At the end of that period, the symptoms had gradually subsided, the sedimentation rate kept varying between 20 and 35 mm in 1 hour, and the PR interval was still 0.22 second, with a ventricular rate of 75. The patient was then given sodium salicylate and continued to improve.

In this case of acute rheumatic fever (polyarthritis, myocarditis and pericarditis) the sedimentation

rate was still elevated after thirty-four days of subenon therapy. It is impossible to establish the nature of the episode that occurred after the administration of subenon had been discontinued, but it was very similar to what is observed in cases of acute rheumatic fever in which aspirin therapy is discontinued prematurely although in such cases, recrudescence of rheumatic activity becomes obvious within a shorter time.<sup>7</sup>

**CASE 10** A 14-year-old girl, who had had a sore throat 1 month before admission, developed migratory polyarthritis 11 days before admission. She was admitted to the hospital with a diagnosis of acute rheumatic polyarthritis. During the first 3 days of her stay in the hospital, her temperature ranged between 100 and 103°F, and on the 4th day it was about 100°F. The administration of subenon (0.6 gm every 6 hours for 2 days and then 1.5 gm every 6 hours for 20 days) was begun on the 5th hospital day. No analgesics were required either before or during the administration of subenon. The temperature, which fell steadily during the period of observation, became normal and remained normal from the 6th hospital day. The sedimentation rate was 43 mm in 1 hour on admission, rising to 60 mm on the 3rd hospital day, it was 52, 45, 22 and 22 mm respectively, on the 2nd, 5th, 9th and 12th days of subenon administration. The rate then rose progressively, being 26, 36 and 41 mm, respectively, on the 14th, 19th and 22nd days of subenon therapy. It was then decided to place the patient on salicylate therapy. The sedimentation rate became normal after 3 weeks of salicylate therapy.

In this case of mild acute rheumatic polyarthritis the sedimentation rate, the only constant sign of rheumatic activity, fell to almost normal after ten days of subenon therapy but rose again while the patient was receiving subenon.

## DISCUSSION

Ten patients with acute rheumatic fever were given subenon (a succinic acid derivative) in doses reported to be adequate for fifteen to forty-six days and were followed carefully. Comparing this series of patients receiving succinic acid therapy with another series of patients receiving small or large doses of salicylates,<sup>8</sup> we can see no reason to believe that the succinic acid derivative is beneficial in acute rheumatic fever. It does not have any of the marked analgesic and antipyretic properties of salicylate. It does not prevent, as salicylate usually does, the involvement of additional joints by the rheumatic process. It does not prevent the appearance of signs of myocarditis any more than salicylate does. After the administration of succinic acid had been discontinued, several patients were given aspirin or salicylate and proved not to be cases refractory to treatment such as are occasionally seen.<sup>6</sup> In view of the comparatively poor results obtained with subenon, more cases were not studied.

## SUMMARY

Ten cases of acute rheumatic fever treated with subenon are reported. Neither the natural course of the disease nor its signs or symptoms were modified by the treatment.

## REFERENCES

- 1 Gubner, R. and Szucs, M. Therapeutic measures in rheumatic fever comparative study of one hundred and fifty cases. *New Eng J Med* 233 652-657 1945
- 2 Editorial. Subenon for arthritis and American Chemical Society. *J A M A* 107 878 1936
- 3 Current Comment. Seydel arthritis treatment-aftermath. *J A M A* 107 1056 1936
- 4 Westergren, A. Studies of suspension stability of blood in palmar artery tuberculosis. *Acta med Scandinav* 54 247 282 1921
- 5 Coburn, A. F. and Pauls, R. H. Studies on immune response of rheumatic subject and its relationship to activity of rheumatic process. *J Exper Med* 62 129 158 1935
- 6 Wegria, R. and Smull, K. Salicylate therapy in acute rheumatic fever. *J A M A* 129 485-490 1945
- 7 Personal observations

## MEDICAL PROGRESS

## PHYSIOLOGY (Continued)\*

HEBBEL E. HOFF, M.D.,† AND H. J. SCOTT, M.D.‡

MONTREAL, CANADA

An idea of the discreteness of the efferent control via the cortex is given by the evidence reported by Chang, Ruch and Ward, who with fixed routine of stimulation were able to delimit cortical areas controlling separately a single muscle operating at the ankle of the monkey, or even single parts of a muscle. Although it is clear from the work of Sherrington himself on the instability of motor points on the cortex that no entirely rigid anatomic pathway is responsible for these results, it is equally clear that out of a combination of anatomic pathway and stimulation characteristics a physiologic connection between cortex and spinal cord is open by which individual muscles or their parts can be reached.

If, then, the pyramidal system and for that matter the extrapyramidal also are to be regarded more in the nature of final common pathways or internuncial relay systems it becomes necessary to look elsewhere for centers of control or regions of decision, not necessarily in the sense of cortical areas but also in the sense of neuronal pattern. Here three general phenomena must be considered.

**Reverberating circuit.** Soon after it was found that area 4 S acts to diminish cord reflexes, presumably by extrapyramidal projections that eventually reach the spinal segments, it was observed that the same area suppresses electrical activity in the precentral cortex operating by a separate circuit through the thalamus.<sup>41</sup> Area 8 is presumably also a suppressor area operating in the same manner, and Penfield and Rasmussen<sup>42</sup> have recently shown that Broca's area can probably be considered to be part of the area 8 suppressor system, because stimulation of this area in man sometimes produced arrest of speech without associated movement or sensation.

\*From the Department of Physiology McGill University Faculty of Medicine.

†Joseph Morley Drake Professor of Physiology McGill University Faculty of Medicine.

‡Research assistant Department of Physiology McGill University Faculty of Medicine.

To such corticocortical circuits through basal ganglia and thalamus can be added circuits that pass through the cerebellum, and in fact the whole of the neocortex of the cerebellum can be considered to be occupied with a long circuit from cortex to the pons, through to the cerebellum and back to the cortex via the thalamus. Basically the paleocerebellum represents a circuit from somatic and vestibular afferents back to the motor system. All represent in various degrees systems whereby activity sets up a chain of reaction by which in turn activity is regulated. To these long-chain reverberating circuits must also be added short chain-circuits within the cortex itself changing the whole relation of afferent and efferent systems from a simple stimulus-response reaction with a short time course to a continuous self-regulation with a long time scale.

**Self-generated rhythm.** Continued neuronal activity for long periods after cessation of input can and undoubtedly does occur by virtue of the long delay paths that the neuronal organization of the central nervous system affords. But there is also evidence that many cells are in themselves spontaneously rhythmic, or are capable of being stimulated to rhythmic activity in the proper circumstances, just as a quiescent frog heart is often brought back to regular spontaneous beating by a few adequate stimuli.

Larrabee and Bronk<sup>43</sup> have noted prolonged afterdischarge, after strong presynaptic stimulation in the sympathetic ganglion where the question of delay paths cannot arise, and Adrian<sup>18</sup> has recorded prolonged afterdischarge from thalamic nuclei after afferent stimulation. Too little is known of the rhythms within the central nervous system, however, for one to be entirely certain what part rhythmic discharge of a single unit and what part rhythmic activity based on interneuronal circuits, respectively, play in the final picture as recorded.

**Field effects.** Thus far the concept has developed of an orderly though complicated interrelation of

cells via synaptic junctions. But it is well to remember that the interrelations of neurones may transcend this orderly pattern. The electrical fields surrounding an active tissue may alter the state of surrounding cells without reference to synaptic junction in a variety of ways. In the proper circumstances adjacent cells may be directly excited, this is the basis for the well known phenomenon of the rheoscopic frog first described by Matteucci, who noted the contraction of a frog muscle whose isolated nerve was looped over the belly of a first-nerve-muscle preparation when this was stimulated. Such field effects are responsible for the reflex volleys seen to emerge from dorsal roots after a single afferent volley as observed by Toennies<sup>44</sup> and for transmission at the artificial synapse as described by Granit<sup>45</sup> in which an impulse descending via a motor fiber becomes able to set up impulses in adjacent dorsal-root fibers at a region of injury or transection. Whether this type of extrasynaptic transmission ever has any real biologic value is problematical, but the suggestion that the poorly adapting pain fibers involved in a region of nerve injury are stimulated by impulses descending via sympathetic fibers constitutes one of the most attractive theories of the genesis of causalgia<sup>45, 46</sup>. Even when by virtue of threshold, geometry or distance the active fiber does not directly evoke an impulse in surrounding tissue, it may condition its activity by inhibiting or facilitating excitation in it. Thus, Segers et al.<sup>47, 48</sup> have shown that excised sections of frog's ventricle beating independently come into synchronization when placed close enough together, and Fessard<sup>49</sup> has demonstrated the same phenomenon in isolated segments of electrical organs. Much of this work dates from Arvanitaki's<sup>50, 51</sup> earlier studies. Bremer<sup>52, 53</sup> induced rhythmic potentials in the frog's spinal cord by strychnine poisoning and found that even after section of the cord the rhythms in the two isolated segments were synchronous, presumably by reason of interaction of the electrical fields of the two segments. Gerard<sup>54, 55</sup> has elaborated this hypothesis most actively in regard to the central nervous system and has listed the following aspects of central-nervous-system function as being more readily explainable on the basis of these field effects than in terms of transmission through established neuronal patterns<sup>56</sup>: the synchronization of spontaneous neurone firing, the establishment of new neuronal connections between brain centers in conditioning, central-nervous-system inhibition, functioning of the cortex in learning, summation of excitatory and inhibitory impulses reaching separate neurone processes, total behavior patterns and the phenomena of sensory equivalent.

But although Bremer considered the persistence of synchronization between anatomically separated segments of the spinal cord as evidence of the action of field effects, Sperry<sup>56</sup> interprets failure of subdivision of the sensorimotor cortex by gridiron incision

to affect the co-ordination of movements of shoulder, elbow, wrists and digits or to produce deficiency in capacity for motor learning as having quite the opposite significance, believing that the self-propagating intracortical potentials cannot spread their excitatory effect across a fresh cut in the mammalian cortex. If the evidence Sperry adduces does have this significance it means that superficial horizontal association is much less important than the deeper and more vertical intercortical communications. Whatever functional importance spontaneous rhythms and field effects may in the future prove to have, they serve at present as a valuable corrective to thinking of the nervous system as a telephone switchboard for the connection of ingoing and outgoing calls, however complicated it may be.

*Contact utile between physical and psychic*. This is the final problem with which the physiologist is confronted, and indeed it is the greatest of his responsibilities to elucidate psychologic events in terms of neurophysiology. Sherrington<sup>5</sup> recognized this when he wrote in the foreword of the 1947 edition of *The Integrative Action of the Nervous System*.

There remains yet another type of integration which claims consideration, although to saddle it upon nerve may perhaps encounter protest. Integration has been traced at work in two great, and in some respects counterpart, systems of the organism. The physico-chemical (or for short physical) produced a unified machine from what without it would be merely a collocation of commensal organs. The psychical, creates from psychical data a perceptive, thinking and endeavouring mental individual. Though our exposition kept these two systems and their integrations apart, they are largely complementary and life brings them co-operatively together at innumerable points. Not that the physical is ever anything but physical, or the psychical anything but psychical. The formal dichotomy of the individual, however, which our description practised for the sake of analysis, results in artefacts such as are not in Nature. Each such is a quasi-organism which does not resemble ourselves, nor does it, *pace* Descartes, resemble dog or cat. For our purpose the two schematic members of the puppet pair which our method segregated require to be integrated together. Not until that is done can we have before us an approximately complete creature of the type we are considering. This integration can be thought of as the last and final integration.

But theoretically it has to overcome a difficulty of no ordinary kind.

To this problem Sherrington was forced to conclude that the time has not yet arrived when one can insist, on the basis of precise knowledge, on the identity of the two.

In all those types of organism in which the physical and the psychical coexist each of the two achieves its aim only by reason of a contact utile between them. And this liaison can rank as the final and supreme integration completing its individual. But the problem of how that liaison is affected remains unsolved, it remains where Aristotle left it more than 2000 years ago. There is, however, one peculiar inconsistency which we may note as marking this and many other psychological theories. They place the soul in the body and attach it to the body without trying in addition to determine the reason why, or the condition of the body under which such attachment is produced. This, however, would seem to be a real question. Instead of, as is usual in physiology, leaving that impasse unmentioned, it seemed better to draw attention to it by the experimental observations in this book's final chapter.

Ritchie,<sup>3</sup> summarizing Sherrington as a philosopher, put the problem and its lack of solution in equally well turned phrases

In the purely material realm things and processes, though in some respects continuous, are in other respects "granular," wrapped in bundles all separate and all similar—the quantum of action, the electron, the atom, the molecule. In the organic realm there are also "granular" entities on a larger scale that are fundamental—the gene, the nervous impulse, the cell. There is in addition a process of co-ordination or integration at work, operating through purely physical and chemical means, yet exemplifying an order over and beyond the physical order. In spite of this integration, the most elaborately integrated of all organisms, the human, though possessing a master organ, the brain, possesses no master cell. Instead, the highest centres of the brain appear to be a kind of republic of millions of cells. Where does the mind come in? Mind is certainly not granular in the way that atoms and nervous impulses are. It is not a special kind of matter or of energy, as earlier speculators often suggested.

The bodily organism which contains millions of cells can do a number of things simultaneously by means of reflexes and acquired habits, but the mind attends to one thing at a time. It goes so far as to see one visual field through the medium of two distinct organs. Moreover, for a great deal of psychology knowledge of brain function is irrelevant. This is seen equally in the modern work of the psychoanalytic school and the many excellent psychological observations of Aristotle, who associated the heart, not the brain with conscious life.

Gerard<sup>54</sup> recognized the problem equally well but expressed it more forcefully

It remains sadly true that most of our present understanding of mind would remain as valid and useful if, for all we knew, the cranium were stuffed with cotton wadding. In time the detailed correlation of psychic phenomena and neural processes will surely come, but today we are hardly beyond the stage of unequivocal evidence that the correlation does exist.

Here Gerard has shown more courage than Sherrington, and it is perhaps significant to recall that when Bernard Sachs first met Freud in Meynert's Clinic, Freud "devoted himself to anatomy like the rest of us."<sup>55</sup>

### CATHETERIZATION OF THE HEART

The value of a new technic is measured not only by the success with which it meets the criteria for which it was introduced but also by the manner in which it opens new and hitherto unrealized approaches to research. One of the most striking illustrations of this is afforded by the method of intravenous catheterization whose application to human physiology must be credited almost entirely to Cournand and his collaborators<sup>58, 59</sup>. Naturally enough, the method has a fairly long background in physiology, although perhaps Chauveau and Marey<sup>60</sup> gave the greatest initial impetus by devising the catheters and transmission systems whereby right and left ventricular curves could be recorded from the intact unanesthetized horse. Sir Charles Sherrington often related to his classes the experience of visiting Chauveau's laboratory at Lyon, where ventricular pressure curves were demonstrated from a horse tranquilly eating hay outside the opened classroom window. In 1929

Forssmann<sup>61, 62</sup> demonstrated that the technic could be applied to man, by introducing a catheter into his own right auricle from a vein at the left elbow. Forssmann had intended the technic to provide a safe direct route for intracardiac injection of drugs, and reported its use in a patient with peritonitis following rupture of an inflamed appendix. The catheter remained in place six and a half hours before the patient died, but at autopsy no signs of damage to the intima or valves of the vessels in which it lay were noticed. The tip of the catheter had passed into the inferior vena cava. In the early years that followed Forssmann's report, the method was employed mainly as a means for introducing substances directly into the heart (not drugs, as Forssmann had intended, but radio-opaque materials for roentgenographic study of the heart and great veins), and this still remains one of its most important usages, despite the difficulty of injecting the material rapidly enough through the catheters usually employed, with a larger catheter (size No 12 to 14) introduced via the jugular vein more adequate rates seem to have been achieved.<sup>63</sup>

It was, however, its value in permitting determination of cardiac output according to the so-called Fick principle that gave the method the importance in human physiology that it holds today. In 1870 Fick<sup>64</sup> called attention to the possibility of calculating cardiac output from the quantity of oxygen or carbon dioxide in arterial and venous blood and the uptake of oxygen or output of carbon dioxide in a given time. This report, only two paragraphs in length, deserves translation and quotation in full.

Herr Fick gave a lecture on the measurement of the quantity of blood ejected by the ventricle of the heart in each systole, a figure the determination of which is without doubt of the greatest importance. Nevertheless the most different opinions thereof have been given. While Th. Young placed the value in question at 45 cc., the newer textbooks of Physiology give much higher values, which, based on the estimations of Volkmann and Vierordt run as high as 180 cc. In such circumstances it is unusual that no one has yet hit upon the following obvious method by which this important value may be determined directly, at least in animals. One determines how much oxygen an animal takes out of the air in a given time and how much carbon dioxide it gives off. During the experiment one obtains a sample of arterial and a sample of venous blood. In both the content of oxygen and the content of carbon dioxide are to be determined. The difference in oxygen contents tells how much oxygen each cubic centimeter of blood takes up in its course through the lungs, and since one knows the total quantity of oxygen absorbed in a given time, one can calculate how many cubic centimeters of blood passed through the lungs in this time, or, if one divides by the number of heartbeats in this time, how many cubic centimeters of blood are ejected with each beat of the heart. The corresponding calculation with the quantities of carbon dioxide gives a determination of the same value, which controls the first.

Since two gas pumps are required to carry out this method, the lecturer is unfortunately not able to report experimental findings. He will therefore give only a calculation of the extent of the circulation in man according to the schema of the method here described, based on more or less arbitrary data. According to experiments carried out by Scheffer in Ludwig's laboratory one cc. of arterial

blood of the dog contains 0.146 cc of oxygen (measured at 0° temperature and 1 meter Hg pressure), 1 cc. venous dog's blood contains 0.0905 cc of oxygen. Each cubic centimeter of blood takes up in its passage through the lungs 0.0555 cc. Assume that this were also true in man. Assume further that a man absorbs 833 g of oxygen out of the air in 24 hours. At 0° and 1 m. pressure this would occupy a space of 433,200 cc. Accordingly 5 cc's of oxygen would be absorbed by the lungs every second. In order to make possible this absorption there must, however, according to the above assumption,  $\frac{5}{0.0555}$  cc of blood flow through the lungs, or 90 cc. Assuming finally 7 systoles take place in 6 seconds, 77 cc of blood would be ejected with each systole of the ventricle.

Fick apparently never achieved, and perhaps never attempted, the actual experimental determination, and it remained for Gréhan and Quinquaud<sup>65</sup> and soon thereafter, Zuntz, to make the first experimental trials in animals. Technical difficulties must have been responsible for the virtual lapse of the method, even in animals, and until its recent revival by Cournand and his associates, few reports of its employment appeared, although an outstanding contribution by Marshall<sup>66</sup> (employing direct cardiac puncture) demonstrated that consistent and repeatable results could be obtained for extended periods.

So far as man is concerned the attempt was made from the first to devise an indirect method to avoid direct sampling of arterial and mixed venous blood, and the most successful of these at first rotated around the analysis of the carbon dioxide content of alveolar air. Normally, the alveolar air is in equilibrium with arterial blood, and from its concentration and a knowledge of the carbon dioxide dissociation curve of a given sample of blood, the arterial content of carbon dioxide could be calculated. The carbon dioxide of mixed venous blood was estimated by a variety of ingenious methods involving rebreathing from one or a series of bags containing carbon dioxide at concentrations up to 10 per cent or occlusion by intubation of part of the bronchial tree<sup>67, 68</sup>. All these methods required co-operation and even training for successful accomplishment, but still retain actual and theoretical usefulness in that they involve a determination of the actual composition of pulmonary capillary blood, and become important, as shall be seen later, in cases in which collateral vessels supply blood to the pulmonary capillaries beyond the larger ramifications of the pulmonary artery.

The methods employing foreign gases came ultimately, in the acetylene methods as developed by Grollman,<sup>69</sup> to be a procedure of arriving indirectly at the Fick calculation, for in it the rebreathing technic furnished basically the relative rates of absorption of oxygen and acetylene from the rebreathing system and the data of partial pressures of acetylene by which the quantity of acetylene absorbed by a given volume of blood could be calculated. From this figure, as well as from the ratio of oxygen to acetylene absorption, the amount of oxygen ab-

sorbed by a quantity of blood in the lungs could be computed—in other words the arteriovenous oxygen difference essential to the Fick calculation. Theoretically faultless, the whole determination must be made while the blood circulating through the lungs contains no recirculating acetylene, otherwise, actual absorption of acetylene will be less than calculated, and in consequence the calculated oxygen absorption will be too high, and the cardiac output proportionally too low.

The appearance of the first reports by Cournand and his associates thus placed the cardiac output of man on a sound experimental basis and gave a reference point by which other methods of great potential value such as the ballistocardiograph<sup>70</sup> could be calibrated. Moreover, it forced the reinvestigation, in terms of a direct experimental approach on man, of many concepts gained from animal experiments and has, paradoxically, renewed interest in animal experimentation, focusing attention upon the cardiovascular system in circumstances as normal as possible and not as isolated components in a heart-lung preparation.

One of the most important of the concepts that comes up for revaluation is the question of regulation of cardiac output. Here the clear-cut experiments of Patterson and Starling<sup>71, 72</sup> on the heart-lung preparation, demonstrating a direct proportionality between cardiac output and venous pressure and raised to the status of a "law of the heart," have long dominated thinking. Nor does the newer approach lead everyone to abandonment of it as a guiding principle. McMichael and Sharpey-Schafer<sup>73</sup> considered that cardiac output was regulated by at least three factors: venous pressure according to Starling's law, the heart rate and epinephrine. Sharpey-Schafer<sup>74</sup> found that anemic patients had a higher than normal cardiac output despite a diminished blood volume, which he related to the increased right auricular pressures observed. Normal persons responded to increased auricular pressure induced by rapid transfusion by marked augmentation of cardiac output. Right auricular pressures in normal persons were closely grouped around -4 cm of saline solution above the sternal angle, and cardiac outputs ranged from 4 to 7 liters. During transfusion pressures rose by 5 to 12 cm of saline solution, and outputs rose as high as 11 liters per minute. On the other hand auricular pressures in anemic patients ranged from slightly below 0 cm of saline solution to +12 cm, and in only 1 of the 7 cases (and that one with a relatively low venous pressure) did transfusion increase output. In all the rest output fell. Sharpey-Schafer concluded that anemic patients have already exploited to the full the benefits of Starling's law, and are at the part of curve where increasing diastolic stretch hampers ventricular contraction. In keeping with this concept is the report by Howarth, McMichael and Sharpey-Schafer<sup>75</sup> that venesection improves car-

- 58 Cournand A., and Ranges H A Catheterization of right auricle in man *Proc Soc Exper Biol & Med* 46 462 1944
- 59 Cournand, A. Riley R. L., Breed E S Baldwin E de F and Richards D W, Jr Measurement of cardiac output in man using technique of catheterization of right auricle or ventricle *J Clin Investigation* 24 106-116 1945
- 60 Marey E *La methode graphique dans les sciences experimentales* Second edition 673 pp Paris Masson 1885
- 61 Forssmann W Die Sondierung des rechten Herzens *Klin Wchnschr* 8 2085 2087 1929
- 62 *Idem* Nachtrag zu der Arbeit in Jg 1929 11 S 2085 dieser Wochenschrift *Klin Wchnschr* 8 2287 1929
- 63 Chavez, I Dorhecker N and Celis A Direct intracardiac angiography its diagnostic value *Am Heart J* 33 560 593 1947
- 64 Fick Über die Messung des Blutquantums in den Herzventrikeln *Verhandl d phys-med Ges zu Würzburg* 2 XVI, 1870
- 65 Grehant, H and Quinquand C. E Recherches experimentales sur la mesure du volume de sang qui traverse les pommions en un temps donné. *Compt rend Soc de biol* 3 159 1886
- 66 Marshall E K Jr Studies on cardiac output of dog I Cardiac output of normal unanesthetized dog *Am J Physiol* 77 459-473 1926
- 67 Loewy A., and von Schrötter, H Ein Verfahren zur Bestimmung der Blutgasspannungen der Kreislaufgeschwindigkeit und des Herzschlagvolumens an Menschen *Arch f Anat u Physiol. (Physiologische Abteilung)* 394-396 1903
- 68 Christiansen, J Douglas C G and Haldane J S Absorption and dissociation of carbon dioxide by human blood *J Physiol* 48 244-271 1914
- 69 Grollman, A. *The Cardiac Output in Health and Disease* 325 pp. Springfield Illinois Charles C Thomas, 1932
- 70 Nicholson, J L Warren, J W and Brannon E S Cardiac output in man Studies with low frequency critically damped ballistocardiograph, and method of right atrial catheterization *J Clin Investigation* 26 1-10 1947
- 71 Patterson S W and Starling, E. H On mechanical factors which determine output of the ventricles. *J Physiol* 48 357 379 1914
- 72 *Idem* Regulation of heart beat. *J Physiol* 48 465-513 1914
- 73 McMichael J., and Sharpey Schafer, E P Cardiac output in man by direct Fick method *Brit Heart J* 6 33-40, 1944
- 74 Sharpey-Schafer E P Transfusion and anemic heart *Lancet* 2 296-299 1945
- 75 Howarth S McMichael J and Sharpey Schafer E P Effects of venesection in low output heart failure *Clin Sc* 6 41 50 1946
- 76 McMichael J Heart. *Ann Rev Physiol* 10 201-224, 1948
- 77 Barcroft, H Edholm O G McMichael J, Sharpey Schafer E. P Posthemorrhagic fainting study by cardiac output and forearm flow *Lancet* 1 489 1944
- 78 McMichael J Clinical aspects of shock *J A M A* 124 275 281 1944
- 79 McMichael J and Sharpey Schafer E P Action of intravenous dioxin in man *Quart J Med* 13 123-135 1944
- 80 Cournand, A et al Studies of circulation in clinical shock *Surgery* 13 964-995 1943
- 81 Stead E A and Warren J V Cardiac output in man analysis of mechanisms varying cardiac output based on recent clinical studies *Arch Int Med* 80 237-248 1947
- 82 Brannon E S, Merrill A G Warren J V and Stead E A Cardiac output in patients with chronic anemia as measured by technique of right atrial catheterization *J Clin Investigation* 24 332-336 1945
- 83 Stead, E A Jr, Brannon E S, Merrill, A. J., and Warren, J V Concentrated human albumin in treatment of shock. *Arch. Int. Med* 77 564 575 1946
- 84 Haynes B W Jr Alterations of cardiac output and plasma volume in normal subject with administration of concentrated human serum albumin *Proc Am Federation Clin. Research* 2 74, 1945
- 85 Warren J V, Brannon, E S Stead, E A, Jr and Merrill, A. J Effect of venesection and pooling of blood in extremities on arterial pressure and cardiac output in normal subjects with observations on acute circulatory collapse in three instances *J Clin. Investigation* 44 337 344 1945
- 86 Nylin G On the amount of, and changes in, residual blood of heart. *Am Heart J* 25 598-608 1943
- 87 Brannon E S Weens, H S and Warren J V Arterial septal defect study of hemodynamics by technique of right heart catheterization *Am J M Sc* 210 480-491 1945
- 88 Massee J C Correlation of autopsy findings with data obtained by right heart catheterization *Am J M Sc* 214 248-251 1947
- 89 Dexter L Burwell C S Haynes F W and Seibel, R. E Venous catheterization for diagnosis of congenital heart disease. *Bull. New Eng M Center* 8 113 121 1946
- 90 Baldwin E de F Moore L V and Noble R P Demonstration of ventricular septal defect by means of right heart catheterization. *Am Heart J* 52 152-162 1946
- 91 Johnson A Wollin D G and Ross J E. Heart catheterization in investigation of congenital heart disease *Canad M A J* 56 249-255 1947
- 92 Howarth S McMichael J, and Sharpey Schafer E. P Cardiac catheterization in cases of patent inter auricular septum primary pulmonary hypertension Fallot's tetralogy, and pulmonary stenosis *Brit Heart J* 2 292 303, 1947
- 93 Dexter L et al Studies of congenital heart disease. I Technique of venous catheterization as diagnostic performance. *J Clin. Investigation* 26 547-553 1947
- 94 Dexter L., et al Studies of congenital heart disease II Pressure and oxygen content of blood in right auricle right ventricle and pulmonary artery in control patients with observations on oxygen saturation and source of pulmonary "capillary" blood. *J Clin. Investigation* 26 554 560 1947
- 95 Dexter, L., et al Studies of congenital heart disease. III Venous catheterization as diagnostic aid in patent ductus arteriosus, tetralogy of Fallot, ventricular septal defect. *J Clin. Investigation* 26 561-576, 1947
- 96 Sosman, M C Venous catheterization of heart. I Indications techniques and errors *Radiology* 48 441-450 1947
- 97 Dexter, L. Venous catheterization of heart II Results interpretations and value *Radiology* 48 451-461 1947
- 98 Bing R J, Vandam L D and Gray F D Jr Physiological studies in congenital heart disease. I Procedures *Bull Johns Hopkins Hosp* 80 107-120 1947
- 99 *Idem* Physiological studies in congenital heart disease. II Results of preparation studies in patients with tetralogy of Fallot. *Bull. Johns Hopkins Hosp* 80 121-141 1947
- 100 *Idem* Physiological studies in congenital heart disease. III. Results in five cases of Eisenmenger's complex. *Bull Johns Hopkins Hosp* 80 323-347 1947
- 101 Vandam L D Bing R J and Gray F D Jr Physiological studies in congenital heart disease IV Measurement of circulation in five selected cases *Bull Johns Hopkins Hosp* 81 192 215 1947
- 102 Gray F D Jr Bing R J and Vandam L. Evaluation of method involving carbon dioxide equilibration for determining cardiac output *Am J Physiol* 151 245 251 1948

## MASSACHUSETTS MEDICAL SOCIETY

## PROCEEDINGS OF THE COUNCIL

Annual Meeting, May 24, 1948

THE annual meeting of the Council was called to order by the president, Dr Edward P Bagg, on Monday, May 24, 1948, at 7 00 p m , in the Georgian Room of the Hotel Statler, Boston

Two hundred and thirty-five councilors were present (Appendix No 1)

After opening the meeting, the President read the following obituaries

**GEORGE JAMES CONNOR**—Another fellow-councilor, Dr George J Connor, a leading citizen of Haverhill, has passed on since our last meeting Trained at Holy Cross, Tufts and the Maryland Medical College, he elected to serve his city on the Board of Health and in the direction of municipal hospitals For twenty-five years he served on the board and held the chairmanship at the time of his death

His main clinical leanings, however, were surgical, particularly in the field of industrial medicine He was a visiting surgeon to the Hale Hospital and a member of the advisory board for more than fifteen years

Dr Connor represented the Essex North District Medical Society on the Council and was a member of the Committee on Industrial Health Likewise, he was a fellow of the American Association of Industrial Physicians and Surgeons

A witty, cheerful soul, quick to make friends, whom he kept, he will be sadly missed in his home and in his civic and medical associations We pay tribute to George Connor, the able physician, for his natural flair for public relations and for his willingness to work for the elimination of health hazards whether industrial or general

**ISAAC S F DODD**—In March, 1930, sixty physicians of central and southern Berkshire arranged a dinner in celebration of the fortieth anniversary of the medical practice of a brisk little man with angular features but not much hair, who was wont to pucker up his lips and whistle as he walked The warmth of the tributes paid to Isaac S F Dodd by his colleagues showed clearly enough that such limitations were purely physical

"In the years I have known him," wrote one of the diners, "he has done more for the young men than any other man in this community He was a lover of the clean life and a great reader of good books His quizzes while operating were outstanding and as peculiarly his own as his whistle Many Berkshire men have had cause to be thankful to him for his advice and teaching"

The Massachusetts Medical Society also acknowledged a debt to Isaac Dodd for his professional attainments and for years of faithful service in the Council by honoring him with the office of vice-president in 1946-1947 Quite in keeping with his character, he stood ready without a moment's hesitation to take over the intricate task of running the annual meeting of the Society when illness threatened to incapacitate President O'Hara last May "Just tell me what there is to do," was all he said

Dr Dodd was equally ready to serve his country in World War I, attaining the rank of captain in the Medical Corps Chief of the Surgical Service at Pittsfield's House of Mercy, he was also an attending staff surgeon at St. Luke's In his turn, he directed the destinies of the Berkshire District Medical Society The American College of Surgeons also elected him to fellowship in due course

Here was a minister's son who made good Indeed, he made good for more than three quarters of a century

after his auspicious arrival in a Presbyterian mission in Hanglow, China New York University numbered him among her high-honor graduates, but most of his clinical ability was developed at first hand with unremitting application to the needs of his patients in general practice

Early in February, 1948, physicians once more gathered in the Berkshire District to pay a final tribute to their friend and mentor, Isaac S F Dodd May we join our hopes to theirs that honor and esteem will follow him in whatever Elysian field he shall be assigned hereafter to serve

**EDWARD JOSEPH O'BRIEN, JR.**—Back in 1933, one of the ablest of all football referees in this or any other country, Dr Edward J O'Brien, Jr, turned in his whistle and folded away the famous white knickers that he had established as a familiar feature of games big and little throughout the land The decision was not easy, but finally he came to agree that medicine is truly a jealous mistress

To the game he had loved, he owed much Not only did it build him a nationwide esteem but also fees he earned by officiating enabled him to train himself at Tufts for a medical career, after earlier preparation at the Boston Latin School and Boston College On his merits he rose to the position of surgeon-in-chief at the Cambridge City Hospital For nearly thirty years he served as urologist to St. Elizabeth's Hospital He was sought also as a consultant in urology at many greater Boston institutions Besides serving on the Council as a representative of Middlesex South District Medical Society, Dr O'Brien was a fellow of the American College of Surgeons and the American Urological Association and a member of the American Board of Urology

On February 16, 1948, the game of life came to an end for our distinguished fellow councilor, who was in there working hard as usual until the final whistle Of the passing of Dr Eddie O'Brien, his good friend Bill Cunningham wrote, in the *Boston Herald* for February 16, 1948 "The shock was tough and personal just as it will be for thousands of others who knew and loved the little guy and yet, I thought, why mourn? What more could a man do with his life? Live a little longer, maybe, but he couldn't live any better"

Dr O'Brien was the father of four fine sons, who all distinguished themselves and fortunately survived active and hazardous war service, and of a beautiful daughter Each must have drawn a full share of inspiration from this yule soul, who brought honest satisfaction to so many contestants and understanding sympathy to those in need, whether on the gridiron, the operating table or in his home.

And so should we be inspired by his example, which speaks so much louder than words

**FREDERICK REIS**—On February 4, 1948, Dr Frederick Reis, another long-time member of the Council, died at his home in Jamaica Plain at the age of seventy-two Besides his service on the Council, he handled the funds of the Norfolk District Medical Society for ten years as treasurer

His friends speak of him as a kindly, companionable person, and say that his passing will be keenly felt, particularly by his students, past and present Born in Boston, Dr Reis was also educated in Boston schools, graduating from Tufts College Medical School in 1903 The greater part of his professional accomplishment was achieved in the same school in the Department of Chemis-

try, where he served as professor for more than a quarter of a century

It should be remembered that he was alert to changes that arose during his lifetime and that his interest in the affairs of the Society was always keen, since the day he was elected to the Council in 1922

It is fitting, therefore, to pay tribute to this man for all that he has contributed to fellow members and to his fellow men through the many students that he had a hand in training

At the request of the President, the Council stood in silent tribute to the departed members

The President then announced the following interim appointments, which were confirmed by vote of the Council

**To the Council**

Arthur W Allen, Suffolk, to replace Wyman Richardson (resigned)

Arnold P George, Essex North, to replace George Connor (deceased)

**To the Committee on Emergency Medical Service**

Reginald Fitz, *Chairman*, Suffolk

Charles H Bradford, Suffolk

Donald E Currier, Essex South

Eugene C Eppinger, Norfolk

J Roswell Gallagher, Essex North

Allen S Johnson, Hampden

Thomas H Lanman, Suffolk

Edward D Churchill, Middlesex South (in consulting capacity)

**To the Committee on Benevolence**

Dwight O'Hara, *Chairman*

Theodore L Badger

Robert W Buck

Eliot Hubbard, Jr

Charles C Lund

**To the Advisory Committee to the Red Cross Blood Bank**

John F Conlin, *Chairman*

F Harold Allen, Jr

William B Castle

Stephen Brown

William P Murphy

Joseph E Ross

C Stuart Welch

**To the Committee on Postgraduate Assembly**

John F Conlin

**To the Massachusetts Central Health Council**

Paul Nathan, Holyoke

Merrill E Champion, Boston

Earle M Chapman, Boston

**To the Committee to Meet with the Massachusetts Hospital Association**

Leland S McKittick

The Secretary presented the record of the meeting of the Council of February 4, 1948, as published in the *New England Journal of Medicine*, issue of April 8, 1948, and moved its acceptance. The motion was seconded and so voted.

The Secretary stated that it had been noted that the minutes of the Executive Committee meeting of January 7, 1948, had not been approved at the Council meeting on February 4, 1948, and moved that they be accepted. The motion was seconded and so voted.

The Secretary then moved the acceptance of the minutes of the Executive Committee meeting of

April 7, 1948, as distributed in the Circular of Advance Information for this meeting. The motion was seconded and so voted by the Council.

**REPORT OF THE TREASURER**

Dr Eliot Hubbard, Jr, Middlesex South, moved the acceptance of this report (Appendix No 2). This motion was seconded and so voted by the Council.

**REPORTS OF COMMITTEES**

*Executive Committee*—Dr H Quimby Gallupe, Middlesex South, *Secretary*

The Secretary submitted the report of the meeting of April 7, 1948, as circulated in mimeographed form (Appendix No 3) and moved its acceptance. The motion was seconded, and it was so ordered by vote of the Council.

*Committee on Nominations*—Dr Albert A Hornor, Suffolk, *Chairman*

The committee had convened at 8 Fenway, Boston, on April 7, 1948, and had nominated the following officers of the Society for the year 1948-1949

President, Dr Daniel B Reardon

President-elect, Dr Arthur W Allen

Vice-president, Dr Donald Munro

Secretary, Dr H Quimby Gallupe

Treasurer, Dr Eliot Hubbard, Jr

Assistant treasurer, Dr Norman A Welch

Orator, Dr C Sidney Burwell

These nominations were unanimous, and Dr Hornor moved the acceptance of the report.

The motion was seconded, and it was so voted.

Dr Bagg asked for any further nominations. There was no response, so that Dr Hornor moved that the nominations be closed. The motion was seconded and carried.

Dr Hornor moved that the Secretary cast one ballot for the list of nominees as presented. The motion was seconded and so voted.

The Secretary cast one ballot as directed. Dr Bagg then introduced Dr Daniel B Reardon as follows:

The man chosen as president has been a member of the Society for a good many years. He first joined in 1905. He attended the Lawrence Scientific School at Harvard and got his medical degree from the same university in 1903. And he served as surgical house officer in the Boston City Hospital. Then he retired to Quincy forty-three years ago. He has been there ever since, which shows that he must amount to something. As a matter of fact, he has been visiting surgeon at the Quincy Hospital for thirty-seven years, and on the consulting staff for the past three years. And for twenty years he has been a member of the American College of Surgeons. For twelve months we have worked hard preparing him for the duties that lie ahead. I can assure you that he has been faithful in his attendance, and promises to make you an excellent presiding officer.

He has a much more eloquent method of speech than mine, so that you will probably understand what is going

on for the next year, and your parliamentary problems will be absent. I take great pleasure in introducing your next President

Dr Reardon replied with an address, which was published in the June 10 issue of the *Journal*

Dr Bagg then said that Dr Arthur W Allen could not be present because he was attending the meeting of the American College of Surgeons in Canada Drs Donald Munro and H Quimby Gallupe were then introduced

*Committee on Public Relations* — Dr Harold R Kurth, Essex North, *Secretary*

President Bagg stated that the report of the committee (Appendix No 4) was largely informational He hoped that the fees of the Blue Shield could be increased before long but believed that this could not be done until the financial reports warranted it He stated that the committee voted to discharge the subcommittee on Blue Shield and Blue Cross and to refer future questions to the Executive Committee, inasmuch as that committee was the incorporator of the Blue Shield He asked for Council approval of that action Dr Elmer S Bagnall, Essex North, so moved The President then said that with Dr Bagnall's permission he would word the motion that the President would appoint a subcommittee of the Executive Committee to oversee the Blue Cross and Blue Shield problems Dr Bagnall gave his permission, and the motion was seconded and so voted

The President then said that Dr Hagler's committee had decided that the best way to correct difficulties arising from failure of doctors answering calls was to refer the matter for solution to the district societies The Public Relations Committee approved this recommendation

Dr Bagg asked for approval of this recommendation by the Council It was so moved The motion was seconded, and it was so voted

The President asked for approval of his action in appointing representatives of the Massachusetts Medical Society to a council for the study of voluntary hospital costs (he had appointed Drs Gallupe and John Spellman) This approval was moved by Dr Richard M Smith (Suffolk), and the motion was seconded and so voted

The President described the amount of work done by Dr John F Conlin and stated that the committee had approved the employment of an assistant, the cost to be met out of his supplementary budget

Dr Bagg asked for Council approval of this action A motion was made to approve the action It was seconded and so voted

Dr Bagnall moved the acceptance of the report. The motion was seconded, and it was so voted

*Committee on Legislation* — Dr George R Dunlop, Worcester, *Chairman*

The report of this committee (Appendix No 5) was presented by Dr Dunlop, who stated that he wished to make an informational supplementary report important enough to bring to the attention of the Council Dr Dunlop mentioned the proposed draft law being considered by Congress, which has specified a special call for physicians up to forty-five years of age The committee believed that this was a reflection on the patriotism of doctors, and had sent telegrams to congressmen opposing such legislation

He pointed out that Governor Warren, a candidate for nomination for President, had come out for compulsory health insurance He said that telegrams had been sent to all Republican delegates from Massachusetts to oppose any such plank in their platform Dr Dunlop said he would like to have Dr Bagnall report on the National Health Assembly held in Washington May 4, 1948

Dr Bagnall described the work of the Assembly and quoted from editorials in the *Journal of the American Medical Association* and ended by saying that the nation seemed to be on the way toward development of a plan for the production and distribution of medical services suitable to the American form of democracy

Dr Bagg suggested that the Council applaud Dr Bagnall's efforts and report (Applause) Dr Dunlop moved the acceptance of both reports The motion was seconded and so voted

*Committee on Publications* — Dr Richard M Smith, Suffolk, *Chairman*

The report of the committee (Appendix No 6) was presented by the Chairman

Dr Smith exhibited a chart showing the growth of the *Journal* during Dr Robert Nye's administration from 1936-1947 Dr Smith moved the acceptance of the report The motion was seconded

Dr Bagg pointed out that the circulation in ten years had jumped from 6,131 to 25,001, and the expenses from \$58,000 to \$240,000 In 1937 the *Journal* cost each fellow \$4.00 In the last three years there has been only income for the Society, but the future might not be so bright because expenses are still mounting

The motion to accept the report was unanimously carried

*Committee on Ethics and Discipline* — Dr Ralph R Stratton, Middlesex East, *Chairman*

Dr Stratton, after drawing attention to the last paragraph of the report (Appendix No 7) and stating that the report was purely informational, moved its acceptance The motion was seconded and so voted Dr Bagg then thanked Dr Stratton and his committee for their efforts in behalf of the Society

*Committee on Membership* — Dr Peirce H Leavitt, Plymouth, *Chairman*

In the absence of the Chairman, Dr Bagg asked the Secretary to read a supplementary report of the Committee on Membership as follows

During a meeting of the Committee, held on Monday, May 24, the name of Sir Reginald Watson-Jones, visiting orthopedic surgeon to His Majesty, King George VI, was presented to the Committee for action by the President and the Secretary. The Committee unanimously approved of this nomination for honorary fellowship and refers it for final decision to the fellows assembled at the annual meeting, as permitted by Article II of the by-laws

A motion to approve the action of the committee subject to the vote of the annual meeting of the Society on May 25, 1948, was made, seconded and carried. The Secretary then moved that the Council grant the honorary fellowship subject to the vote of the Society. The motion was seconded and carried

*Committee on Public Health* — Dr Roy J Ward, Worcester, *Chairman*

In the absence of the chairman, Dr Bagg asked Dr Conrad Wesselhoeft (Suffolk) to present the report (Appendix No 7)

Dr Wesselhoeft moved the acceptance of the report. The motion was seconded

Dr Frank B Carr addressed the Council as follows

In this very difficult era, we are all cognizant of the need for reliable statistics regarding the epidemiology of heart disease. Mortality figures in this disease have made it imperative for the American Heart Association and the United States Public Health Service to do something about it

The United States Public Health Service offers to make an epidemiologic study, and the New England Heart Association naturally offers its support to such an investigation

There are, however, certain queries that arise in the minds of some of the Worcester councilors

How complete and comprehensive is this study to be? The diagnosis of heart disease may be as simple as the application of a stethoscope by one qualified to hear. It may depend merely on the proper evaluation of symptoms of precordial pain, which requires no great experience. Or the diagnosis of heart diseases in certain cases may become quite an elaborate procedure, requiring electrocardiograms, x-ray films, fluoroscopy, determinations of blood chemistry and basal metabolism and so forth. There is no one simple system applicable to all cases, as in the diagnosis of diabetes

Before supporting a federal survey of the epidemiology of such a complex condition as heart disease, we should want to be informed about how complete the study would be. We should want to be assured of the validity of the diagnosis established, and we should like to know how much such a project is going to cost.

In the diabetic survey in the town of Oxford, it has been estimated by some, although not officially expressed, that the cost was about \$1,000 apiece for the discovery of some 25 cases of diabetes

The diagnosis of heart disease is a much more complicated problem. The setup would have to be infinitely more elaborate and expensive, and we wonder if the results ascertained would be of the value we might hope

We do not like investigations for the sake of investigation. We want to be assured that the methods used will be scientifically sound, and that the statistics derived

from such a study will be of general value sufficient to warrant the expenditure of what will be a considerable amount of money

Dr Bagg thanked Dr Carr and asked for a vote on the motion of acceptance of the report. It was so voted

Dr Bagg then asked Dr Wesselhoeft if he wished to move the adoption of the committee's endorsement of the cardiac surveys in Newton and Framingham. Dr Wesselhoeft replied as follows

This study has been requested by Newton, and I understand that arrangements have been completed with Framingham Union Hospital. This study is to be made by the Massachusetts Department of Public Health, Harvard Medical School and the United States Public Health Service

It is supported by the Commissioner, and it has the approval of the New England Heart Association. It seems to me that any such investigation carried out under such auspices would be carried out thoroughly and well

Dr Wesselhoeft moved the endorsement of the program, which had been recommended by the committee. Dr Richard M Smith seconded the motion. In discussion Dr Vlado A Getting, Middlesex South, spoke as follows

This study will be composed of two phases. The phase to be carried out in Newton is entirely an educational program, designed to convince patients to seek medical advice if they suspect that they have heart disease, and to seek periodic examinations

The project at Framingham is the development of case finding procedures and will be carried on by cardiologists who are actually employed by the Public Health Service and by men practicing in the community and in the surrounding communities

In each instance of this project Public Health Service personnel are lent to the Massachusetts Department of Public Health and by the Department of Public Health to the city of Newton and to Framingham, being under the direction, while working in those communities, of the local boards of health

The staffs of the Newton-Wellesley Hospital and of the Framingham Hospital are thoroughly acquainted with each of these projects and have given their approval, as have advisory committees. An advisory committee on this project, consisting of many cardiologists and including representatives not only from the Society but also from medical schools and schools of public health and from the Department of Public Health, have carefully reviewed these projects

We are trying to do two things to determine, as early as possible, which persons may develop heart disease, and to bring them under the attention of physicians

It seems that if we can discover cases early, before actual clinical onset, the patients will have a more useful and productive life and will be able to continue to be supporting citizens in the community, rather than incapacitated, perhaps disabled in some way, and thus a burden upon their families and the communities

The two projects — one case finding, and the other educational — are companion projects. We are not going to give any medical care in either project.

The physical examinations and the electrocardiograms and other studies will be carried on in Framingham by expert cardiologists employed by the Public Health Service, under the direction of the local board of health, and will be selected only with the advice of the New England Heart Association

I want to assure the councilors of Worcester (of which I had the honor of being a member some time ago) and I had the honor of being a member some time ago) and the entire Society that there is nothing in this program that smacks of either state or socialized medicine. We

are not contemplating medical care. This is nothing more than case finding and education.

If these programs succeed, it will enable the general practitioner and the cardiologist to be of greater service to their patients.

Dr. Bagg then called for a vote, and the motion was carried after a show of hands and a count by the Secretary. Dr. Wesselhoft moved acceptance of the committee report. The motion was seconded and so voted.

*Committee on Medical Defense*—Dr. Horatio Rogers, Suffolk, *Chairman*

Dr. Rogers stated that as of January 1, 1948, there were 9 cases of malpractice pending. One case was disposed of during 1947. Total bills for legal services and legal disbursements for 1947 were \$1474.51. There were no other expenses.

Dr. Rogers moved acceptance of the report. It was seconded and so voted.

*Committee on Finance*—Dr. Robert W. Buck, Middlesex South, *Chairman*

Dr. Buck said that the committee had met on April 28, 1948, to discuss the problems arising from a change in classification of the Society by the Treasury Department from 101 (6) to 101 (7) and that this change made the Society liable for Social Security taxation. The committee authorized the Treasurer to assume 50 per cent of the tax burden of the *Journal*. Gifts to the Society were discussed because that might in the future make the Society liable for income tax. The committee recommended that all gifts be accepted with the condition that they be used only for clearly scientific, educational, charitable and literary purposes.

The committee also recommended that the salary of Miss Barbara Adler be raised from \$35 to \$40 a week beginning July 1, 1948.

Dr. Buck moved the acceptance of the report. It was seconded and carried.

A motion was then made to suspend the rules. This motion was seconded and so voted.

Dr. Buck moved that the Council approve the payment of the tax. The motion was seconded. Dr. Hubbard then told about other states in which the tax was paid. The motion was put to vote and carried. A motion to approve payment of 50 per cent of the *Journal* tax was made, seconded and so voted. Dr. Buck made a motion to approve the committee recommendation concerning the use of moneys received in the form of gifts. This motion was seconded. After much discussion a motion was made to refer the matter to the Executive Committee. This was seconded and so voted. Dr. Buck's motion was then voted and carried. Dr. Bagg then asked for an approval of Miss Adler's salary increase, and this was given unanimously.

Dr. John E. Moran, Franklin, moved that the Council instruct the Executive Committee that it

is not in favor of accepting any gifts as described in the report of the Committee on Finance. This motion was seconded. Dr. Bagg called for a vote. The Secretary declared a tie. Dr. Bagg voted in favor, and the motion was carried.

A motion was made to end the suspension of rules. This was seconded and so voted.

*Committee on Society Headquarters*—Dr. Frank R. Ober, Suffolk, *Chairman*

The chairman stated that the Committee on Society Headquarters had made no progress in its efforts to make more room for the Massachusetts Medical Society. The Committee was still working on this problem, which has proved to be a difficult one.

The Secretary moved its acceptance. The motion was seconded and so voted.

*Committee on Industrial Health*—Dr. Daniel L. Lynch, Norfolk, *Chairman*

Dr. Lynch presented the report of the Committee (Appendix No. 9) and moved its acceptance. This motion was seconded and carried.

*Committee to Consider Expert Testimony*—Dr. Francis P. McCarthy, Norfolk, *Chairman*

The original committee of five members was appointed by the President in 1936, to consider expert medical testimony.

After failing to function, a revision of the membership was made in 1942 and again in 1947. The last committee report was laid on the table, and the present committee submitted its report for consideration by the Council.

The present Committee met and discussed all phases of the subject of medicolegal testimony, including ordinary as well as expert testimony.

The Committee, with members of the Massachusetts Judiciary and Bar and the chairman of the Committee on Ethics and Discipline and Board of Registration in Medicine met and agreed on the importance of having a functioning committee deal with medicolegal testimony and problems.

The states of Minnesota and California have established permanent committees on medical testimony, and reports indicate that these committees are functioning well.

The Committee, together with the chairman of the Committee on Ethics and Discipline and the Board of Registration in Medicine, as well as members of the legal profession, agreed that a group of so-called "listeners" should be appointed to serve when requested, to check on medical testimony.

It was agreed that the presence of a "listener" in court would definitely act as a deterrent in controlling medical testimony and serve to make the medical witness more cautious and docile in his testimony.

A panel system of choosing representatives of the Society who are specialists in their various fields to testify as experts was discussed, but no conclusion was arrived at, that could be considered satisfactory under the present legal statutes.

All the members of the Committee, together with those consulted, agreed that the Committee should be a standing one and collaborate with the Committee on Ethics and Discipline and the Committee on Medical Defense. The Committee would act as a clearing house for all cases in which ordinary or expert medicolegal testimony was concerned.

It was proposed that the by-laws of the Society be amended to the effect that a standing committee be appointed annually by the President, to be known as the Committee on Medico-Legal Testimony.

That the duties of this committee be educational on medicolegal matters, and that it collaborate with the legal profession and concern itself in the investigation of all questions relative to medicolegal testimony that may be considered irregular by the complainants.

Dr McCarthy moved the acceptance of the report. The motion was seconded and so voted.

Dr McCarthy then stated that the report contained a recommendation for a proposed amendment to the by-laws of the Society providing for a standing committee appointed annually by the President to be known as the Committee on Medico-Legal Testimony, that the duties of the committee be educational on medicolegal matters, and that it collaborate with the legal profession and concern itself in the investigation of all questions concerning medicolegal testimony that might be considered irregular by the complainants.

Dr Bagg suggested that the request might be referred to the Executive Committee. The motion was seconded.

Dr McCarthy then moved that the committee be discharged. The motion was seconded and so voted.

Dr Donald Munro, Suffolk, asked if he might discuss the report. President Bagg said that the report had been accepted and was open for discussion. Dr Munro stated that he believed the use of the word "listeners" might embarrass the Society.

Dr Carl Bearse, Norfolk, said that the Committee on Malpractice Insurance had discussed the subject and believed the whole subject in all aspects should be studied.

Dr Vlado Getting, Middlesex South, rising to a point of order said that the motion was for acceptance of the report. No motion had been made recommending "listeners."

Dr Bagg agreed with Dr Getting and called for a vote on the motion. It was so voted.

### *Committee to Meet with the Massachusetts Hospital Association — Dr Albert E Parkhurst, Essex South, Chairman*

The Committee, to which the Council had assigned the duty of negotiating with the Hospital Association regarding its approval of the principles proposed by the Committee appointed to study special services, had held two meetings.

At its first meeting, on February 25, 1948, which was attended by Drs Bagg, Reardon and Gallupe, in addition to the members of the Committee, there was a general discussion of principles recommended by the Committee appointed to define and study hospital services and medical services, and to establish proper relations between physicians and hospitals, which were approved by the Council at its October meeting. It seemed highly desirable that this conference with the Hospital Association be held before its annual meeting scheduled for March 15, and a date (March 3) was arranged through Dr Norbert A Wilhelm, chairman of its Committee on Professional Services, this problem having been assigned by the Massachusetts Hospital Association.

At this conference, the Society was represented by Drs Bagg and Gallupe and four members of the Committee. Representing the Hospital Association was Dr Wilhelm, of the Peter Bent Brigham Hospital, as chairman, and Mr Warren Cook, of the New England Deaconess Hospital. The third member of the Committee, Miss Amy Birge, of the Cooley Dickinson Hospital, in Northampton, was unable to attend because of illness.

Arguments about why these principles should be approved by the Hospital Association were presented, chiefly by Drs Bagg and McKittrick. Dr Wilhelm stated that his committee had met the day previously and had voted that "no action be taken at this time." Their decision was based chiefly upon their belief of the uncertainty whether the Blue Cross could continue to provide adequate prepaid hospital insurance. As hospital administrators they believed its successful operation was essential to the welfare of hospitals, and they refused to approve anything they thought might further embarrass it. They also said that because of poor public relations on the part of the hospitals, a more complicated system of billing hospital costs to the patient would be too confusing and undesirable to be undertaken. Incidentally, they stated they believed that very few hospitals had a system of accounting sufficiently comprehensive to be able to work out all details of cost accounting that would be necessary under this plan.

There was a great deal of discussion during which the representatives of the Society tried unsuccessfully to convert the representatives of the Association to its point of view. They were unwilling to grant their approval of these principles.

even though the Society agreed to the postponement of their adoption until a later date because they believed that in these days when the Blue Cross and so many hospitals are in great financial distress, the whole question of voluntary hospital service is at stake. They insisted that now was not the time to undertake the adoption of these principles. Although the Committee believed in the fairness of these principles and urged their adoption, it was believed that the representatives of the Association were sincere in their point of view. As a result of this conference, it was believed that nothing more could be done at present.

Dr Parkhurst moved the acceptance of this informational report. The motion was seconded, and it was so voted.

Dr A J A Campbell (Suffolk) moved that the committee continue its efforts along the same lines and report to the Council. This motion was seconded and so voted. Dr Bagg asked Dr Daniel B Reardon if he had appointed the same committee and Dr Reardon said he had.

The motion was put to a vote and carried unanimously.

#### *Committee on Postgraduate Medical Education— Dr W Richard Ohler, Norfolk, Chairman*

The report of the Committee was as follows:

##### *Brief Outline of Present Plan of Postgraduate Teaching*

The present concept of postgraduate medical education as conducted by the Massachusetts Medical Society is to provide such teaching to all physicians in the Commonwealth, without charge, to divide the Commonwealth into teaching districts and to provide to each district such programs as are selected by the local committee, to serve the Greater Boston area and such other areas as can participate with a series of exercises given at Sanders Theater, in addition to the Greater Boston area, the other teaching areas are as follows:

- Number 1 Pittsfield-North Adams District
- Number 2 Springfield-Holyoke-Northampton-Greenfield District
- Number 3 Worcester District
- Number 4 North Shore District
- Number 5 Haverhill-Fall River-New Bedford District
- Number 6 Plymouth District (this District is new for 1947-1948)
- Number 7 Lowell-Haverhill-Lawrence-Newburyport District

##### *Results of This Year's Activities*

During the year 1947-1948, a total of 27 exercises has been given in the outlying districts. The total registration for the Sanders Theater program was 1101 at the date of this report.

Thirteen hundred and sixty-eight replies were received to a postcard questionnaire, 735 of those replying had not attended last year's exercises, 1322 believed that the exercises should be continued, 905 of those who replied were fellows of the Society. It is of interest that the 463 physicians who are not Society members represent a third of the total number of replies received and constitute a much larger proportion of those who have registered for the exercises.

It is not necessary to remind the Council about weather conditions during the late fall and winter season. Despite all sorts of difficulties, instructors have been very co-operative, and attendance has been excellent. On the basis of general interest, therefore, your committee can

report that the district programs have been a success. And, so far as the Sanders Theater program is concerned, the large registration speaks for itself.

##### *Suggestions for Future*

Your committee believes that the Massachusetts Medical Society should continue a program of postgraduate medical instruction and that this program should be open to all physicians in the Commonwealth without charge. We also believe that the Sanders Theater exercises should be continued.

The method of conducting exercises in the districts apart from Greater Boston is open to discussion. The whole conception of postgraduate teaching in the past three years has been to break away from the district geographical limits. The reason for this has been to attract physicians who are not members of any district. In other words, the intent of this program has been to attract all physicians, whether or not they are members of any district society.

This idea may be all right in theory, but it does bring up certain practical difficulties. For example, certain teaching centers have morning and afternoon programs and others evening programs, and, needless to say, all want evening programs. In addition, the present plan does throw quite a transportation burden on the instructing teams, especially in certain districts. All this could be settled if we planned our programs on the basis of the geographical limits of the various district societies. However, there are certain practical difficulties to this idea. First, your committee doubts that the district-society idea would attract physicians who are not members of any District Society, and, incidentally, it is this group that we are eager to reach. Second, such a change would involve an increase in the budget.

##### *Conclusion*

Despite the fact that the present idea involves certain local complications as well as a certain amount of stress and strain on the instructing teams, your committee believes that to keep the budget within certain limits and to make the greatest appeal to physicians not members of any society, it is desirable to continue with the present plan. In making this recommendation, it is understood that the committee can work still harder in building up proper local co-operation.

Dr Ohler stated that the report was purely informational, and noted that the registration at Sanders Theater was 1101, the total being 1400, and that 7400 doctors were in attendance during the course. The average was 400. Dr Ohler moved the acceptance of the report. The motion was seconded. Dr Bagg pointed out the excellence of the report and that more than half the doctors in attendance were from substandard schools. The motion was put to vote and carried unanimously.

Dr Ohler moved that the recommendation to continue the program in 1948-1949 as in 1947-1948 be approved. The motion was seconded and so voted.

#### *Committee on Medical Economics—Dr Leland S McKittrick, Suffolk, Chairman*

The report, which was presented by the chairman, was as follows:

The Committee met on March 10. Drs Elmer S Bagnall, and Allan M Butler, of the committee, President Edward P Bagg, President-Elect Daniel B Reardon and the Secretary were present.

The objectives of the National Physicians' Committee are defined in a recent communication as follows:

In the public interest to preserve, in the United States, our system of private medical practice

Familiarizing the public with the facts in connection with the values, the methods and the achievements of American Medicine.

To aid in the development of plans and to encourage the utilization of facilities that will result in the most widespread distribution of the most effective medical care and surgery

The Committee voted to approve the objectives of the National Physicians' Committee but disapproved some of the methods employed

Dr McKittrick moved acceptance of the report. The motion was seconded. Dr Bagg said that he had had a letter from Dr Allan M Butler, of the Committee, stating that he wished to change his vote and withdraw his approval.

Dr Bagnall said that Dr Butler's letter was not pertinent because surely the committee could not assume any responsibility for anything the National Physicians Committee did.

Dr McKittrick added that the subject of changing or attempting to change the policies of the National Physicians Committee had not been discussed.

Dr Bagg called for a vote, and the motion was passed. He assured Dr McKittrick that the subject was closed.

Dr Bagg then asked for final approval of the changes in the by-laws as printed and noted two errors in the use of "Inc" after Massachusetts Medical Service in the first paragraph.

Dr Barse then pointed out that Chapter 4, Section 1, as amended, did not include the vice-president of the Society. Dr Bagg thanked Dr Barse and called for a vote accepting the amended by-laws. The motion was carried.

*Committee on Physical Medicine*—Dr Arthur L Watkins, Middlesex South, *Chairman*

No new business had been referred to the Committee.

The American Board of Physical Medicine, Inc., had been approved by the Advisory Board for Medical Specialties and the first examinations had been conducted in Minneapolis in September, 1947, approximately 100 physicians had been certified to date.

An annual review of physical medicine was prepared for publication in the Medical Progress section of the *New England Journal of Medicine* entitled "Technical Advances in Physical Medicine."

*Committee to Make Recommendations for Directors of the Blue Shield*—Dr Leland S McKittrick, Suffolk, *Chairman*

The Committee submitted the names of the following men

To hold office until 1949

Mr Eben H Ellison, Jr, Proctor Ellison Co, 26 South Street, Boston, to replace Mr Hugh Nawn

Mr Joseph K Milliken, Jr, reappointment.

Dr Samuel A Robbins, reappointment.

Dr James C McCann, reappointment.

Mr Harold B Leland, reappointment

To hold office until 1950

Mr Philip Morgan, reappointment

Dr Norman Welch, reappointment

Dr Arthur W Allen, reappointment

Mr J H Humphrey, reappointment

Mr Roswell Phelps, reappointment

To hold office until 1951

Mr Benjamin Hull, Department of Labor and Industries, State House, Boston, to replace

Mr Ernest Johnson

Mr Thomas G Brown, reappointment.

Dr Elmer S Bagnall, reappointment.

Mr Daniel J Boyle, reappointment

Dr Eugene Walker, reappointment.

Dr McKittrick moved the adoption of the report and it was seconded. Dr Bagg asked if there were any other nominations. There being none, the motion was put to vote and carried.

*Committee on Veterans Affairs*—Dr G Philip Grabfield, Norfolk, *Chairman*

The Committee on Veterans Affairs had held no meetings since its reappointment at the annual meeting in 1947. It was understood at that time that the Committee would not meet unless something arose that required its consideration or unless some individual or corporate body brought some subject to it for consideration. If no matters requiring consideration came up by the time of the Annual Meeting in 1948 it was the opinion of the committee that it should be discharged.

Dr Grabfield was not present, and Dr Bagg noted that the committee asked to be discharged. Dr Albert A Hornor, Suffolk, moved acceptance of the report. The motion was seconded.

Dr Lewis S Pilcher (Middlesex South) spoke as follows

Gentlemen, there is just one point I think should be brought out before we proceed to accept the discharge of the Committee. There is a group of younger veterans in the Society who have been quite dissatisfied with the Society's interest in veterans' affairs.

I am quite certain that if the Society discharges the Committee on Veterans Affairs, these veterans will form their own organization outside the Society, and take over the interest in veterans' affairs that previously had been the province of the Society.

This matter was discussed at the annual meeting in 1947. At that time representatives of the Society and of the Veterans' Committee very strongly opposed the formation of a Veterans' Medical Society outside the Massachusetts Medical Society, and promised the veterans who were present that the Society would adequately represent their interests and would take whatever action was necessary to rule out any complaints they might have, and to make adjustments that were necessary.

I do not know whether there is any need for such action or not, but obviously the Committee has taken no action and has taken no initiative. As the report states,

it was their understanding that nothing was to be done unless complaint was made.

I have no recommendation to make, one way or the other, except to mention the fact that if we discharge the Committee on Veterans Affairs, I know that the veterans will organize a society of their own outside the Massachusetts Medical Society.

They have already had their organizational meeting, and another meeting is, I believe, to be held tomorrow morning at the Copley Plaza Hotel.

I should be grateful if some of the men who are very familiar with veterans' affairs and medical circles would state what they feel, and whether we could accept the discharge of this committee, whether we should appoint a more active committee, or whether we should leave things to a veterans' society outside the Massachusetts Medical Society.

Dr Bagg replied as follows

Thank you for bringing up that matter. We were entirely ignorant of such a situation, because no reports had come to us at all, and there were no items to refer to Dr Grahfield's committee.

I will say this when I was getting together the list of committees last year, this committee seemed to be a very cumbersome one, and I have a feeling that a smaller committee, perhaps more actively made up of veterans themselves, might function better.

Therefore, the only way out of this situation that I can see is to refuse to discharge the committee, and then have a subsequent motion that the Committee be re-organized on the lines laid down.

Dr Bagnall then spoke as follows "It occurs to me that one way out of this would be to have this committee resign and let the president-elect, who will be the next president, appoint an appropriate committee, and that will take care of it all right."

Dr Bagg considered that a good suggestion. He stated that some definite information should be obtained from the veterans, adding that if the Society asked them for suggestions for appointments, that might solve the difficulty.

Dr John J. Curley, Worcester North, then spoke as follows

Last year the veterans met downstairs here, and we were promised that we would have either a section or some sort of committee within the Society that would be representative of the veteran physicians. This committee was appointed, and I know that one man in each district was appointed as a member of the committee, but to my knowledge, the man in my district was never asked to go to a meeting. So that whether the committee ever met or not, I do not know.

But the veterans, especially the veterans of World War II, who are physicians are especially desirous of having some section within the Massachusetts Medical Society. Whether it be a separate section or a separate society is up to the Society. But as we understood last year, the veterans were to have a committee and were to be allowed to form some sort of section within the Society, and to date nothing has been done about it.

Whether we need a new committee or whether we need some different type of committee or not, is the question.

But I can speak on behalf of the fellows who are councilors and who would make good live wires. I can think of a few men who could get this thing organized so there would not have to be any separate society within the state of Massachusetts.

A postcard notice has been sent out that there will be a meeting tomorrow. I should like to suggest to the President that he appoint somebody to go to that meeting

and speak for the Massachusetts Medical Society, as Dr Pilcher and I did last year at the meeting downstairs. And I think Dr Pilcher would be a very good one to send.

Dr John F. Conlin, Suffolk, spoke as follows

The matter of forming a new group is a matter that has been discussed quite a bit around the Commonwealth, and as long as it is this far on the agenda, I should like to rise to the point, although I am not a voting member of the Council. The chief argument that is put forth for organizing a veterans' group of World War II physicians is that they would be in a position to carry veterans' organizations along with them in the event that a matter such as compulsory national health insurance or something came up.

Whether that is enough to warrant a complete society or not, I hold in very serious doubt. I believe that just as much and just as effective work can be done by physicians working in existing veterans' organizations as members of those organizations, and spreading the word, whatever it may be.

Along that line, I believe very strongly, after covering the state, — and the things I say here I hope to say at the meeting at 10 o'clock on Wednesday when the World War II physicians are in meeting, — that one of the greatest dangers in medicine right now is this tangle system of the successive groups that will grow up.

It has been said very well in recent days that first all the members of one specialty get together and form a society, then a college is formed within that society, and then an academy within that society, and then perhaps a board. And then there are multiple specialty groups. And in this monstrous growth we are losing sight of the distinct medical societies and the local groups that (and I do not think it needs any urging with this group) are the basis of our entire medical structure.

They come first and are the thing we are most interested in. The Society is based on district societies and the national organization is based on state societies. Consequently, unless a very definite need exists, we should not multiply societies.

There is an organization already existing that embraces all physicians and veterans of all wars, the Association of Military Surgeons, to which many of us already belong, and, in the event that an organization is needed, that does fill the bill.

Consequently, I want to get this information before this gathering, so that you will have some of the background of the thinking that is going forward at the Wednesday meeting.

Dr Bagg stated that it was probably wise to follow Dr Conlin's point of view. During the year, as occasion arose, the President has tried to appoint veterans to the various committees in the Society, to take part in various functions of the Society, rather than as a separate branch. So long as Dr Conlin was speaking to the veterans, Dr Bagg suggested that he carry that as the point of view that the Society has been trying to follow.

The Secretary then spoke as follows

About two weeks ago Dr Kenneth A. Brown, of Weston (he is not a member of the Council), came into the headquarters of the Society and asked for information concerning veterans' affairs. I think Dr Brown is one of the moving spirits in this proposed veterans' organization. I spent an hour with him trying to explain to him that I was sure that the Massachusetts Medical Society, being made up of perhaps mostly veterans of some war, would see to it that veterans' affairs were considered as a very serious and important part of the Society's activities, and that if he would leave it to the men who are interested in the veterans' affairs in the Council and in the various committees and that if we could have a veterans' affairs committee, a new one perhaps appointed by the incoming president, his ends would be better met.

In the public interest to preserve, in the United States, our system of private medical practice

Familiarizing the public with the facts in connection with the values, the methods and the achievements of American Medicine.

To aid in the development of plans and to encourage the utilization of facilities that will result in the most widespread distribution of the most effective medical care and surgery

The Committee voted to approve the objectives of the National Physicians' Committee but disapproved some of the methods employed

Dr McKittrick moved acceptance of the report. The motion was seconded. Dr Bagg said that he had had a letter from Dr Allan M Butler, of the Committee, stating that he wished to change his vote and withdraw his approval.

Dr Bagnall said that Dr Butler's letter was not pertinent because surely the committee could not assume any responsibility for anything the National Physicians Committee did.

Dr McKittrick added that the subject of changing or attempting to change the policies of the National Physicians Committee had not been discussed.

Dr Bagg called for a vote, and the motion was passed. He assured Dr McKittrick that the subject was closed.

Dr Bagg then asked for final approval of the changes in the by-laws as printed and noted two errors in the use of "Inc" after Massachusetts Medical Service in the first paragraph.

Dr Bearse then pointed out that Chapter 4, Section 1, as amended, did not include the vice-president of the Society. Dr Bagg thanked Dr Bearse and called for a vote accepting the amended by-laws. The motion was carried.

*Committee on Physical Medicine* — Dr Arthur L Watkins, Middlesex South, *Chairman*

No new business had been referred to the Committee.

The American Board of Physical Medicine, Inc, had been approved by the Advisory Board for Medical Specialties and the first examinations had been conducted in Minneapolis in September, 1947, approximately 100 physicians had been certified to date.

An annual review of physical medicine was prepared for publication in the Medical Progress section of the *New England Journal of Medicine* entitled "Technical Advances in Physical Medicine."

*Committee to Make Recommendations for Directors of the Blue Shield* — Dr Leland S McKittrick, Suffolk, *Chairman*

The Committee submitted the names of the following men

To hold office until 1949

Mr Eben H Ellison, Jr, Proctor Ellison Co, 26 South Street, Boston, to replace Mr Hugh Nawn

Mr Joseph K Milliken, Jr, reappointment.

Dr Samuel A Robbins, reappointment.

Dr James C McCann, reappointment.

Mr Harold B Leland, reappointment.

To hold office until 1950

Mr Philip Morgan, reappointment.

Dr Norman Welch, reappointment.

Dr Arthur W Allen, reappointment.

Mr J H Humphrey, reappointment.

Mr Roswell Phelps, reappointment.

To hold office until 1951

Mr Benjamin Hull, Department of Labor and Industries, State House, Boston, to replace

Mr Ernest Johnson

Mr Thomas G Brown, reappointment.

Dr Elmer S Bagnall, reappointment.

Mr Daniel J Boyle, reappointment.

Dr Eugene Walker, reappointment.

Dr McKittrick moved the adoption of the report and it was seconded. Dr Bagg asked if there were any other nominations. There being none, the motion was put to vote and carried.

*Committee on Veterans Affairs* — Dr G Philip Grabfield, Norfolk, *Chairman*

The Committee on Veterans Affairs had held no meetings since its reappointment at the annual meeting in 1947. It was understood at that time that the Committee would not meet unless something arose that required its consideration or unless some individual or corporate body brought some subject to it for consideration. If no matters requiring consideration came up by the time of the Annual Meeting in 1948 it was the opinion of the committee that it should be discharged.

Dr Grabfield was not present, and Dr Bagg noted that the committee asked to be discharged. Dr Albert A Hornor, Suffolk, moved acceptance of the report. The motion was seconded.

Dr Lewis S Pilcher (Middlesex South) spoke as follows:

Gentlemen, there is just one point I think should be brought out before we proceed to accept the discharge of the Committee. There is a group of younger veterans in the Society who have been quite dissatisfied with the Society's interest in veterans' affairs.

I am quite certain that if the Society discharges the Committee on Veterans Affairs, these veterans will form their own organization outside the Society, and take over the interest in veterans' affairs that previously had been the province of the Society.

This matter was discussed at the annual meeting in 1947. At that time representatives of the Society and of the Veterans' Committee very strongly opposed the formation of a Veterans' Medical Society outside the Massachusetts Medical Society, and promised the veterans who were present that the Society would adequately represent their interests and would take whatever action was necessary to rule out any complaints they might have, and to make adjustments that were necessary.

I do not know whether there is any need for such action or not, but obviously the Committee has taken no action and has taken no initiative. As the report states,

it was their understanding that nothing was to be done unless complaint was made.

I have no recommendation to make, one way or the other, except to mention the fact that if we discharge the Committee on Veterans Affairs, I know that the veterans will organize a society of their own outside the Massachusetts Medical Society.

They have already had their organizational meeting, and another meeting is, I believe, to be held tomorrow morning at the Copley Plaza Hotel.

I should be grateful if some of the men who are very familiar with veterans' affairs and medical circles would state what they feel, and whether we could accept the discharge of this committee, whether we should appoint a more active committee, or whether we should leave things to a veterans' society outside the Massachusetts Medical Society.

Dr Bagg replied as follows

Thank you for bringing up that matter. We were entirely ignorant of such a situation, because no reports had come to us at all, and there were no items to refer to Dr Grabfield's committee.

I will say this when I was getting together the list of committees last year, this committee seemed to be a very cumbersome one, and I have a feeling that a smaller committee, perhaps more actively made up of veterans themselves, might function better.

Therefore, the only way out of this situation that I can see is to refuse to discharge the committee, and then have a subsequent motion that the Committee be re-organized on the lines laid down.

Dr Bagnall then spoke as follows "It occurs to me that one way out of this would be to have this committee resign and let the president-elect, who will be the next president, appoint an appropriate committee, and that will take care of it all right."

Dr Bagg considered that a good suggestion. He stated that some definite information should be obtained from the veterans, adding that if the Society asked them for suggestions for appointments, that might solve the difficulty.

Dr John J. Curley, Worcester North, then spoke as follows

Last year the veterans met downstairs here, and we were promised that we would have either a section or some sort of committee within the Society that would be representative of the veteran physicians. This committee was appointed, and I know that one man in each district was appointed as a member of the committee, but to my knowledge, the man in my district was never asked to go to a meeting. So that whether the committee ever met or not, I do not know.

But the veterans, especially the veterans of World War II, who are physicians are especially desirous of having some section within the Massachusetts Medical Society. Whether it be a separate section or a separate society is up to the Society. But as we understood last year, the veterans were to have a committee and were to be allowed to form some sort of section within the Society, and to date nothing has been done about it.

Whether we need a new committee or whether we need some different type of committee or not, is the question.

But I can speak on behalf of the fellows who are counselors and who would make good live wires. I can think of a few men who could get this thing organized so there would not have to be any separate society within the state of Massachusetts.

A postcard notice has been sent out that there will be a meeting tomorrow. I should like to suggest to the President that he appoint somebody to go to that meeting

and speak for the Massachusetts Medical Society, as Dr Pilcher and I did last year at the meeting downstairs. And I think Dr Pilcher would be a very good one to send.

Dr John F. Conlin, Suffolk, spoke as follows

The matter of forming a new group is a matter that has been discussed quite a bit around the Commonwealth, and as long as it is this far on the agenda, I should like to rise to the point, although I am not a voting member of the Council. The chief argument that is put forth for organizing a veterans' group of World War II physicians is that they would be in a position to carry veterans' organizations along with them in the event that a matter such as compulsory national health insurance or something came up.

Whether that is enough to warrant a complete society or not, I hold in very serious doubt. I believe that just as much and just as effective work can be done by physicians working in existing veterans' organizations as members of those organizations, and spreading the word, whatever it may be.

Along that line, I believe very strongly, after covering the state, — and the things I say here I hope to say at the meeting at 10 o'clock on Wednesday when the World War II physicians are in meeting, — that one of the greatest dangers in medicine right now is this tangle system of the successive groups that will grow up.

It has been said very well in recent days that first all the members of one specialty get together and form a society, then a college is formed within that society, and then an academy within that society, and then perhaps a board. And then there are multiple specialty groups. And in this monstrous growth we are losing sight of the district medical societies and the local groups that (and I do not think it needs any urging with this group) are the basis of our entire medical structure.

They come first and are the thing we are most interested in. The Society is based on district societies and the national organization is based on state societies. Consequently, unless a very definite need exists, we should not multiply societies.

There is an organization already existing that embraces all physicians and veterans of all wars, the Association of Military Surgeons, to which many of us already belong, and, in the event that an organization is needed, that does fill the bill.

Consequently, I want to get this information before this gathering, so that you will have some of the background of the thinking that is going forward at the Wednesday meeting.

Dr Bagg stated that it was probably wise to follow Dr Conlin's point of view. During the year, as occasion arose, the President has tried to appoint veterans to the various committees in the Society, to take part in various functions of the Society, rather than as a separate branch. So long as Dr Conlin was speaking to the veterans, Dr Bagg suggested that he carry that as the point of view that the Society has been trying to follow.

The Secretary then spoke as follows

About two weeks ago Dr Kenneth A. Brown, of Weston (he is not a member of the Council), came into the headquarters of the Society and asked for information concerning veterans' affairs. I think Dr Brown is one of the moving spirits in this proposed veterans' organization. I spent an hour with him trying to explain to him that I was sure that the Massachusetts Medical Society, being made up of perhaps mostly veterans of some war, would see to it that veterans' affairs were considered as a very serious and important part of the Society's activities, and that if he would leave it to the men who are interested in the veterans' affairs in the Council and in the various committees and that if we could have a veterans' affairs committee, a new one perhaps appointed by the incoming president, his ends would be better met.

In the public interest to preserve, in the United States, our system of private medical practice

Familiarizing the public with the facts in connection with the values, the methods and the achievements of American Medicine

To aid in the development of plans and to encourage the utilization of facilities that will result in the most widespread distribution of the most effective medical care and surgery

The Committee voted to approve the objectives of the National Physicians' Committee but disapproved some of the methods employed

Dr McKittrick moved acceptance of the report. The motion was seconded. Dr Bagg said that he had had a letter from Dr Allan M Butler, of the Committee, stating that he wished to change his vote and withdraw his approval.

Dr Bagnall said that Dr Butler's letter was not pertinent because surely the committee could not assume any responsibility for anything the National Physicians Committee did.

Dr McKittrick added that the subject of changing or attempting to change the policies of the National Physicians Committee had not been discussed.

Dr Bagg called for a vote, and the motion was passed. He assured Dr McKittrick that the subject was closed.

Dr Bagg then asked for final approval of the changes in the by-laws as printed and noted two errors in the use of "Inc" after Massachusetts Medical Service in the first paragraph.

Dr Bearer then pointed out that Chapter 4, Section 1, as amended, did not include the vice-president of the Society. Dr Bagg thanked Dr Bearer and called for a vote accepting the amended by-laws. The motion was carried.

*Committee on Physical Medicine*—Dr Arthur L Watkins, Middlesex South, *Chairman*

No new business had been referred to the Committee.

The American Board of Physical Medicine, Inc., had been approved by the Advisory Board for Medical Specialties and the first examinations had been conducted in Minneapolis in September, 1947, approximately 100 physicians had been certified to date.

An annual review of physical medicine was prepared for publication in the Medical Progress section of the *New England Journal of Medicine* entitled "Technical Advances in Physical Medicine."

*Committee to Make Recommendations for Directors of the Blue Shield*—Dr Leland S McKittrick, Suffolk, *Chairman*

The Committee submitted the names of the following men

To hold office until 1949

Mr. Eben H Ellison, Jr., Proctor Ellison Co., 26 South Street, Boston, to replace Mr Hugh Nawn

Mr Joseph K Milliken, Jr., reappointment.  
Dr Samuel A Robbins, reappointment.  
Dr James C McCann, reappointment.  
Mr Harold B Leland, reappointment.

To hold office until 1950

Mr Philip Morgan, reappointment.  
Dr Norman Welch, reappointment.  
Dr Arthur W Allen, reappointment.  
Mr J H Humphrey, reappointment.  
Mr Roswell Phelps, reappointment.

To hold office until 1951

Mr Benjamin Hull, Department of Labor and Industries, State House, Boston, to replace Mr Ernest Johnson.  
Mr Thomas G Brown, reappointment.  
Dr Elmer S Bagnall, reappointment.  
Mr Daniel J Boyle, reappointment.  
Dr Eugene Walker, reappointment.

Dr McKittrick moved the adoption of the report and it was seconded. Dr Bagg asked if there were any other nominations. There being none, the motion was put to vote and carried.

*Committee on Veterans Affairs*—Dr G Philip Grabfield, Norfolk, *Chairman*

The Committee on Veterans Affairs had held no meetings since its reappointment at the annual meeting in 1947. It was understood at that time that the Committee would not meet unless something arose that required its consideration or unless some individual or corporate body brought some subject to it for consideration. If no matters requiring consideration came up by the time of the Annual Meeting in 1948 it was the opinion of the committee that it should be discharged.

Dr Grabfield was not present, and Dr Bagg noted that the committee asked to be discharged. Dr Albert A Hornor, Suffolk, moved acceptance of the report. The motion was seconded.

Dr Lewis S Pilcher (Middlesex South) spoke as follows

Gentlemen, there is just one point I think should be brought out before we proceed to accept the discharge of the Committee. There is a group of younger veterans in the Society who have been quite dissatisfied with the Society's interest in veterans' affairs.

I am quite certain that if the Society discharges the Committee on Veterans Affairs, these veterans will form their own organization outside the Society, and take over the interest in veterans' affairs that previously had been the province of the Society.

This matter was discussed at the annual meeting in 1947. At that time representatives of the Society and of the Veterans' Committee very strongly opposed the formation of a Veterans' Medical Society outside the Massachusetts Medical Society, and promised the veterans who were present that the Society would adequately represent their interests and would take whatever action was necessary to rule out any complaints they might have, and to make adjustments that were necessary.

I do not know whether there is any need for such action or not, but obviously the Committee has taken no action and has taken no initiative. As the report states,

it was their understanding that nothing was to be done unless complaint was made.

I have no recommendation to make, one way or the other, except to mention the fact that if we discharge the Committee on Veterans Affairs, I know that the veterans will organize a society of their own outside the Massachusetts Medical Society.

They have already had their organizational meeting, and another meeting is, I believe, to be held tomorrow morning at the Copley Plaza Hotel.

I should be grateful if some of the men who are very familiar with veterans' affairs and medical circles would state what they feel, and whether we could accept the discharge of this committee, whether we should appoint a more active committee, or whether we should leave things to a veterans' society outside the Massachusetts Medical Society.

Dr Bagg replied as follows

Thank you for bringing up that matter. We were entirely ignorant of such a situation, because no reports had come to us at all, and there were no items to refer to Dr Grahfield's committee.

I will say this when I was getting together the list of committees last year, this committee seemed to be a very cumbersome one, and I have a feeling that a smaller committee, perhaps more actively made up of veterans themselves, might function better.

Therefore, the only way out of this situation that I can see is to refuse to discharge the committee, and then have a subsequent motion that the Committee be re-organized on the lines laid down.

Dr Bagnall then spoke as follows "It occurs to me that one way out of this would be to have this committee resign and let the president-elect, who will be the next president, appoint an appropriate committee, and that will take care of it all right."

Dr Bagg considered that a good suggestion. He stated that some definite information should be obtained from the veterans, adding that if the Society asked them for suggestions for appointments, that might solve the difficulty.

Dr John J. Curley, Worcester North, then spoke as follows

Last year the veterans met downstairs here, and we were promised that we would have either a section or some sort of committee within the Society that would be representative of the veteran physicians. This committee was appointed, and I know that one man in each district was appointed as a member of the committee, but to my knowledge, the man in my district was never asked to go to a meeting. So that whether the committee ever met or not, I do not know.

But the veterans, especially the veterans of World War II, who are physicians are especially desirous of having some section within the Massachusetts Medical Society. Whether it be a separate section or a separate society is up to the Society. But as we understood last year, the veterans were to have a committee and were to be allowed to form some sort of section within the Society, and to date nothing has been done about it.

Whether we need a new committee or whether we need some different type of committee or not, is the question.

But I can speak on behalf of the fellows who are councilors and who would make good live wires. I can think of a few men who could get this thing organized so there would not have to be any separate society within the state of Massachusetts.

A postcard notice has been sent out that there will be a meeting tomorrow. I should like to suggest to the President that he appoint somebody to go to that meeting

and speak for the Massachusetts Medical Society, as Dr Pilcher and I did last year at the meeting downstairs. And I think Dr Pilcher would be a very good one to send.

Dr John F. Conlin, Suffolk, spoke as follows

The matter of forming a new group is a matter that has been discussed quite a bit around the Commonwealth, and as long as it is this far on the agenda, I should like to rise to the point, although I am not a voting member of the Council. The chief argument that is put forth for organizing a veterans' group of World War II physicians is that they would be in a position to carry veterans' organizations along with them in the event that a matter such as compulsory national health insurance or something came up.

Whether that is enough to warrant a complete society or not, I hold in very serious doubt. I believe that just as much and just as effective work can be done by physicians working in existing veterans' organizations as members of those organizations, and spreading the word, whatever it may be.

Along that line, I believe very strongly, after covering the state, — and the things I saw here I hope to say at the meeting at 10 o'clock on Wednesday when the World War II physicians are in meeting, — that one of the greatest dangers in medicine right now is this tangle system of the successive groups that will grow up.

It has been said very well in recent days that first all the members of one specialty get together and form a society, then a college is formed within that society, and then an academy within that society, and then perhaps a board. And then there are multiple specialty groups. And in this monstrous growth we are losing sight of the district medical societies and the local groups that (and I do not think it needs any urging with this group) are the basis of our entire medical structure.

They come first and are the thing we are most interested in. The Society is based on district societies and the national organization is based on state societies. Consequently, unless a very definite need exists, we should not multiply societies.

There is an organization already existing that embraces all physicians and veterans of all wars, the Association of Military Surgeons, to which many of us already belong, and, in the event that an organization is needed, that does fill the bill.

Consequently, I want to get this information before this gathering, so that you will have some of the background of the thinking that is going forward at the Wednesday meeting.

Dr Bagg stated that it was probably wise to follow Dr Conlin's point of view. During the year, as occasion arose, the President has tried to appoint veterans to the various committees in the Society, to take part in various functions of the Society, rather than as a separate branch. So long as Dr Conlin was speaking to the veterans, Dr Bagg suggested that he carry that as the point of view that the Society has been trying to follow.

The Secretary then spoke as follows

About two weeks ago Dr Kenneth A. Brown, of Weston (he is not a member of the Council), came into the headquarters of the Society and asked for information concerning veterans' affairs. I think Dr Brown is one of the moving spirits in this proposed veterans' organization. I spent an hour with him trying to explain to him that I was sure that the Massachusetts Medical Society, being made up of perhaps mostly veterans of some war, would see to it that veterans' affairs were considered as a very serious and important part of the Society's activities, and that if he would leave it to the men who are interested in the veterans' affairs in the Council and in the various committees and that if we could have a veterans' affairs committee, a new one perhaps appointed by the incoming president, his ends would be better met.

than by any separate veterans' medical organization that tried to work perhaps at cross purposes with the Society

I thought he was convinced and I hope if somebody, from the Council appears at the veterans' meeting, that person will convince the whole group, because I think it is extremely important that no separate group appear medically, certainly, to work at cross purposes with this one

Dr Bagg stated that he would tell Dr Grabfield of the discussion and suggest that, inasmuch as he wanted to be relieved, he resign, and let the incoming president choose a new committee

*Auditing Committee* — Dr Howard B Jackson, Norfolk, Chairman, and Dr Frank T Downey, Middlesex South

The members of this committee were not present, and the President asked the Secretary to read the report. The Secretary read as follows

The Auditing Committee appointed the firm of Hartshorn and Walter, accountants and auditors, to audit the books and accounts of the Massachusetts Medical Society. This audit and account are hereby approved by us

The analysis of the revenues and expenses of the Society and the balance sheet of the condition of the funds of the Society have been inspected and approved by us

It was moved and seconded that the report be accepted. It was so voted by the Council

The President, according to the by-laws, stated that he would appoint two fellows, not members of the Council, as members of the Auditing Committee for 1948-1949. The President appointed the same fellows, Dr Howard B Jackson and Dr Frank T Downey

It was then moved that these appointments be confirmed. The motion was seconded and it was so voted by the Council

*Committee on Benevolence* — Dr Dwight O'Hara, Middlesex South, Chairman

The Committee on Benevolence had held one meeting, which Dr Ober attended by invitation, and had discussed the preliminary aspects of a plan to activate the desire of the Council to make provision for certain fellows or their families who have come upon hard times through no fault of their own. This was therefore a report of progress and merely indicated that the Committee hoped to submit definite recommendations at a future meeting of the Council

Dr O'Hara moved acceptance of the report. The motion was seconded and so voted

*Report of the Delegates to the American Medical Association*

The report was as follows

The first interim meeting of the House of Delegates of the American Medical Association was held in Cleveland, Ohio, on January 5 and 6, 1948. All your delegates or their alternates were present. Drs Phippen and Gear served on Reference Committees

The first business transacted was the selection of the recipient of the General Practitioners award. It was the first time the medal had been offered. There were 149 general practitioners suggested to the trustees by medical organizations, civic organizations, patients and others. Following the routine adopted for many years in awarding the Distinguished Service Medal, the trustees presented three names for the consideration of the House. After the ballot was taken it appeared that Dr Archer C. Sudan, of Colorado, had been chosen. Dr Sudan has practiced medicine in Kremmling, Colorado, a town of 567 population but with many outlying ranches. He has been interested in civic and public-health matters and has been president of the Colorado State Medical Society. He came on from Colorado and addressed the assembled general practitioners

The delegates to the World Medical Association were commended for their efforts in bringing about the formation of that organization last September in Paris. It was reported that forty-eight nations had joined together in the hope that such an organization would help to promote world peace as well as world health. The Permanent Secretary will have an office in the headquarters of the New York Academy of Medicine

The committee appointed last year to study the nursing situation brought in an interesting report of progress and believed they could offer a final report at the June meeting. Among other suggestions were bedside nursing under uniform standards and careful supervision, Social Security for nurses and the possibility of coverage of nursing service by insurance. Finally, a permanent committee was authorized to confer with the American Hospital Association and the American Nursing Association to study this problem

There was some discussion about limiting the tenure of office of members of the House, but it was finally determined that this matter should be left to each state society. As in any other business — costs have risen, and the American Medical Association faces a deficit of \$170,470 this year. Hence the House voted to raise the fellowship dues from \$8 to \$12

There was considerable discussion on the training and, more particularly, the distribution of interns. It was pointed out that many hospitals apparently are not living up to the gentleman's agreement to make their appointments on a certain specific day. Some believed that a year of rotating internship was advisable for any graduate in medicine — others thought the internship for general practitioners should be improved and lengthened. Finally, it was voted to set up a special committee on intern training and placement consisting of five members of whom two should be general practitioners — this committee to co-operate with the Council on Medical Education and Hospitals, and report at the next meeting

The perennial question regarding the practice of medicine by hospitals (that is, the employment of pathologists, radiologists and anesthetists directly by the hospitals, without staff status, and using the profits of their respective departments for general hospital purposes) produced several resolutions and much discussion. Many remedies and penalties were suggested, but it was finally left to a committee of five to confer with the various specialist organizations and to report at the next meeting. In the field of public relations several new workers were introduced but it was pointed out that each doctor in his daily contact with patients and their friends was the best possible agent for friendly relations with the public

These are some of the high lights of the session, which was conducted with dispatch and decorum

Dr Richard M Smith (Suffolk) moved that the report be accepted. The motion was seconded, and it was so voted

## NEW BUSINESS

Dr Leroy E Parkins, Suffolk, made a motion that the Committee on Postgraduate Assembly be

made a subcommittee of the Committee on Post-graduate Education

Dr Bagg, according to Council rules, referred the matter to the Executive Committee

Dr Bagg then read a letter from Dr John F Conlin urging the Society to conduct a health assembly in Massachusetts in 1949 Dr Bagg referred this matter to the Committee on Public Relations

Dr Augustus Thorndike, Suffolk, read the following resolution

Whereas at the October meeting of the Council the Committee on Rehabilitation and Industrial Health reported that a need existed for the establishment of a rehabilitation center in Boston under local management,

And Whereas the Secretary of State has issued a charter for the Bay State Medical Rehabilitation Clinic under local management,

Be it resolved that the President be authorized to appoint a committee of the Society to confer with the officers and directors of the newly formed Bay State Medical Rehabilitation Clinic and to consider in what manner the Society may best assist in the establishment of the clinic or clinics, the committee to report its recommendations with appropriate drafts of resolutions at the next meeting of the Council

Dr Bagg referred this matter to the Committee on Public Relations

Dr N S Scarcello, Worcester, presented the following statement

Disapproval is expressed of the manner of physician procurement and assignment as administered during the past war It is believed that any committee set up to determine the availability of fellow doctors for military service should be elected by the Society and not be an appointed body

Realizing that future warfare will be an all-out affair most likely involving a completely mobilized civilian as well as military population, a much more comprehensive plan for the utilization of physicians will be required than the relatively simple decision by a board regarding a doctor's dispensability or indispensability to the community

This matter, therefore, is one that involves not only doctors who were in military service during the last war (and who will be the first to be recalled in the event of another emergency) but also, most certainly, all doctors The problem thus requires the thought of the Society as a whole

It is therefore moved that the president of the Worcester District Medical Society be empowered to appoint a committee of seven to be known as the Committee of National Emergency Medical Service The duties of this committee will be to study the problem of physician mobilization in the event of national emergency, to keep the Society informed of state and national developments along these lines, and to make recommendations to the Society as occasion may arise

In view of the fact that the nation as a whole is preparing once again for national defense and that as a part of this plan the American Medical Association, under the supervision of the United States Government, is organizing a plan for obtaining physicians necessary for the needs of the armed forces, it is moved that the Worcester District Medical Society, through its councilors, place before the Massachusetts Medical Society a plan for procurement. Each district society within the Commonwealth will be instructed to elect a representative committee, to be known as "The National Emergency Medical Service Committee" One member of this committee shall be selected to represent his district on the State Executive Committee The State Executive Committee, which shall be composed of only the elected dele-

gate from each district, shall then elect a chairman, who will be designated as the Massachusetts representative head of the National Emergency Medical Service

Dr Bagg referred this matter to the Committee on Emergency Medical Service

Dr Robert W Buck, Middlesex South, read the following statement

The Massachusetts Physicians Art Association invites the Massachusetts Medical Society to sponsor officially an annual art exhibit to be held in connection with the annual meeting of the Society Our association is state wide in its membership and is made up of members of the Society In the past we have benefited greatly from the unofficial but generously given co-operation of the Executive Secretary and Committee on Arrangements Our purpose in asking official sponsorship is to simplify the problem of obtaining adequate show space farther in advance of the date of the annual meeting than our club has been able to do working independently and to ensure that the art show will be an annual affair

Dr Bagg referred this matter to the Executive Committee

Dr M J Schlesinger, Middlesex South, read the following resolution

Whereas the membership of the Massachusetts Medical Society includes a considerable group engaged solely in the practice of pathology and

Whereas this group has no specific identity other than general membership in the Society and

Whereas the problems peculiar to the practice of pathology make it desirable that this group be recognized as a well defined unit functioning within the structure of the Society and

Whereas the New England Pathological Society has been recorded as favoring the recognition of such a unit within state medical societies,

Be it resolved that the Council of the Massachusetts Medical Society is herewith petitioned to establish a Section on Pathology among the membership of the Society

Dr Bagg referred this matter to the Executive Committee

Dr Howard Root, Suffolk, then asked that the President be empowered to appoint a committee of not less than three and not more than seven to consider the possible action that the Society might take in the attempt to bring about better public understanding of diabetes, its early diagnosis and treatment

Dr Bagg referred this matter to the Committee on Public Relations

## COMMITTEE APPOINTMENTS

Dr Reardon read a list of nominations to committees for the year 1948-1949 Dr Reardon moved that the Council confirm his appointments The motion was seconded and carried

A motion to adjourn was made, seconded and carried The meeting adjourned at 11 05 p m

H QUIMBY GALLUPE, Secretary

## APPENDIX NO 1

## BARNSTABLE

P P Henson  
J I B Vail

## BERKSHIRE

Helen M Scoville  
P J Sullivan

## BRISTOL NORTH

M E Johnson  
J L Murphy  
W M Stobbs

## BRISTOL SOUTH

G W Blood  
R B Butler  
R H Goodwin  
William Mason  
D R Mills  
C C Tripp  
Henry Wardle

## ESSEX NORTH

H M Allen  
E S Bagnall  
R V Baketel  
Elizabeth Councilman  
N F DeCesare  
H F Fenton  
A P George  
S P Humphreys  
H R Kurth  
P J Look  
R C Norris  
G L Richardson  
F W Snow  
C F Warren

## ESSEX SOUTH

W W Babson  
R E Foss  
S E Goulding  
Loring Grimes  
C A Herrick  
P P Johnson  
A. E. Parkhurst  
E D Reynolds  
H D Stebbins  
P E Tivnan  
C F Twomey  
C A Worthen

## FRANKLIN

L R Dame  
J E Moran  
W D Thomas

## HAMPDEN

F H Allen  
E P Bagg  
R L Barrett  
W A R. Chapin  
J L Chereskin  
G B Corcoran  
E C Dubois  
Adolph Franz, Jr  
P E Gear  
Frederic Hagler  
F S Hopkins  
R T Miller  
A G Rice  
A H Riordan  
G L Schadt  
J A Seaman  
G L Steele

## HAMPSHIRE

L B Pond

## MIDDLESEX EAST

J L Anderson  
E M Halligan  
D L Joyce  
R W Layton  
K L MacLachlan  
M J Quinn  
R R Stratton

## MIDDLESEX NORTH

R E Cole  
W M Collins  
S A Dibbins  
L J Hall  
W F Ryan  
A J Stewart

## MIDDLESEX SOUTH

E W Barron  
J M Baty  
W O Blanchard  
H K Bloom  
G F H Bowers  
Madeline R Brown  
R N Brown  
R W Buck  
E J Butler  
J F Casey  
E A Cooney  
W H Crosby  
C L Denick  
J G Downing  
A G Engelbach  
C W Finnerty  
H Q Gallupe  
V A. Getting  
H W Godfrey  
J L Golden  
A D Guthrie  
Eliot Hubbard, Jr  
F R Jouett  
S B Kelley  
A A Levi  
A N Makechnie  
R A McCarty  
J H McSweeney  
C E Mongan  
Dwight O'Hara  
Fabyan Packard  
L G Paul  
L S Pilcher  
Max Ritvo  
G A Saunders  
M J Schlesinger  
A B Toppan  
J H Townsend  
C F Walcott  
A L Watkins  
R H Wells  
B M Wein  
Hovhannes Zovickian

## NORFOLK

C E Allard  
B E Barton  
Carl Bearse  
Elizabeth Broyles  
G L Doherty  
Albert Ehrenfried  
Susannah Friedman  
T R. Goethals  
D L Halbersleben  
J B Hall  
H B Harris  
R J Heffernan  
P J Jakmauh

I R Jankelson  
C J Kickham  
D L Lionberger  
D S Luce  
C M Lydon  
D L Lynch  
T F P Lyons  
F P McCarthy  
H L McCarthy  
F J Moran  
H R Morrison  
Hyman Morrison  
D J Mullane  
H A Novack  
J J O'Connell  
W R Ohler  
E E O'Neil  
R S Palmer  
H C Petterson  
H A Rice  
S A Robins  
D D Scannell  
J A Seth  
J A Sieracki  
S L Skvirskv  
Kathleyne S Snow  
J W Spellman  
W J Walton  
N A Welch  
P R Withington  
Marjorie Woodman

## NORFOLK SOUTH

D L Belding  
W R Helfrich  
Frederick Hinchhiffe  
E K Jenkins  
N R Pillsbury  
D B Reardon  
H A Robinson  
R G Vinal

## PLYMOUTH

J C Angley  
G A Buckley  
A L Duncombe  
P H Leavitt  
C D McCann  
G A Moore  
E L Perry

## SUFFOLK

H L Albright  
T J Anglem  
C H Bradford

W J Brckley  
W E Browne  
A J A. Campbell  
E M Chapman  
M H Clifford  
A. P. Der Hagopian  
H H Faxon  
N W Faxon  
Maurice Fremont Smith  
A. A. Hornor  
C S Keefer  
H A Kelly  
R. I. Lee  
C F Maraldi  
F W Marlow, Jr  
L S McKittick  
Donald Munro  
F R Ober  
F W O'Brien  
J P O'Hare  
L E Parkins  
Helen S Pittman  
J J Regan  
W H Robey  
Horatio Rogers  
H F Root  
C G Shedd  
R. M. Smith  
C M Stearns  
Augustus Thorndike  
Conrad Wesselhoeft

## WORCESTER

A W Atwood  
George Ballantyne  
F T Bousquet  
F B Carr  
A J Crane  
Paul Dufault  
W J Elliott  
John Fallon  
D G Ljungberg  
J A Lundy  
D K McClusky  
F A O'Toole  
E L Richmond  
N S Scarcello  
J J Tegelberg  
B C Wheeler

## WORCESTER NORTH

J J Curley  
C B Gay  
J C Hales  
J V McHugh  
C S McPeak  
J G Simmons

## APPENDIX NO 2

## REPORT OF THE TREASURER

Increased membership in the Society and the return of more fellows to a civilian status has raised the income from resident dues from \$51,752 in 1946 to \$59,020 in 1947. Non-resident dues correspondingly increased from \$1776 to \$2244. *The New England Journal of Medicine* presented the Society with \$9000 in 1946 but was unable to contribute this year, \$5000 was advanced to the *Journal* in 1947, and paid back before the end of the year. In 1947, \$1335 was received from censor fees, as compared with \$1242 in 1946. Net profit from the Committee on Arrangements was \$6234, or \$966 more than last year. Profit from the New England Postgraduate Assembly was \$528, or \$193 less than last year.

The annual income from endowment funds rose from \$503 to \$548 and from the General Fund from \$5162 to \$5893, but fell in the Building Fund from \$1989 to \$1906. Profit from sale of securities was \$861 in the General Fund and \$1048 in the Building Fund. Subscriptions to *The New*

England Journal of Medicine from men in service fell from \$26 to \$76, which sum was turned over to the Journal office.

The book value of securities in the General Fund increased from \$179,094 to \$199,150 and in the Building Fund from \$9,665 to \$74,308. The endowment funds increased from \$23,166 to \$28,166 owing to the addition of \$5000 received by bequest from the estate of the late Samuel B Woodward, of Worcester, for the Cotting Fund.

Total revenue in the General Fund fell from \$78,072 in 1946 to \$76,679 in 1947, even in the face of increased income from dues, but this is understandable when it is recognized that the \$9000 from the Journal's activities is reflected in the 1946 figure. Total expenses rose from \$51,424 to \$64,630 in 1947, and increase in revenue over expenditure fell from \$26,026 to \$12,049. An income of \$76,679 on the basis of dues of \$10 confronted with a budget for expense of \$86,359 in 1948 explains why an increase in dues is unavoidable in 1948. It is practically certain that the budget for 1949 will be higher when provisions will undoubtedly be made or some sort of aid to members "who, through no fault of their own, find themselves incapacitated through illness, injury or age," and to "needy widows and orphans."

The total Building Fund assets stand at \$76,072 and total General Fund assets at \$243,226. The latter figure has not yet reached \$250,000, when by vote of the Council, any excess will be transferred to the Building Fund.

The Society ends 1947 with a grand total of assets in cash and securities of \$357,528, an increase of \$23,092 over 1946.

On advice of our investment counselors, the following changes have been made in the portfolio of investments. Conveyancers Realty debentures were sold, and the proceeds invested in American Telephone and Telegraph convertible 275 per cent bonds. Funds available throughout the year were invested in 10 shares of Hartford Fire Insurance Company, 25 shares of Chemical Bank and Trust, 25 shares of Cleveland Electric Illuminating Company and 100 shares of Southern California Edison 448 convertible preferred stock in the Building Fund. Corresponding investments in the General Fund included 25 shares of Hartford Fire Insurance Company, 50 shares of Fidelity-Phenix Fire Insurance Company, 10 shares of Guaranty Trust, 75 shares of Cleveland Electric Illuminating Company, 300 shares of Philadelphia Electric \$1 preference stock and 300 shares of Southern California Edison 448 convertible preferred stock. Certain long-term railway bonds and long-term Government bonds were sold to buy an equivalent amount of short-term Government bonds. This was advised because the firming of interest rates tends to depreciate the sales value of long-term bonds.

During the year a retirement plan policy was taken out for the one full-time employee who so far qualifies through length of service. The Postwar Loan Fund ceased making new loans at the end of the fiscal year, and the collateral held by the bank to cover these loans was reduced from \$25,000 to \$5000 inasmuch as seven loans made during the latter part of the year will run into 1948, \$1180 was paid to the Boston Medical Library, representing \$5 from each of the \$25 dues collected from 236 new members admitted in December, 1947. Although the Society is still exempt from income taxation, the Department of Internal Revenue has transferred the exemption from Section 101(6), corporations exclusively educational and charitable, to Section 101(7), corporations predominantly educational but making some profits. This change has brought with it our liability for federal old age and unemployment taxation, and state unemployment taxation, all coming under the Social Security regulations. An opinion was obtained from our legal advisers to the effect that the only thing was to concur in submitting to this taxation.

This year has been the first in which the Massachusetts Medical Society has had its exclusive office staff. The Treasurer wishes to express his appreciation of the very complex activities have been taken in hand, of the fine co-operation that has been shown and especially of the aid given by the Secretary handling his particular assignment.

#### COMPARATIVE EXPENSES, 1946 AND 1947

Salary	1946	1947
Secretary	\$3,500 00	\$3,820 64
Executive Secretary	4,400 00	4,800 00
Treasurer	2,250 00	2,500 00
Director of Medical Information and Education	0	3,750 00

#### Expenses

President	154 39	214 82
President-Elect	0	74 04
Secretary	4,594 36	2,779 61
Treasurer	2,516 33	2,059 00
Director, Medical Information and Education	0	469 39
Delegates to A.M.A.	3,380 01	676 23
Cotting Incheons	543 20	450 00
Refund to district societies	4,000 00	4,000 00
New Eng and Council	100 00	100 00
Clinical	1,405 00	5,162 00
General administrative	4,701 22	3,562 89
Shattuck Lecture	200 00	200 00
Gift to Boston Medical Library	0	1,180 00
Pension plan premium	0	4,233 80

#### Committees

Arrangements	0	0
	(profit)	(profit)
To Appoint a Director of Education and Information	14 55	0
Ethics and Discipline	147 41	60 49
Executive	246 80	232 09
Fee Schedule	689 48	348 35
Finance	3 00	0
Industrial Health	79 93	17 80
Headquarters Committee	4,078 63	7,421 19
Legislation	3,841 73	4,311 30
Massachusetts Hospital Association	5 66	0
Medical Economics	0	63 54
Medical Defense	1,167 75	1,474 51
Membership	225 07	137 77
Military Postgraduate	0 52	0
Postwar Loan Fund	313 33	151 12
Postwar Planning	4,084 04	0 62
Information Bureau	3,403 79	3,128 72
Postgraduate Education	0	3,097 14
	(under P.W.P.I.)	
Public Health	108 67	195 91
Public Relations	636 49	451 61
Publications	3 12	2,346 12
Rehabilitation	0	71 03
Special Services	0	561 28
To Study Malpractice Insurance	607 23	148 91
Tax Supported Medical Care	22 53	0
Advisory on School Medical Services	0	29 88
To Consider Secretary as Full-Time Position	0	19 74

#### Taxes

Federal Unemployment	0	462 99
Federal Old Age	0	65 58
	\$51,424 24	\$64,630 11

### APPENDIX NO 3

#### REPORT OF THE EXECUTIVE COMMITTEE

President Bagge called the meeting to order at 4:00 p.m. The Secretary called the roll, members from Barnstable, Berkshire and Hampden were absent.

The report of the last meeting of the committee, held January 7, 1948, was accepted as printed in the April 7, 1948, number of the Journal.

#### COMMITTEE REPORTS

##### Committee on Public Relations

Dr. Bagge pointed out that Blue Cross and Blue Shield relations and problems seemed to be better and that the Blue Cross had to retain the special services in their contract to meet commercial competition and until a Blue Cross reserve fund is built up.

It was then moved, seconded and voted that the report of the subcommittee on Blue Cross and Blue Shield problems be approved. Dr. Bagge then stated that since the Executive Committee is the voting corporation of Blue Shield, the problems of Blue Cross and Blue Shield should be referred to this committee and that the subcommittee be discharged as approved by the Committee on Public Relations.

It was then moved by the Secretary that the subcommittee be discharged and that in the future Blue Cross and Blue Shield problems be handled by a subcommittee of the Executive Committee and that the President appoint such a subcommittee. The motion was seconded and passed.

President Bagge then mentioned the suggestion of a subcommittee (Chairman, Dr. Hagler) that each member of the Committee on Public Relations be asked to suggest to each district society that it set up machinery to handle calls for doctors at all times and that the Committee on Public Relations approve that method of action. The Secretary then pointed out that this subject was an extremely important one and that the Society office received many calls from people asking "Where can we get a doctor?" and

"Why don't doctors answer their telephones?" and "Why do doctors go away and leave nobody covering for them?" and "What happens on Wednesdays when every doctor is out of town?"

The Secretary said that he believed that this was a distinct duty of the Society, and that it had been so mentioned in the State Legislature and at the last meeting of the House of Delegates. He also said that the Massachusetts Medical Society is the only body able to take a step to see to it that the people get medical care when they need it. The Secretary moved that the action of the Committee on Public Relations on this matter be approved. The motion was seconded and passed unanimously.

It was then moved and seconded that the President appoint a committee to act in an advisory capacity in the procedure of transferring the Blood Bank from the Massachusetts Public Health Service to the Red Cross and in supervising the work thereafter. This motion was passed.

Dr. Bagg then stated that he had appointed Drs. Gallupe and John W. Spellman to work with the Hospital Presidents' Joint Committee to discuss voluntary hospital costs and to assist in passing Senate Bill 430, which was drawn to set up a purchasing commission to determine the costs of caring for patients whose bills are paid by a third party. The Secretary stated that he and Dr. Spellman had attended the meeting and had made it plain that they could not be held as representing the Society until the action of President Bagg had been approved by the Council. The Secretary then moved that the Committee approve the action of the President in appointing such a subcommittee and that the program instituted by the Hospital Presidents' Association be approved. The motion was seconded and so voted.

Dr. Root's suggestion that the responsibility of detecting untreated latent cases of diabetes should be borne by the medical profession was read by the Secretary. It was then moved and seconded that this matter be referred to the Committee on Public Health. It was so voted.

Dr. Bagg then complimented Dr. John Conlin for his work on the Nolen-Miles bill and commented upon the dinners given to the Legislative Committee on Public Health by the Committee on Legislation of the Society. Dr. Bagg also stated that the Committee on Public Relations had approved the employment by Dr. Conlin of an assistant (paid for out of his budget) to help him in his fight for this valuable legislation. It was then moved that the Committee recommend that this action be subject to approval by the Committee on Finance. The motion was seconded and so voted.

#### *Committee on Legislation*

It was moved that this informative report be accepted. The motion was seconded and so voted.

#### *Committee on Publications*

It was moved that this informational report be accepted. The motion was seconded and so voted.

#### *Committee on Ethics and Discipline*

It was moved and seconded that this informational report be accepted. The motion was seconded and so voted.

#### *Committee on Membership*

The Treasurer made two corrections and it was moved that the report be accepted. The motion was seconded and so voted.

#### *Committee on Public Health*

The Secretary moved that the Executive Committee endorse the program for the study of heart disease by the Massachusetts Department of Public Health in co-operation with the United States Public Health Service and Harvard Medical School. This motion was seconded and it was so voted.

#### *Committee on Medical Defense*

It was moved that the report of this committee be accepted. The motion was seconded and it was so voted.

#### *Committee on Society Headquarters*

It was moved that the report of this committee be accepted. The motion was seconded and it was so voted.

#### *Report of the Treasurer*

It was moved that this report be accepted. The motion was seconded and it was so voted.

The Treasurer remarked that up to April 2 he had received \$113,414 in dues and \$2298 in nonresident dues. The Boston Medical Library had been paid \$22,380. Men had paid their dues by the first of March than had last year. Dr. Phippen said that the Library Trustees were very grateful and that they had started to do what they could to put the Library on a firm, working basis. He stated that the Library was being talked about all over the Commonwealth and that it is a place worth talking about.

#### *Committee on Expert Testimony*

This report recommended that the Committee be a standing committee and that it co-operate with the Committee on Ethics and Discipline and the Committee on Medical Defense. The committee would act as a clearing house for all cases in which ordinary or expert medicolegal testimony is concerned.

It was moved that the recommendations of the committee and the proposed amendment to the by-laws be approved. The motion was seconded. In the discussion it was brought out that by-law changes should be referred to a committee for that purpose. It was also brought out that so-called "listeners" would be used in cases concerning malpractice suits and that these "listeners" could be requested by counsel on either side and that there would be no fees paid to "listeners." The President called for a vote on the above motion, and it was so voted.

#### *Committee to Meet with the Massachusetts Hospital Association*

It was moved that the report be accepted. It was seconded and so voted.

#### *Committee on Postgraduate Medical Education*

It was moved that the report be accepted and the recommendations in it be approved. Dr. Bagg pointed out that the committee wants suggestions regarding its activities and is open minded about having clinics rather than didactic lectures. The motion was seconded and so voted.

#### *Committee on Medical Economics*

It was moved by the Secretary to accept the report and approve the committee's approval of the objectives of the National Physicians' Committee, but to disapprove of some of the methods employed by that organization. This motion was seconded, and it was so voted.

#### *Committee on Physical Medicine*

It was moved that the report be accepted. The motion was seconded and so voted.

#### *Committee to Make Recommendations for Directors of Blue Shield*

It was moved to accept the report. The motion was seconded and so voted.

#### *Committee on Veterans' Affairs*

The Secretary moved that this committee be discharged. The motion was seconded, and it was so voted.

#### *Committee on Benevolence*

The President remarked that when the Society dues were increased benevolence was to be considered and that he was authorized to appoint a Committee on Benevolence. Dr. O'Hara was good enough to act as chairman and the others accepting were Drs. Badger, Buck, Hubbard and Lund. It was moved to accept the report. The motion was seconded and so voted.

#### *Report of the Delegates to the House of Delegates of the American Medical Association*

It was moved to accept the report. The motion was seconded, and it was so voted.

#### *OTHER BUSINESS*

Dr. Bagg suggested that it would be in order to make a motion to have appointed a standing committee to consider and properly to write suggested changes in the by-laws and that the Committee on Council Rules might be expanded for this purpose. It was then moved that it be recommended to the Council that the Committee on Council

ules he made a standing committee on constitution and by-laws and council rules. This motion was seconded and was so voted.

The Secretary gave each member a copy of the changes in the by-laws already approved by the Council and written properly by Dr Hornor at the request of the President. The President stated that he would take it for granted that they were approved by the Executive Committee unless errors had been detected. No errors were noted.

Dr Bagg then stated that the Council had previously recommended a committee on emergency medical service and that he had received an acceptance from Dr Reginald Fitz, as chairman of such a committee.

Every state governor has been asked to set up a program to care for emergencies and the Massachusetts Medical Society committee would be expected to co-operate with the Governor's committee. It was moved that the recommendation of the American Medical Association to activate such a committee be approved. The motion was seconded and so voted.

The Secretary then stated that he had attended a meeting of the Council on National Emergency Medical Service at Chicago, April 5 and 6, at the request of Dr Bagg. The purpose of the meeting was to acquaint the doctors with the civilian-defense problems of an atomic war and to present a resolution against a special draft call for physicians.

Dr Bagg then presented a request from the Biological Laboratory Department asking for support from the Society in getting more money to maintain and continue their work in Rh blood testing. It was moved that the Executive Committee go on record as favoring the expenditure of public funds for the maintenance of this service. The motion was seconded and so voted.

A motion to adjourn was made, seconded and so voted.

H QUIMBY GALLUPE, *Secretary pro tempore*

## APPENDIX NO 4

### REPORT OF COMMITTEE ON PUBLIC RELATIONS

The meeting of the Committee was held at the Harvard Club at 6 00 p m on March 3, 1948. In addition to the representatives of thirteen district societies there were present President Edward P Bagg, who acted as chairman of the Committee, Dr Daniel B Reardon, president-elect, Dr H Quimby Gallupe, secretary of the Massachusetts Medical Society, and Dr John F Conlin, Director of Medical Education and Information.

The report of the Secretary, as printed in the advance notice of the meeting of the Council on February 4, 1948, was accepted.

A resolution was adopted that in the future the meetings of the Public Relations Committee be held at 5 00 p m on Wednesday, but not on the second Wednesday of the month.

Dr Charles D McCann, chairman of the Committee on Blue Cross-Blue Shield Problems, presented the following report.

A meeting of the Sub-committee of the Public Relations Committee was held at the Harvard Club, Boston, on January 28, 1948, with the following members of the Society present: Edward P Bagg, president, H Quimby Gallupe, secretary, Nicholas Scarcello (Worcester), Charles G Hayden, medical director of the Blue Shield, Albert A Hornor (Suffolk), Harold R Kurth (Essex North), and Charles D McCann (Plymouth).

The resolution of Dr Scarcello, "That the Blue Shield, through its employees, determine accurately an applicant's yearly earnings before issuing a policy and secondly, that these earnings be reviewed each year," was discussed and it was learned that a new system of notification was being tried out in Worcester District, and that if this new form proved satisfactory it would be extended into all the districts of the Society.

Dr Scarcello was satisfied with this progress.

The resolution of the Middlesex North District Medical Society, that the Blue Shield fees be increased, was discussed, and Dr Hayden reported that the Blue Shield lost about \$12,000 last year, but that if the fee table was right in 1939 the payments to physicians should be increased.

The situation, brought to light by Dr S A Dibbins, Middlesex North, whereby bills of patients hospitalized for diagnosis were paid in some cases and not in others, was discussed, and the Committee had the assurance of Dr Hayden that the condition would be corrected.

A report by Dr Scarcello, Worcester District, on the lack of information given members of the Society regarding Blue Cross and Blue Shield, was discussed, and Dr Hayden stated that the presidents of the district societies had been asked to appoint an administrative committee to work with the Blue Cross and Blue Shield, and through this committee better information would be available to the members of the Society.

The resolution of Dr Bernard Appel, Essex South, that "The medical staff of the Salem Hospital unanimously opposed the inclusion of professional services in the Blue Cross policy," was discussed, and the Committee voted to bring this resolution before the Public Relations Committee.

The meeting was adjourned at 10 15 p m.

ALBERT A HORNOR

HAROLD R KURTH

CHARLES D MCCANN, *Chairman*  
of the Sub-committee of the  
Public Relations Committee

This report was accepted by the Committee on Public Relations. A motion was then proposed and adopted that this committee be discharged, and that any future problems with reference to Blue Cross and Blue Shield be directly referred to the Executive Committee of the Council, which is the corporate body of the Blue Shield.

President Bagg reported to the Committee on Public Relations that at a Directors' Meeting of the Blue Cross he presented the report of the Special Services Committee. This report was approved by the Directors in principle, but it was felt that at present the special services of roentgenology, pathology, and anesthesiology must continue as part of the Blue Cross coverage to meet the competition of the regular insurance companies. It was felt that as the financial condition of the Blue Cross improved, more consideration could be given to the recommendations of the Special Services Report.

Dr Frederic Hagler, Hampden District, reported for his subcommittee. At present all calls and inquiries with reference to physicians that were being sent in to headquarters were being dispersed to the respective district secretaries. It was felt that this procedure was very unsatisfactory and at times quite confusing. As a result of this report Dr Nicholas S Scarcello, Worcester District, presented the following resolution.

That each member of the Public Relations Committee present to his District Society the problem of handling such calls and inquiries and that each District Society set up the machinery whereby such calls and inquiries could be satisfactorily handled.

When such an organization has been created the district secretary will so inform the secretary of the Massachusetts Medical Society of the procedure. This resolution was adopted.

President Bagg reported that there had been numerous complaints and criticisms that it was becoming increasingly difficult to obtain medical service during the night, on holidays, and over week ends. Dr James V McHugh offered the following resolution as a solution of this problem.

That the question of medical coverage for nights, holidays, and week ends be presented by each member of the Public Relations Committee to his district medical society, and that the district medical society initiate such programs as will satisfactorily solve this situation.

This resolution was also adopted.

President Bagg requested that the Committee on Public Relations recommend that he, as president of the Massachusetts Medical Society, be empowered to appoint a committee that would act in an advisory capacity in the procedure of transferring the Blood Bank from the Public Health Service to the Red Cross. This recommendation received unanimous support.

Mr Arthur G Rotch, a member of the Hospital Presidents' Association, had recommended the setting up of a council for the study of the cost of voluntary hospitals. He had requested President Bagge to appoint two representatives of the Massachusetts Medical Society to this council. The Public Relations Committee endorsed this request.

A booklet entitled "Our Bay State 'Dreyfus' Scandal and Snake Pits," by Lockwood Myrick, a member of the Massachusetts Legislature, has been sent to each member of the Public Relations Committee. It was the unanimous expression of the members that the secretary of the Public Relations Committee write Mr Myrick an appreciative letter of his report with reference to the state of mental hospitals in Massachusetts. The following letter was sent to Mr Lockwood Myrick by the Secretary.

As Secretary of the Public Relations Committee of the Massachusetts Medical Society I have been directed by that Committee to send you this letter of appreciation of the booklet which you have sent to each member of our Committee.

It is the opinion of the Committee that you have given much time, thought, and effort to this report concerning the state of mental hospitals in Massachusetts. One finds much information here which will serve as a basis for serious thought and consideration on the part of the medical profession.

Dr Howard F Root, Suffolk District, called to the attention of the Committee that according to a survey made by the United States Public Health Service there are probably close to a million undiscovered or latent cases of diabetes in this country. The American Diabetes Association, composed of a thousand physicians interested in diabetes, has appointed a committee to consider means of discovering these latent cases. This committee is considering a "Diabetes Week" for some time in November or December. It was Dr Root's opinion that it would be a great advantage if a concerted effort to carry out this program was made by proper publicity and local committees under the supervision of the medical profession. He furthermore felt that it was the responsibility of the medical profession to seek out these untreated latent cases of diabetes rather than to have lay organizations or public health officials initiate such a program. The Public Relations Committee endorsed Dr Root's opinion.

Dr John F Conlin, Director of Medical Education and Information, stated that he had complete confidence in the eventual passage of the Nolen-Miles Pound Bill.

He stated that it would soon be necessary for him to have an assistant to help him prepare some of the special material that is necessary in the proper function of his office as Director of Medical Education and Information. This part-time public relations assistant would require a supplementary budget of approximately \$1500 a year. The Committee recorded itself as endorsing this recommendation.

The meeting adjourned at 9 30 p m

HAROLD R KURTH, Secretary

## APPENDIX NO 5

### COMMITTEE ON LEGISLATION

Since January 1, 1948, the Committee on Legislation has reviewed and taken action on seventy-nine bills coming before the State Legislature this year. In general it opposed any legislation that, in its opinion, would lower the standards of medical care in the Commonwealth, or would transfer the responsibility for the treatment of the patient from a local to a state level. The Committee observed that, whereas it could approve of a number of bills in principle, many were so loosely drawn as to permit unpredictable expansion and possible participation of the state in the field of personal health services for individuals.

The Sub-Committee on National Legislation continued to study bills coming within the scope of its special interest. It approved the objectives of the National Science Foundation Act of 1948 (HR4852), preferring, however, that the director of the Foundation be approved by the President, by and with the consent of the Senate from a panel of nominees selected by the members of the Foundation.

Attention was called to S 2189, a bill to "assist the State in the development and maintenance of local public health units and for other purposes," drawn up by the Association of State and Territorial Health Officers. This bill has been commended to the president of the Society by the Massachusetts Commissioner of Public Health. Whereas the American Medical Association has recorded its approval of federal aid to assist in the development of local health units under point two of the Ten-Point National Health Program, the Board of Trustees have placed emphasis on the principle that medical care and treatment are not properly functions of public-health units. The Committee, in reviewing S 2189, approved of the broad principles of the bill, but believed that it should contain restrictions that would make it clear that the Surgeon-General may not, by regulation, require that local health units engage in treating the sick. Section five (B) (4) permits the surgeon-general of the Public Health Service, by regulation, to prescribe the "types of health services" that shall be considered basic health services.

On March 3, 1948, Senator Saltonstall called hearings on S 1290. This bill calls for the development of school health services defined as being "services for the prevention, diagnosis, and TREATMENT of physical and mental defects, and conditions of school children." The bill calls for no means test, and would use public funds for services to those unable to pay their own way. The Committee on Legislation was not given sufficient notice to consider this bill, and it is mentioned in this report only to call it to the attention of the Society.

GEORGE R DUNLOP, Chairman

## APPENDIX NO 6

### COMMITTEE ON PUBLICATIONS

*The New England Journal of Medicine* and the Massachusetts Medical Society sustained a great loss in the death of Dr Robert N Nye, on September 10, 1947. Dr Nye had been editor of the *Journal* since January 1, 1937, so that his tenure of office was nearly eleven years. When the Massachusetts Medical Society purchased the *Journal*, Dr Walter P Bowers became the editor. He managed it so well that, when he relinquished his responsibilities to Dr Nye, it had already become recognized as a journal of outstanding merit. Dr Nye built upon the solid foundation that Dr Bowers had established, and, at the time of his death, the *Journal* was one of the best medical weeklies in the country. Dr Nye brought to the duties of editor a keen mind, an acute business sense, a critical, scientific judgment and a commanding personality. He was devoted to the best interests of the *Journal* and the Massachusetts Medical Society. His superior abilities are evidenced by the progress the *Journal* made under his editorship.

On January 1, 1937, the total circulation of the *Journal* was 6131, and only 1006 copies went to others than members of the Massachusetts Medical Society. At the end of 1947, 25,001 copies of the *Journal* were distributed—19,241 to others than members of the Society. This is a clear demonstration of the fact that the *Journal* is now a national medical publication and that its high quality is appreciated beyond the confines of the Society. In 1936, the last year before Dr Nye became editor, the income from advertising was \$19,984.65, in 1947, income from this source was \$117,804.23. The total operating expense for 1936 was \$58,682.56, and for 1947, \$240,630.54. In 1937, the Society contributed \$20,500 toward the publication of the *Journal*—a cost of approximately \$4.00 per member. For the past three years the *Journal* has been published without expense to the Society, and the *Journal* has paid to the treasury of the Society the sum of \$31,800. This is a record of which the *Journal* and the Society may well be proud. The Committee on Publications pays affectionate and admiring tribute to Dr Nye.

The Committee was confronted with a grave responsibility in appointing a new editor of the *Journal*. It was fortunate, in the interim, that Miss Davies' devotion and mastery of all the details of publication, and Mr O'Leary's editorial skill, made possible the uninterrupted publication of the *Journal*. We appreciate, also, the loyalty and unselfish service of the office staff during this period. Dr Nye, when he was taken ill, had asked Dr Garland to be acting

ditor during his absence, and he continued in that capacity, it the Committee's request. Dr Garland performed this interim service at a real personal sacrifice, and the Committee is appreciative of this. The Committee, after due consideration, appointed Dr Joseph Garland as editor, and he assumed his duties on November 1, 1947. Dr Garland has been associated with the *Journal* for many years as a member of its editorial board and as an editorial writer. The Committee is grateful to Dr Garland that he was willing to accept the editorship. It involved the relinquishment of his private practice and a complete readjustment of his activities. The Committee is confident that the *Journal* will continue to go forward under his guidance and congratulates itself and the Society upon its good fortune.

During the year 1947 *The New England Journal of Medicine* continued to expand. As of the issue of December 25, *Journals* were sent to 14,375 regular subscribers, — a gain of 2301

upon prior to January 1, 1947, became effective. These changes should result in a moderate increase of income, which will help to offset the increased costs of publication.

During the year the Editorial Board has considered a total of 306 manuscripts, of which 188, or 64 per cent, were accepted. The corresponding figures in 1946 were 292 and 201, and, in 1945, 203 and 129. The number of text pages increased from 1834, in 1946, to 2000 in 1947.

New, machine-coated paper stock has become available and will be put into use as soon as the old stock is exhausted. This will make a great improvement in the appearance of the *Journal*, particularly in the reproduction of cuts.

The outlook for 1948 appears good, although no one can predict with certainty what economic conditions may prevail. An abundance of manuscripts seems assured, which permits the Editorial Board to exercise even higher standards of acceptance than formerly.

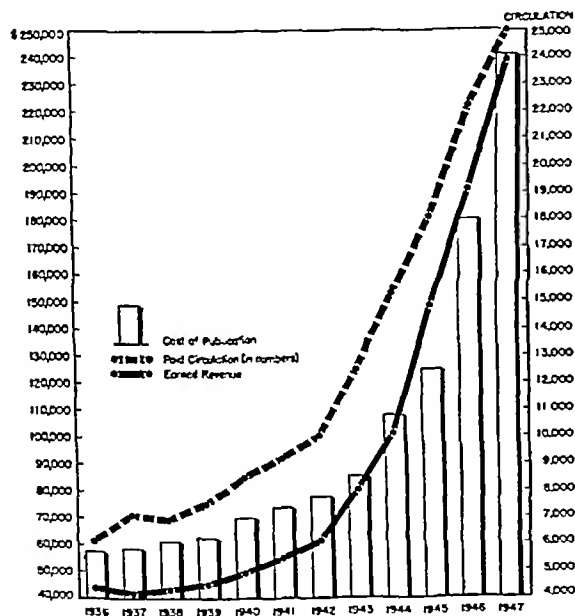
On January 1, 1948, a pension plan for employees of the *Journal*, which had been considered for a long time, came into operation for three individuals. Other members of the staff will be added to the plan as they become eligible. The expenses of the *Journal* will be increased about \$3500 yearly. This amount will be modified later by dividends and additional pensions.

The Registry of Fellows was published in 1947 and distributed to Members of the Council and to the Officers of District Medical Societies. The cost was \$1,515.31.

A summary of the financial transactions for the year is appended to this report. The accounts have been audited by Hartshorn and Walter. Their report and the detailed financial report are in the hands of the Treasurer of the Society.

OLIVER COPE  
JOHN FALLON  
JAMES P. O'HARE  
CONRAD WESSELHOEF  
RICHARD M. SMITH, *Chairman*

## NEW ENGLAND JOURNAL OF MEDICINE



over 1946, 4081 student subscribers, — a gain of 779 over 1946, 5770 members of the Massachusetts Medical Society, — a gain of 390, 251 "once-a-month" subscribers from the New Hampshire Medical Society, 219 "regular" subscribers from the New Hampshire Medical Society, 172 exchanges, 58 complimentary recipients and 75 advertisers, — a total circulation of 25,001, as compared with 21,384 at the end of 1946.

The publication cost of the *Journal*, including all charges for printing, binding, mailing and stock, was \$165,062.16 in 1947, as compared with \$120,531.42 for 1946. The total costs were \$240,630.54, as compared with \$180,327.86 for 1946. The revenue from advertising was \$117,804.23 in 1947, as compared with \$93,345.21 in 1946. The revenue from subscriptions in 1947 was \$106,916.22 as compared with \$84,792.33 in 1946. The total revenue for the year was \$224,720.45 as against \$188,140.52 for 1946. There was a net loss of \$1081.61 in 1947 as compared with a net profit of \$11,277.71 in 1946. A new item of expense was added in 1947, amounting to \$3684.78 for policies under the new Employee's Pension Plan.

The \$5000 appropriated by the Society for the *Journal's* use, which had been expended in the purchase of paper, was returned to the Treasurer at the end of the year.

On January 1, 1948, subscription rates were increased to \$7.00 per annum for regular subscribers, and \$4.00 for New Hampshire regular subscribers and for students. Also, on that date, the increased advertising rates determined

## ABSTRACT OF AUDITOR'S REPORT

Current assets	
Cash	\$5 671 50
Accounts receivable	10 126 21
Capital assets	1 914 28
Total	\$17 711 99
Current liabilities	644 35
Surplus	\$17 067 64
Expenses	
Publication of <i>Journal</i>	\$165 062 16
Publication of reprints	10 208 04
Office and other salaries	40 900 03
Commissions fees etc.	13 677 34
Office and sundry expense	7 098 19
Pension Fund	3 684 78
Total	\$240 630 54
Revenue	
Advertising	\$117 804 23
Engraving	609 69
Reprints	10 456 36
Subscriptions (other than M. M. S.)	106 916 22
Miscellaneous	3 762 43
Total	\$239,548 93
Net Loss to M. M. S.*	\$1 081 61

\*No contribution from Society

## APPENDIX NO 7

### COMMITTEE ON ETHICS AND DISCIPLINE

The work of the Committee during the past year has been varied and interesting. The usual number of complaints by laymen against physicians are of the usual type, overcharging, improper treatment and refusal to attend emergencies. These have been considered and resulted in clearance of the doctors involved. A third of the complaints were based on the refusal of doctors to attend an emergency. Following the report of the findings of the Committee to the plaintiffs several letters were received, each one closing with the comment "another vote for socialized medicine."

Seventeen requests for advice regarding ethical procedure have been received. These varied from questions concerning newspaper insertions of notices announcing opening of

office for practice to questions about the doctor's duty to his patient while on the witness stand. Two inquiries recently received asked, "Was it ethical for an expert witness to charge ten per cent of the total sum received as damages in a tort case as his fee for giving testimony in the plaintiff's behalf?" and "Was it ethical for a doctor, having referred a patient to a surgeon who sent his bill and was paid, and the doctor having sent his bill and been paid, to ask the patient for an additional amount equal to fifty per cent of the surgeon's bill for referring the case?" Most of these inquiries were answered by the Chairman, the answers being referred to the Committee for approval and in many instances a letter was received from the inquiring doctor thanking us for our advice.

While these complaints and inquiries constituted a greater part of the work of the committee, there have been numerous complaints of more serious nature. These resulted in conversations with the chairman and hearings before the full Committee and were decided by the Committee.

A group of cases were of such importance that they should be mentioned here briefly.

First, a complaint was received against a fellow for deliberate violation of Section 4 of Chapter 3 of the Principles of Medical Ethics of the American Medical Association. Investigation showed that the fellow was guilty as charged. This is considered a more serious infringement as the fellow had been advised previously by the Committee regarding his procedure in these matters. He was severely reprimanded by the Committee and was told that his future connections with the Society would depend upon his subsequent actions in this regard. The case was placed on file.

Second, two complaints against fellows of sex perversion were received. The first fellow was convicted in a Court of lewd practices. After thorough investigation, the Committee decided that the defendant was more sinned against than sinning. He was cautioned by the Committee and the case placed on probation, pending any further complaint. The second complaint against a physician was of improper actions during the course of an examination. The doctor denied the truth of any such accusations. Owing to the lack of corroborative evidence on either side, no action was taken. This case was also placed on file.

Third, a complaint was received from a certain welfare society in a neighboring city charging two doctors with having entered into a conspiracy to aid and abet the adoption of an unborn child under "black market" methods. The director of the society appeared and claimed that this practice had been going on for some time in her city and was viewed by her society with a good deal of concern. After consultation with an attorney she brought it to our attention. A hearing was given to her and to the parent of the child. The doctors in question were called in consultation with the chairman and by him referred to the full Committee. Following the hearings of the two doctors before the Committee, it was their unanimous opinion that the doctors had been unethical and were guilty as charged. They were so informed. The penalty for this act was taken under advisement. Following this meeting, subsequent investigation brought forth evidence that one of the doctors, attempting to intimidate the plaintiff, brought threats against her that would definitely violate Section 1 of Chapter 2 of the Principles of Medical Ethics. The other doctor was found to be definitely guilty of attempts at extortion. A second discussion was carried out at the December meeting of the Committee, and the decision of the Committee again postponed to the January meeting. At the meeting on January 24, the matter was again discussed, and it was unanimously voted by the Committee that the two erring fellows be asked to resign from the Society. A request to this effect was sent to each of them and their resignations followed. These resignations were sent through the usual channels to the Committee on Membership for action, and the case was considered closed.

In closing we wish to call attention once again to the number of complaints received from disgruntled laymen concerning the attitude of the members in responding to emergency calls. This is not restricted to members of the

Massachusetts Medical Society. It seems to be prevalent throughout certain parts of New England. It is the duty of all of us to see that no action on the part of any of us should detract from the honor and dignity and usefulness of the Society.

RALPH R. STRATTON, *Chairman*

## APPENDIX NO 8

### COMMITTEE ON PUBLIC HEALTH

As secretary of the Public Health Committee of the Massachusetts Medical Society, I herewith submit the resolution of that Committee that "we endorse in principle and support" the following Heart Disease Epidemiological Studies to be conducted by the Massachusetts Department of Health, Harvard Medical School, and the United States Public Health Service. Dr. Vlado Gettung, Commissioner of Public Health, has requested such endorsement. These studies have the approval of the New England Heart Association. The Executive Council of the New England Heart Association constitutes the Advisory Committee to the conducting the program.

The first of the two studies referred to above is known as "The Heart Disease Epidemiology Study." This will consist of examination and long-term follow-up study of a sample adult population in the city of Framingham to detect what will be considered an average incidence of heart disease. Arrangements have been completed with the Framingham Union Hospital, the physicians in the community and the local board of health for co-operation. Findings in individual cases will be communicated to the family physician. The duration of the study will be approximately five years.

The second aspect of the study is known as "The Public Health Aspect of Heart Disease." Its objective is to find ways further to reduce cardiovascular disease and conserve cardiac function in the general population. The Board of Health of Newton has invited the Department of Public Health to use the City of Newton for this purpose. It is planned to develop the Public Health Nursing aspect, morbidity and mortality reporting and health education. It is also planned to promote the general study of heart disease and control methods in the community by such agencies as the Newton Medical Club, Newton-Wellesley Hospital, Newton Health Department, Visiting Nurses Association, Social Welfare Groups and so forth. The proposed duration of this study, which will be limited to heart disease among adults, is three years. It is recommended that the Council, at its next meeting, approve endorsement of the above by the Society.

JOHN J. POUTAS, *Secretary*

## APPENDIX NO 9

### COMMITTEE ON INDUSTRIAL HEALTH

This report is informational only for the reason that the chief efforts of the Committee during the year were devoted to the convention or annual meeting of several professional groups held in Boston in the latter part of March and early April. It seemed impractical to prepare the Committee's report on or before March 15, 1948, the deadline for publication in the circular of Advance Information for the Council. It seemed desirable to delay the report to evaluate the work of the Committee.

In September, 1947, the Committee was asked by and agreed with the officers and directors of the American Association of Industrial Physicians and Surgeons and affiliated groups to function as the Local Arrangements Committee and to prepare the program for the annual meeting of the Association, to be held in Boston from March 27 to April 4, 1948, inclusive, and to co-operate with the several committees representing the Conference of Governmental Hygienists, American Association of Industrial Hygienists, American Association of Industrial Dentists and American Association of Industrial Nurses.

The scientific meeting of the Association of Industrial Physicians and Surgeons began with a clinical conference at the Massachusetts General Hospital on Tuesday morning,

March 30, continuing on that afternoon at the Boston City Hospital and thereafter at the Hotel Statler on the following three days

Many members of the Massachusetts Medical Society graciously gave their time and talent to participate in the program, and their presentations were very well received

There was a total registration of 1652 persons. In attendance were physicians and nurses engaged in or interested in industrial health from nearly every state in the Union, many from Canada and a few from foreign countries

It has been stated verbally over and over again and reported by uncounted letters that the meeting was an outstanding success

The Committee expresses its appreciation and its gratitude to the members of the Society who helped to make this

national meeting on industrial health the success that it has been acclaimed

Two of the members of the Committee with the Chairman represented the Society at the Congress on Industrial Health of the American Medical Association at Cleveland in January. That also was a successful meeting, as one would expect it to be under the management of Dr. Carl M. Peterson, secretary of the Council of Industrial Health of the American Medical Association

Other activities of the Committee were confined to offering suggestions and help to a few industrialists interested in organizing medical services in their plants, meeting with industrial nurses concerning their particular problems and directing physicians interested in industrial work toward potential positions

DANIEL L. LYNCH, *Chairman*

## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

EDITH E. PARRIS, *Assistant Editor*

#### CASE 34301

##### PRESENTATION OF CASE

*First admission.* A fifty-eight-year-old woman was admitted to the hospital complaining of pruritus and jaundice

She was perfectly well until five months before admission, when she first noted persistent generalized pruritus. Two months later the stools became lighter, and the urine became "tea colored." Two and a half months before admission the pruritus became intense, and icterus of the skin and scleras appeared. Her appetite became poor after the onset of jaundice, but in about two weeks it returned to normal. There was no abdominal pain, back pains, chills or fever. Except for an occasional sensation of epigastric pressure following meals, she had had no gastrointestinal symptoms until the onset of the present illness.

There was no history of alcoholic intake, ascites, intolerance to fatty foods or previous jaundice and no history of drug habits or blood or plasma transfusions. One month before the onset of pruritus she visited relatives, two of whom were in bed with jaundice (allegedly, "infectious hepatitis").

Physical examination showed the skin and scleras to be icteric. There was slight palmar erythema, which was prominent at the fingertips. About the cheeks, neck, arms, trunk and legs were numerous "pea-to-bean-sized, soft, intracutaneous cysts." Numerous café-au-lait spots were present over the trunk bilaterally. No spider angiomas were present.

The liver edge was palpable three fingerbreadths below the costal margin and was smooth and nontender. The spleen could not be felt.

The temperature was 98.6°F, the pulse 80, and the respirations 20. The blood pressure was 125 systolic, 80 diastolic.

Examination of the blood revealed a white-cell count of 7700, with a normal differential. The hemoglobin was 12 gm.

The urine was normal, no bile was present. Urinary urobilinogen varied from 0.4 to 1.8 Ehrlich units. The stools were brown, formed and guaiac negative. The prothrombin time, which was 55 seconds, promptly returned to normal after one dose of vitamin K. The van den Bergh reaction was 2+ mg per 100 cc direct, 2.7 mg indirect. The cephalin-flocculation test was + in twenty-four and forty-eight hours. The serum albumin was 4.12 gm, and the globulin 2.56 gm per 100 cc. The alkaline phosphatase was 12.5 units. A week later the van den Bergh reaction was 1.3 mg per 100 cc direct, 1.8 mg indirect. The cephalin-flocculation test was negative, and the alkaline phosphatase was 22.9 units per 100 cc. A bromsulphalein test demonstrated 35 per cent retention of the dye in forty-five minutes.

X-ray examination of the chest and a gastrointestinal series were negative. There was no evidence of widening of the duodenal loop. The gall bladder did not concentrate the Graham dye, and no opaque stones were seen.

During the three weeks of hospitalization the patient was entirely afebrile and felt exceptionally well except for mild pruritus. Jaundice gradually subsided clinically and by chemical tests.

*Second admission* (two months later). At home the patient was on a high-vitamin, high-calorie, high-carbohydrate diet, with pyribenzamine for the pruritus. For about six weeks she felt well, except for pruritus, which was most severe at night. She gained 6 pounds. However, after this interval slight jaundice reappeared, the urine became dark, and she was readmitted to the hospital.

On examination the scleras were muddy and the skin deep tan. She complained of severe pruritus. Physical signs were unchanged since the first ad-

mission The prothrombin time was normal, the thymol turbidity 10 unit per 100 cc, thymol flocculation negative, cephalin flocculation negative in twenty-four hours and ++ in forty-eight hours The van den Bergh reaction was 2.6 mg per 100 cc direct, 3.7 mg indirect A bromsulfalein test demonstrated 41 per cent retention of the dye

On the fifth hospital day an operation was performed

DIFFERENTIAL DIAGNOSIS

DR EARLE M. CHAPMAN There was no history of blood or plasma transfusions We can exclude homologous serum jaundice by that statement

We do not know whether the relatives who were sick in bed with "infectious hepatitis" had Weil's

hepatitis, biliary cirrhosis and an obstructive process due to a silent stone in the common duct, to stenosis of the duct or to tumor

We are presented with a wealth of laboratory data, and yet this evidence does not point clearly to which one of the above horses is going to win the race I think it is fair to say that no one can make a positive diagnosis in such cases of jaundice by means of laboratory technics We are still searching for a reliable test that will differentiate the mildly or intermittently obstructive type of jaundice from the jaundice caused by intrinsic liver cell damage In this case the clinician first made a diagnosis of hepatitis and so allowed the patient to go home Then, when she became more jaundiced with bile in the urine and yet gained weight,

TABLE 1 Laboratory Findings in Favor of Portal Cirrhosis or Hepatitis and Biliary Cirrhosis, with or without Obstruction

DISEASE FAVORED	ALKALINE PHOSPHATASE	VAN DEN BERGH REACTION		BROMSULFAL- EIN RETENTION	CEPHALIN FLOCCULATION	OTHER DATA
	units/100 cc	DIRECT mg/100 cc	INDIRECT mg/100 cc	%		
Portal cirrhosis or hepatitis	12.5	2.4	2.7	35 and 41	++ in 48 hr	Dark stools
Biliary cirrhosis with or without obstruction	22.9	2.4	2.7	35 and 41	—	Low urobilinogen prompt response to vitamin K

disease, infection due to *Leptospira canicola* or other infectious hepatitis

One wonders if the "intracutaneous cysts" were spread out and also in the liver That is a rarity I would not put past the Pathology Service to spring on me

May we see the x-ray films?

DR STANLEY M. WYMAN This is a single postero-anterior film of the chest and shows no gross evidence of disease in the lung fields or in the heart The diaphragm is not remarkable The film of the stomach and duodenum shows a grossly normal-appearing stomach The duodenal cap is better seen on several spot films and is probably not remarkable There is a strong suggestion on several spot films of a pressure defect on the medial aspect of the wall of the second portion of the duodenum at about its midpoint

DR CHAPMAN I would like to interrupt at this point to say that such an observation is not recorded in the protocol

DR WYMAN I may be wrong, but I think there is a small pressure defect on the wall, present in almost all the films The Graham test shows no evidence of excretion of contrast substance, and I see no opaque stones There is some dye in the stomach, which might explain why the gall bladder did not excrete the dye

DR CHAPMAN The differential diagnosis here appears to be one of the most difficult ones in clinical medicine — namely, between infectious

he decided that there might be biliary obstruction Surgical procedures are then the only way to make a positive diagnosis by obtaining a liver biopsy or exploring the whole biliary tree, or both This may occasionally surprise all hands by effecting a brilliant result by removal of a silent stone in the common duct or alleviating the chief symptom of itch by T-tube drainage in cases of so-called xanthomatous biliary cirrhosis

Unfortunately, the Graham test is of little aid in such a case The liver cell is injured, and so the iodine dye cannot get through into the biliary passage in sufficient amounts to render the gall bladder opaque, and we have learned that about 20 per cent of gallstones do not cast a shadow

Let us make a scoreboard of the laboratory tests and see which side is favored (Table 1) All the tests indicate damaged liver cells, and the low total protein indicates that the duration of damage was long enough to interfere with the blood protein manufacture But what we would like to know is whether the injury is from back-pressure or intrinsic disease

The first consideration is the urobilinogen test. Damage to the liver cells causes them to lose the ability to convert urobilin and urobilinogen into bile pigment, with the result that these bodies accumulate in the blood and are excreted in the urine This change precedes the appearance of actual bile pigment by a considerable time. Watson<sup>1,2</sup> applied this color reaction to this same

differential diagnostic group and found that in jaundice due to stone there was no increase in the urinary urobilinogen *except* in the presence of a complication such as acute cholecystitis, cholangitis, obstructive cirrhosis or severe anemia. However, in hepatitis a marked increase in urinary urobilinogen was usually found. In this case the low value favors obstructive jaundice.

Now a word about the alkaline phosphatase reaction. Roberts,<sup>3</sup> an Englishman, was the first (in 1933) to note an increase in plasma alkaline phosphatase in some cases of obstructive jaundice. A study of the level of this enzyme was originally put forward as a means of distinguishing obstructive from nonobstructive jaundice. It tends to be higher in biliary cirrhosis or obstructive jaundice than in hepatitis. Here we have a slightly elevated value at first favoring hepatitis and later a higher figure in favor of obstruction.

We have all been disappointed by the failure of the van den Bergh reaction to point a diagnosis for us. In obstructive jaundice the pigment in the plasma is mainly of the direct-reacting type, accompanied by an appreciable amount of the indirect-reacting type. In hepatitis, and in hepatitis with cirrhosis, both kinds of bilirubin are found in proportions resembling that obtained in obstructive jaundice. A positive direct van den Bergh reaction may not differentiate obstructive from nonobstructive jaundice. It must be kept in mind that all serums giving a direct reaction also give a positive indirect reaction, but the reverse does not always hold true. Thus, I have put the van den Bergh test in both columns in Table 1.

The cephalin-flocculation test was at first negative and later slightly positive, so that this test is inconclusive, as is the bromsulfalein test. The dark stools obviously favor a nonobstructive process, whereas the prompt response to vitamin K is frequently seen in obstructive jaundice.

Thus, the laboratory evidence finishes in a dead heat. The poor doctor has to fall back on his hunch, his horse sense or his clinical experience. And as I look over this situation, I am going to call it biliary cirrhosis. If the patient had had xanthelasma or high cholesterol value I would favor the rare nonobstructive form. As it is, I hope that a common-duct stone was discovered. And why do I say this? Because of two points — she maintained a good appetite and gained weight despite a jaundice that waxed and waned.

I shall never forget a patient under the care of experts, who pointed out that all the tests indicated clearly that the poor man had a hopeless cancer of the head of the pancreas, and there was nothing to do for him. When Dr. Arlie V. Bock visited and from a distance of thirty feet saw the man devouring a huge meal, he simply said, "No man with cancer would eat like that. We will explore him

for stone." The patient had a huge gallstone wedged in the common duct.

DR. EDWARD L. YOUNG: What is the advantage of a liver biopsy?

DR. DANIEL ELLIS: In this case a liver biopsy was not done because there was a feeling that the patient had either nonobstructive biliary cirrhosis or obstructive jaundice and that we would consequently not have been able to differentiate the cause in the biopsy specimen. If the diagnosis of infectious hepatitis had been entertained, it would have been worth while to do a biopsy.

I would like to take issue, in a friendly way, with Dr. Chapman. I realize that he was listing the laboratory findings and discussing the figures from an academic standpoint. I do not believe however that we can let the laboratory findings go without saying that here is a case in which obstruction played some part, as indicated by the laboratory findings. I do not believe that there is anything in the reports given that would really allow us to make a diagnosis of infectious hepatitis, and Dr. Chapman arrived at the same conclusion. The important thing about the alkaline phosphatase is the increase in titer between the two determinations. An alkaline phosphatase of 12.5 units is considered high in this laboratory. Usually with hepatitis one finds it below 10 units. The fact that at one time it was 12 and the next time 22 units is in favor of obstructive jaundice or so-called biliary cirrhosis. The van den Bergh reaction cannot be counted on, as Dr. Chapman has pointed out. In the presence of jaundice the bromsulfalein test does not tell much. The cephalin-flocculation test mentioned in the discussion is essentially normal. So that all in all, one should not have arrived at a diagnosis of infectious hepatitis.

As to why this patient was allowed to go home, I find myself in the position of not having the old record here so I do not know what I wrote at that time. So far as I recall, Dr. Fairlie and I saw the patient on the ward at the request of the Service, and we thought that she had obstructive jaundice of some kind and that there was a possibility that she had so-called biliary cirrhosis. We thought that we would lose nothing by sending her home and following her closely in the Out Patient Department for a limited period. We set the maximum limit of time for her to stay away at four weeks. At the time of discharge the jaundice had disappeared, and there seemed to be so much improvement clinically that we let her go. We saw her four weeks later, at that time the improvement had continued. The itching was a very minor problem four weeks after discharge.

DR. CHAPMAN: Do you attribute that to the pyribenzamine?

DR. ELLIS: I do not know. It does help some patients.

DR C W FAIRLIE The patient felt that pyribenzamine definitely helped her although she did not continue it.

DR ELLIS At the end of four weeks we felt justified in continuing the observation. When she came in three weeks later there was no question that she had jaundice again, and the itching had returned. Dr Fairlie saw her and thought that she should be admitted for exploration.

DR CHAPMAN The whole complexion of this was changed by the surprise finding brought out in the x-ray film. In the light of that finding one has to listen to the X-ray Department very closely. This obstruction is demonstrated very nicely on this film, even though the laboratory evidence is not conclusive. The only thing that could produce this is cancer of the head of the pancreas.

DR WYMAN I have seen a stone wedged in the ampulla produce a similar picture.

DR BENJAMIN CASTLEMAN If this was a tumor how do you account for the intermittent jaundice?

DR ELLIS It is a common belief that cancer does not lead to intermittent jaundice. That is not true. Time and time again in the presence of common-duct stone the jaundice waxes and wanes and one should not be misled by the fact that the patient's symptomatology is relieved for a short time only to recur.

#### CLINICAL DIAGNOSIS

Obstructive jaundice

#### DR CHAPMAN'S DIAGNOSES

Common-duct stone

Cancer of the head of the pancreas (after additional x-ray interpretation)

#### ANATOMICAL DIAGNOSIS

*Adenocarcinoma of duodenum at ampulla of Vater*

#### PATHOLOGICAL DISCUSSION

DR CASTLEMAN Intermittent jaundice is very often a clue in locating the site of the tumor because it is well known that tumors at the ampulla of Vater become necrotic and a great deal of the necrotic material sloughs out, relieving obstruction for a time. That is what was found in this case—a tumor of the duodenum beginning at the upper edge of the ampulla of Vater and extending for 3 cm into the pancreas, obstructing, of course, the common bile duct. The tumor was a well differentiated adenocarcinoma, but it had invaded the entire wall of the duodenum. A Whipple operation was performed, and the patient is still on the ward. How is she at present, Dr Fairlie?

DR FAIRLIE She is well.

DR CASTLEMAN There were no metastases to the regional lymph nodes.

DR CHAPMAN Did you do a biopsy of the liver?

DR CASTLEMAN The liver looked all right to the surgeons. The common bile duct, removed with the specimen, was markedly dilated, measuring 3 cm in circumference in some places, further evidence that it was a fairly slowly growing tumor.

DR CHAPMAN Then the X-ray Department actually made the diagnosis.

DR ELLIS They did not make the diagnosis when they had the chance. Dr Wyman just made it this morning.

#### REFERENCES

- 1 Watson C. J. Studies of urobilinogen: urobilinogen in urine and feces of subjects without evidence of disease of liver or biliary tract. *Arch. Int. Med.* 59:196-205, 1937.
- 2 Idem. Studies of urobilinogen: per diem excretion of urobilinogen in common forms of jaundice and diseases of liver. *Arch. Int. Med.* 59:205-231, 1937.
- 3 Roberts W. M. Blood phosphatase and van den Bergh reaction: differentiation of several types of jaundice. *Brit. M. J.* 1:37-738, 1933.

#### CASE 34302

#### PRESENTATION OF CASE

A twenty-one-month-old girl entered the hospital because of respiratory distress and cyanosis. Pregnancy had been uneventful, and delivery normal. The first year of the child's life was unusual only in that the birth weight was not regained until two months of age and that during the first winter she suffered numerous colds. These were characterized by three to four days of coryza and dry cough. The weight at one year of age was 18 pounds, and development appeared to be entirely normal. At about this time, however, the child ceased gaining weight, and the stools became foul smelling, although they were not described as ever being bulky, fatty or foamy. Four months after admission the appetite, which had previously been excellent, began to fail, and the child lost her bright, alert personality. Vomiting, abdominal pain, constipation, diarrhea and melena were all denied. Rectal prolapse occurred on two occasions. Respiratory difficulty, consisting of a chronic, dry cough, also appeared approximately one year before admission, and four months before admission a chest x-ray film was said to have shown chronic bronchitis. For this sulfadiazine was given—two tablets each day until the time of admission. Two or three weeks before admission the cough became productive of whitish phlegm, dyspnea on exertion developed, and grunting noises in both phases of respiration were noted. During the three days before admission respiratory difficulty increased, and the child became cyanotic on one occasion. Physical examination showed a poorly nourished, pale, apprehensive girl. The throat contained a thick, whitish, mucoid secretion. The intercostal spaces retracted on inspiration, as did the lower border of the rib cage. Expiration was grunting. The chest was hyper-resonant to percussion. Fine

dry rales were heard throughout on inspiration, and squeaks and rhonchi throughout on expiration. The heart was unusual only in that the left border of cardiac dullness could not be percussed. The liver edge was felt three fingerbreadths below the costal margin.

The temperature was 101°F, the pulse 150, and the respirations 60.

The hemoglobin was 12.2 gm, and the white-cell count 13,800, with 51 per cent neutrophils. The urine showed an occasional white cell. A stool was described as brown, soft, greasy and foul smelling. Tuberculin and blood Hinton tests were negative. Cultures of the nose and throat grew abundant colonies of *Staphylococcus aureus*. An x-ray film of the chest showed widespread infiltrative changes in all lobes with areas of consolidation and atelectasis interspersed. Both leaves of the diaphragm were low. A vitamin A tolerance test gave the following figures: fasting levels in the serum, 0.2 unit of vitamin A per cubic centimeter (normal 0.4 to 1.0 unit), and 0.2 unit of carotenoids per cubic centimeter (normal 1.0 to 3.0 units), after oleum percomorphum (0.1 cc per kilogram of body weight) 0.7 unit of vitamin A per cubic centimeter and 0.3 unit of carotenoids per cubic centimeter. A duodenal drainage was not done.

The patient was given penicillin, sulfadiazine, oxygen and intravenous fluid. The temperature rose daily to 100 to 101°F, the pulse varied from 110 to 188, and the respiratory rate from 30 to 60. Respiratory difficulty increased. Terminally, circulatory collapse appeared. A transfusion was given, but the beneficial effect was only temporary, and the patient died on the fifteenth hospital day.

#### DIFFERENTIAL DIAGNOSIS

DR NATHAN B. TALBOT: I should like to take a chance and guess at the outset that this patient had pancreatic fibrosis. That condition is well described in an article by Blackfan and May,<sup>1</sup> published in 1938 and in another article by May and Lowe<sup>2</sup> reported in 1948. If my guess is wrong, at least these are good references to have at hand.

The symptoms and signs to be reviewed may be divided into three groups: gastrointestinal complaints, respiratory symptoms and metabolic changes.

Regarding the gastrointestinal signs it is noteworthy that this child failed to regain her birth

weight on time and even after the neonatal period gained only at an abnormally slow rate. In addition, there was during the neonatal period a diarrhea, with green stools. Somewhat later the stools were described as putrid. Such stools are suggestive of steatorrhea. Though we do not have objective measurements of stool-fat content, we have measurements of the vitamin A and carotenoid concentration values in the serum. Both of these were abnormally low. Moreover the vitamin A level failed to rise normally following a standard dose of material containing vitamin A. Since vitamin A and carotene are lipid-soluble materials, failure of normal absorption of these substances suggests failure of fat absorption and hence is consistent with the thought that there was steatorrhea. Steatorrhea such as this child presumably had can be caused by a variety of conditions as well as by pancreatic fibrosis. Thus, the diagnosis of pancreatic fibrosis must rest upon more than this evidence alone. A positive diagnosis of pancreatic fibrosis could have been made by analysis of fluid obtained by duodenal drainage for pancreatic enzyme activity. Pancreatic fibrosis is about the only condition in which alkaline duodenal fluids are found to be entirely devoid of pancreatic enzyme activity.

Regarding this child's respiratory symptoms, it will be remembered that there had been a dry cough since birth. As time went on the respiratory signs took on the characteristics of mixed, partial and complete bronchiolar obstruction—namely, rapid respiration, scattered fine rales, low diaphragm and x-ray findings suggestive of emphysema and possibly scattered atelectasis. Perhaps we should look at the x-ray films. I expect to see scattered patches of atelectasis and possibly actual pneumonitis, with a low diaphragm on both sides indicative of generalized emphysema.

DR JOSEPH HANELIN: There is a tremendous amount of pulmonary emphysema. There are marked bulging of the thorax anteriorly and posteriorly and a low, flattened diaphragm, with scattered areas of density throughout the lung field, fairly typical of the picture that Dr Talbot has been describing.

DR TALBOT: Because of the expiratory grunt I should not be surprised if there was some evidence of pleuritis. I think I see some thickening of the pleural line along the periphery.

DR HANELIN I cannot see it

DR TALBOT In conjunction with these pulmonary findings we are told that there was a predominant growth of *Staph aureus* in the sputum. For some reason this is very characteristic of patients of this sort. They almost always have *Staph aureus* in the sputum, and they are apt to have a *Staph aureus* infection of low grade in the pulmonary tract.

We may now consider the third group of signs, which are predominantly of metabolic nature. The serum carbon dioxide content was increased, and the serum chloride concentration was slightly decreased. Although we do not have a measurement of the serum pH, I would be willing to say that the high carbon dioxide value was due to a failure of excretion of carbon dioxide by the lungs with a compensatory decrease in serum chloride and acidosis due to the retained carbon dioxide. This illustrates the fact that an elevation of the carbon dioxide does not necessarily mean alkalosis. It can signify a respiratory acidosis. While we do not have measurements of the oxygen content of the blood we were told that the patient suffered from cyanosis. Presumably this was due to a failure of absorption of oxygen just as we have evidence that there was a failure of excretion of carbon dioxide because of the pulmonary pathologic process.

Before closing our comments we may be permitted to make a guess about the pathological findings. I expect inspissation of the secretions of certain excretory passages, especially the pancreatic acinar ducts, the bronchiolar-gland ducts and also possibly the salivary-gland ducts. Proximal to the obstruction caused by this inspissated material there should be dilatation of the passages and of the acini. In addition, there should be an apparent, if not a true, fibrosis of the surrounding tissues. In the lungs one may also find low-grade scattered pneumonitis, possibly bronchiectasis and possibly even small pulmonary abscesses. In addition, there may be signs of vitamin A deficiency with metaplasia of epithelial elements. Fatty infiltration of the liver would not be surprising.

The differential diagnosis is, I think, rather limited. Tuberculosis can be ruled out on the basis of a negative tuberculin test. Monilia infection might conceivably cause the picture, but there is nothing specifically indicative of that disease. Patients born with congenital malformations of

the gastrointestinal tract (malrotation of the large bowel and so forth) may suffer from chronic nutritional disturbances, but they are not apt to have pulmonary changes. Chronic infection located almost anywhere in the body may also cause chronic gastrointestinal insufficiency. Celiac disease and celiac syndrome are terms often applied to such nutritional disturbances when they are not due to pancreatic fibrosis. The possibility of a pancreatic cyst with nutritional disturbance should be mentioned. However, patients with these conditions ordinarily do not have the combination of pulmonary and nutritional signs indicated here. The only exception to such a statement that might be considered is chronic pulmonary disease resulting in a secondary, functional type of chronic intestinal insufficiency. For these reasons I will make the diagnosis of fibrosis of the pancreas my first and only choice.

DR PERRY CULVER I want to emphasize that Dr Talbot used the presence of pulmonary changes to make the diagnosis of pancreatic fibrosis as contrasted with the other form of celiac syndrome.

DR MARTIN QUINN In general, what is the prognosis?

DR TALBOT Prior to chemotherapy the majority of patients died at about the age that this child died. However, occasional children with this disease live much longer. Antibiotics such as penicillin and streptomycin given by injection or by aerosol inhalation, or both, may prolong life expectancy to an appreciable extent by retarding the development of pulmonary changes. Unfortunately such chemotherapy does not cure the disease, it merely acts to ameliorate it temporarily.

#### CLINICAL DIAGNOSES

Emphysema  
Pneumonia (diffuse), *Staph aureus*  
Pancreatic fibrosis

#### DR TALBOT'S DIAGNOSIS

Pancreatic fibrosis

#### ANATOMICAL DIAGNOSES

*Pancreatic fibrosis*  
Acute and chronic tracheobronchitis, *Staph aureus*  
Pulmonary emphysema  
Fatty infiltration of liver

## PATHOLOGICAL DISCUSSION

DR TRACY B MALLORY Autopsy showed extensive fibrosis of the pancreas with inspissated secretions in the small ducts and dilatation of the acini as Dr Talbot prophesied. We did not demonstrate similar changes in any other organs and, unfortunately, the salivary glands were not examined. We might have seen them there. The bronchial tree was filled from top to bottom with a purulent exudate. There was considerable peribronchitis and some actual increase in fibrous tissue around the bronchi. The alveolar tissue was emphysematous, and there were almost no foci of atelectasis or pneumonia. The process stopped abruptly at the terminal bronchioles. The one other organ that showed well marked changes was the liver, which weighed 450 gm. It was the only organ in the body that had not shrunk considerably below normal weight. This enlargement was obviously due to very extensive stores of fat.

DR CHARLES LOWE Dr Talbot asked me to say a few words about the manner of death in children with this disease. It is interesting that most people assume that fibrosis of the pancreas is a nutritional problem, and therapy is directed accordingly. However, I think that most youngsters who die with this disease do so from one of three causes, none of them nutritional. The first cause is an overwhelming infection. Some of this group show extensive pneumonia, abscesses and empyema. The second group undoubtedly die as much from anoxemia as anything else. Their elevated carbon dioxide reflects it. The third group die from right-sided heart failure with anasarca. They are the least understood. As you already know, the present patient showed relatively little pulmonary fibrosis at autopsy, while the electrocardiogram showed right-axis deviation. For this we have no explanation.

DR MALLORY I think it might be quite similar to the situation in chronic bronchial asthma, in which a significant number of patients eventually die of right-sided heart failure, even though the degree of anatomic emphysema is not very great. I think that permanent overdilatation of the lung probably causes resistance to the flow of blood in

the pulmonary arteries just as prolonged atelectasis does. I believe that alternation of expansion and contraction of the alveoli is necessary to normal circulation of blood through the lungs.

DR JAMES HEYL Might I ask about the bronchial and salivary-gland secretion? I cannot see the connection with pancreatic fibrosis.

DR MALLORY I cannot answer that. Dr Lowe, can you?

DR LOWE All one can say is that at autopsy one occasionally finds some disease of the parotid gland and the salivary ducts. Rarely, one sees some dilatation of the secreting glands in the bronchi. I am sure it is the extraordinary case and not the ordinary one that shows these changes, however.

DR MALLORY There may have been occlusion of the glands in the bronchial wall in this case. We were not able to demonstrate any changes of vitamin A deficiency. Presumably the child died too rapidly for that.

DR CULVER Would you care to say anything about your concept of the etiology of pancreatic fibrosis?

DR MALLORY I do not believe I have the right to. I know too little about it.

DR JAMES H TOWNSEND Would anyone care to? How about you, Dr Talbot?

DR TALBOT No, but I should like to ask Dr Mallory if he accepts the thesis that it is inspissation of the secretion of these glands that causes the trouble.

DR MALLORY We occasionally see in adults fairly marked inspissation of secretion in the pancreatic ducts, which does not result in cystic disease or fibrosis. It presumably appears and spontaneously disappears again, but I am not sure that we really know that. It can be rather marked and for some reason that I do not understand, I saw a great deal in soldiers during the war but I have seen very little in civilian life.

## REFERENCES

- 1 Blackfan K D., and May C. D. Inspissation of secretion dilatation of ducts and acini atrophy and fibrosis of pancreas in infants. clinical note. *J. Pediat* 13: 627-634, 1938.
- 2 May C. D. and Lowe C. U. Treatment of fibrosis of pancreas in infants and children. *Pediatrics* 1: 159-173, 1948.

# The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established 1828

Official Organ of

THE MASSACHUSETTS MEDICAL SOCIETY  
and

THE NEW HAMPSHIRE MEDICAL SOCIETY

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND  
PUBLISHED WEEKLY UNDER THE JURISDICTION OF THE  
COMMITTEE ON PUBLICATIONS

James P. O'Hare M.D. Richard M. Smith M.D., Chairman  
Oliver Cope M.D. Conrad Wesselschoeff M.D.  
John Fallon M.D.

Joseph Garland M.D. Editor

ASSOCIATE EDITORS

Thomas H. Lanman M.D. Donald Munro M.D.

Henry Jackson, Jr., M.D.

Clara D. Davies EXECUTIVE EDITOR

Robert O. Leary, ASSISTANT EDITOR

EDITORIAL BOARD

C. Guy Lane M.D.	Maxwell Finland M.D.
Henry R. Viets M.D.	James M. Faulkner M.D.
Robert M. Green M.D.	Carroll B. Larson M.D.
Dwight O'Hara M.D.	Francis D. Moore M.D.
Fletcher H. Colby M.D.	C. Stuart Welch M.D.
Robert L. Goodale M.D.	Vernon P. Williams M.D.
Chester M. Jones M.D.	Benjamin Castleman M.D.
Harvey R. Morrison, M.D.	Hugh R. Leavell M.D.

SUBSCRIPTION TERMS \$7.00 per year in advance postage paid for the United States (medical students \$4.00 per year) Canada \$8.00 per year (Boston funds) \$9.50 per year for all foreign countries belonging to the Postal Union

MATERIAL should be received not later than noon on Thursday three weeks before date of publication

THE JOURNAL does not hold itself responsible for statements made by any contributor

COMMUNICATIONS should be addressed to the *New England Journal of Medicine* 8 Fenway Boston 15 Massachusetts Telephone KE 6-2094

NEW ENGLAND ADVERTISING REPRESENTATIVE Edwin B. Tyler 89 State Street Boston Massachusetts Telephone LA 3-5516

## "OF THEE I SING"

THE communication from Dr. A. J. A. Campbell published elsewhere in this issue of the *Journal* calls attention to a situation that requires prompt and decisive action. The Veterans Administration, apparently unaware of the consequences of such a policy, seems to have drawn a blank check designed to pay for the medical education of any presumably qualified United States veteran in any medical school of Europe.

The warning is sounded by Dr. J. L. Lochner, Jr., to whose paper in the *Journal of the American Medical Association* Dr. Campbell refers.\* Dr. Lochner briefly reviews the recent history of European medical education as it has affected

\*Lochner, J. L., Jr. Licensure evaluation of European medical graduates. *J. A. M. A.* 137:16, 1948.

practice in this country. For a half century prior to 1913 European standards of education were high, but they suffered a serious and prolonged eclipse after the first world war. An invasion of the United States by graduates of foreign schools began about 1926. In the face of this sharp increase in the number of immigrant physicians seeking admission to practice, many states stiffened their requirements for licensure.

In New York State particularly, for which Dr. Lochner speaks, the record established by foreign physicians taking examinations in the last two decades has not been good, the over-all failures have amounted to 66 per cent, with over 72 per cent failing in the period from June, 1945, to February, 1947.

The present policy of the New York Board of Regents has resulted. Graduates of European medical schools who matriculated since January 1, 1940, are not admitted to the New York State medical licensing examination, with the possible exception of those whose medical courses were completed in the Universities of Cambridge or of London, the University of Dublin or the University of Ireland. The laws of Massachusetts, in similar manner, currently permit the registration of no graduate of any foreign school of medicine, Canada excepted, who matriculated later than January 1, 1941.

In the face of the qualifying restrictions that have been established by the various states of the Union, some admittedly more lax, some more stringent than others, the Veterans Administration now offers to those citizens for whom it has accepted a considerable degree of responsibility a free ticket to attend medical school in postwar Europe at Government expense! The list of schools approved, so far as can be ascertained, is all-inclusive. Santa Claus does not intend to miss a chimney or leave a stocking empty.

The effect of such a policy on the standards of medical practice in this country can be imagined; we may hope that we will not need to witness it. Those states now maintaining high standards will refuse to admit to practice the newly returned doctors with their ersatz sheepskins — until the pressure builds up. Then the standards will go down. In a free country such as this no legislature can continue long to deny the right to practice to those veterans

who have been educated at the taxpayers' expense — nor, in a free country, can those responsible for the demolition of the standards be required to employ these same poorly trained physicians for the care of their own families

It is not only in respect to medical education that this indiscriminate largess is being distributed. Under the title "Veterans' Training The \$500,000,000 Boondoggle," *Collier's* published in May an analysis of the situation. *The Reader's Digest* presented the *Collier's* story in condensed form the following month.

The Veterans Administration, according to this report, is presently engaged in spending a half billion dollars on a veterans' school program that includes, in addition to foreign-made medical education, courses in flying, ballroom dancing, bartending, amateur photography, piccolo playing, radio and television engineering and chicken sexing. The last named classic, consisting in the identification of the sex of newly hatched chicks, may be mastered through a four-week \$40 course in Missouri or a seven-month \$500 course, with subsistence, in Illinois. It all depends.

And so the great University of America operates, all paid for out of Uncle Sam's pants pockets, with courses ranging from piccolo playing to amateur photography, from chicken sexing to a complete curriculum in foreign schools of medicine, now mainly low grade no matter how famous they might once have been or how excellent they may again become.

Of these various activities, the encouragement of those to whom a debt of gratitude may be owed, to become ill trained physicians, represents the most serious mistake. All the good will in the world toward the country's veterans should not be allowed to promote this particular folly, rather should a true regard for their welfare cause its abandonment forthwith.

---

#### PHILOSOPHIA MEDICI

"'For this' he said, 'is the great error of our day in the treatment of the human body, that physicians separate the soul from the body.'"

After nearly twenty-five hundred years, this comment from Plato<sup>1</sup> is still an apt criticism of the medical profession. Now the advocates of psychosomatic medicine, proclaiming the truth again, deserve well of their patients and of their fellow-practitioners for their effort to correct this "great error of our day." Whether they will be able to provide a more adequate and enduring corrective than that offered by Socrates the Great Gadfly can be determined perhaps only after the lapse of another two and a half millennia.

A modern sage, Alfred North Whitehead,<sup>2</sup> says that philosophy asks the simple question "What is it all about?" He defines speculative philosophy as the endeavor to construct a system of general ideas "in terms of which every element in our experience can be interpreted."<sup>3</sup> It is the comprehensiveness of the philosophical scope that needs emphasis.

In the narrower view of the practicing physician, speculative philosophy is often too recondite for him to be at home in it, and perhaps for many physicians the upper limit of attainment will be an awareness that their special field has implications in and connections with the vast body of knowledge that represents the intellectual side of civilization.

The beginning student of medicine, sometimes clearly called, sometimes vaguely but no less strongly drawn, to this way of life, asks the question "What is medicine all about?" The reply by contemporary medical education is not satisfying. It shows him great accomplishments of science in the past, active progress in the present and promise of greater things to come. But what answer does he receive, if he goes on to say, "I want a philosophy of medicine?" Perhaps a cynical smile and a shrug of the shoulders and the words, "It is enough for you to be a scientist, science is to be your life." If he is offered more, it is likely to be a materialistic philosophy.

The student will fashion his own philosophy in time, but what the medical school should do is assist him, as it does all too little today, in acquiring a sense of direction and in becoming familiar with and at home in the great humanistic tradition in which some of the finest flowers of the profession have had their roots. In this tradition there are

many names, but three come to mind at once Sir Thomas Browne, Sir William Osler and Harvey Cushing. Of the first it has been said, "A certain air of mystery and consecration, as of one dedicated, for whom nothing could be common or unclean, to whom his own life seemed 'a common miracle of thirty years,' and the visible world 'a hieroglyphical and shadowed lesson' of the thoughts of God, surrounded the man from childhood to old age."<sup>1</sup> The dedication of Osler is clear in his writings and was constantly manifest to those who were associated with him. Cushing<sup>2</sup> wrote of the "Consecratio Medici" as one having immediate knowledge

"There were giants in the earth in those days." Their culture was broader and their roots deeper, and part of their secret we know: they contemplated greatness. With gifts beyond the ordinary, they transmuted and transmitted it with the stamp of their own personality set upon it.

Today, as one looks around, how many physicians are there to be found who have so grasped the principles of the science and of the art of medicine that it can be said of them that they know what it is all about? Fortunate is the medical school that has on its faculty even one such wise man. His influence may be supplemented, but not replaced, by the study of the lives of other wise physicians of the past, and such study may be a stimulus and an inspiration to the young physicians, even in the absence of a notable example on the faculty.

The great need in medical education today is not to direct less attention to the science of medicine and to its training and development of specialists but to make a new and vigorous effort to foster in the student a wise philosophy of the science and of the art, in the hope that there may result therefrom the fairest of all gifts that the physician can possess, an understanding heart.

#### REFERENCES

1. Charmides. In *The Dialogues of Plato*. Translated by B. Inge. Vol. 1. Third edition. 594 pp. New York: Oxford University Press, 1892. P. 13.
2. Whitehead, A. N. *Wisdom and Wisdom*. 102 pp. Boston: Beacon Press, 1947. P. 73.
3. *Idem*. *Process and Reality*. 547 pp. New York: The Macmillan Co., 1929. P. 4.
4. Symonds, J. A. Introduction to Sir Thomas Browne's *Religio Medici*. 262 pp. London: W. Scott, 1886. P. ix.
5. Cushing, H. W. *Consecratio Medici*. *J. A. M. A.* 87:539-542, 1926.

#### ON THE PRIZING OF LIFE APART FROM ITS CONTENT

SHOULD the medical interest in old age and the dollars spent in pharmaceutical research on its diseases be matched by the hoped-for effective prevention, the second age of dependency may equal the hitherto allotted life span, and could be twice as long as man's productive life. The Pharmaceutical Medical Research Foundation plans to spend a quarter of a million dollars on degenerative disease. Dr. Edward L. Bortz, president of the American Medical Association, on the basis of animal physical maturity and life expectancy, thinks that man should live to be a hundred and fifty years old. Unless physical well-being and, even more important, unless productive activity is provided for the aged, not the first but the last hundred years will be the hardest and will be a dog's life indeed.

There is no doubt that the population is aging, that men over fifty are less readily employed in industry than formerly and especially so if partially disabled by degenerative disease. The medical care, the rehabilitation and the productive employment of the aging and the aged is already a serious medical and social problem. How often we see a widow alone in her room, with no one to mother or mend for, depressed that she is no longer needed, her children long since busy with their own young families. How often we see the once competent man, now retired, depressed and becoming decayed in person, irritable and contentious in minor affairs or, sadder of all the prey of chance delusions — professional, political or amorous. To live on indefinitely and idly with old-age assistance may be more cruel than to be allowed an earlier and peaceful terminal illness.

Geriatrics is not a medical specialty but is a field of human endeavor with medical and sociologic aspects and with many potential resources of manpower. In its medical aspect geriatrics, like pediatrics, refers to general medicine applied to a particular age group. Cosin\* has made some pertinent suggestions for organizing a geriatric department in the hospital system providing for acute geriatric wards for investigation and treatment, long-stay

\*Cosin, L. Organizing geriatric department. *Brit. M. J.* 2:1044-1046, 1947.

annex wards for patients permanently bedfast, long-stay annex wards for frail ambulant patients and the resident-home type of accommodations for the more robust patients. He discusses the requirements of the medical-staff nurse, orderly and practical nurse according to need. In a large community of this country, such as Boston, an organization of this sort might be worked out. A close relation could be established between privately endowed homes for the aged and general hospitals, some of the income of the former being allocated for beds in the latter. The homes for the aged could care for long-stay patients in two divisions, one for the bedfast and one for the frail ambulatory. The general hospital might provide visiting physicians and specialists of various sorts, including experts in rehabilitation, nurses, dietitians and externs. The advantages would be mutual. Finally there should be home care of the aged living in families or in boarding houses on old-age assistance with social-service supervision from the hospital or state social service.

Undoubtedly, the most important emphasis should be on rehabilitation and re-employment graded from occupational therapy for the bedfast through "made work" for the frail ambulatory and simple piecework brought to the home, to light domestic service, outside tasks, timekeeping and baby sitting for the aged on old-age assistance. "The length of days is vanity," said the preacher, and it has been said again by the philosopher who decried our "uncritical prizing of life apart from its content." In our plans to spend brains and money on lengthening our days let us allocate a goodly portion to devising ways of filling them with suitable and rewarding labor.

### MILIARY LESIONS OF THE LUNG

MANY diseases that have come into prominence in recent years have been associated with miliary infiltrations of the lung. The more recent of these include such diverse conditions as the viral pneumonias, certain bacterial pneumonias, pulmonary lesions in Q fever and other rickettsial diseases, histoplasmosis, beryllium and cadmium poisoning, bagassosis, Loeffler's eosinophilia and acute diffuse

interstitial fibrosis of the lung — to mention only a few. Some of the better known conditions, such as sarcoidosis and miliary tuberculosis, have now assumed new significance from a differential diagnostic point of view because of the effectiveness of streptomycin in acute miliary tuberculosis.

Many of these miliary diseases of the lung are of considerable interest and offer puzzling problems to the internist. In 1942 Austrian and Brown<sup>1</sup> were able to list twenty-two separate states in which miliary lesions of the lung were encountered. Their list was based on personal clinical observations made over almost a quarter of a century and supplemented by only a cursory reference to the literature and did not include any of the relatively new conditions referred to above.

The most recent compilation by Felson and Heublein<sup>2</sup> of conditions that give rise to diffuse pulmonary lesions is therefore of considerable interest. These authors have classified the various conditions under fifteen separate major headings, such as cystic lesions, vascular, inhalation, infections, malignant lesions and embolization, with from two to as many as twenty separate diseases or conditions listed under each heading.

In spite of the length of this list, the authors admit that it is incomplete. Such conditions as Q fever, other rickettsial infections and amyloidosis, for example, have been overlooked. Their classification will, however, prove to be a very distinct aid in the evaluation of the various diffuse pulmonary lesions. These authors emphasize that it is hazardous to express an opinion of etiology solely on the basis of a single roentgenologic study. Even multiple examinations, which carry considerable weight because they allow for the evaluation of progression or retrogression, may not be absolutely diagnostic. However, as they point out, in a vast majority of cases correct interpretation can be accomplished after careful correlation of both roentgenographic and clinical studies but in a few cases the correct diagnosis will necessarily wait until autopsy.

### REFERENCES

1. Austrian C R. and Brown W H. Miliary diseases of lungs. *Am Rev Tuberc* 45:751-755 1942.
2. Felson H and Heublein G W. Some observations on diffuse pulmonary lesions. *Am J Roentgenol* 59:59-61 1948.

many names, but three come to mind at once Sir Thomas Browne, Sir William Osler and Harvey Cushing Of the first it has been said, "A certain air of mystery and consecration, as of one dedicated, for whom nothing could be common or unclean, to whom his own life seemed 'a common miracle of thirty years,' and the visible world 'a hieroglyphical and shadowed lesson' of the thoughts of God, surrounded the man from childhood to old age"<sup>4</sup> The dedication of Osler is clear in his writings and was constantly manifest to those who were associated with him Cushing<sup>5</sup> wrote of the "Consecratio Medici" as one having immediate knowledge

"There were giants in the earth in those days" Their culture was broader and their roots deeper, and part of their secret we know they contemplated greatness With gifts beyond the ordinary, they transmuted and transmitted it with the stamp of their own personality set upon it

Today, as one looks around, how many physicians are there to be found who have so grasped the principles of the science and of the art of medicine that it can be said of them that they know what it is all about? Fortunate is the medical school that has on its faculty even one such wise man His influence may be supplemented, but not replaced, by the study of the lives of other wise physicians of the past, and such study may be a stimulus and an inspiration to the young physicians, even in the absence of a notable example on the faculty

The great need in medical education today is not to direct less attention to the science of medicine and to its training and development of specialists but to make a new and vigorous effort to foster in the student a wise philosophy of the science and of the art, in the hope that there may result therefrom the fairest of all gifts that the physician can possess, an understanding heart

#### REFERENCES

1. Charmides In *The Dialogues of Plato* Translated by B Jowett. Vol 1 Third edition 594 pp New York Oxford University Press, 1892 P 13
2. Whitehead, A N *Wis and Wisdom* 102 pp Boston Beacon Press 1947 P 73
3. *Idem Process and Reality* 547 pp New York The Macmillan Co 1929 P 4
4. Symonds, J A Introduction to Sir Thomas Browne's *Religio Medici* 262 pp London W Scott 1886 P ix
5. Cushing H W Consecratio medici *J A M A* 87 539-542 1926

#### ON THE PRIZING OF LIFE APART FROM ITS CONTENT

SHOULD the medical interest in old age and the dollars spent in pharmaceutical research on its diseases be matched by the hoped-for effective prevention, the second age of dependency may equal the hitherto allotted life span, and could be twice as long as man's productive life The Pharmaceutical Medical Research Foundation plans to spend a quarter of a million dollars on degenerative disease Dr Edward L Bortz, president of the American Medical Association, on the basis of animal physical maturity and life expectancy, thinks that man should live to be a hundred and fifty years old Unless physical well-being and, even more important, unless productive activity is provided for the aged, not the first but the last hundred years will be the hardest and will be a dog's life indeed

There is no doubt that the population is aging, that men over fifty are less readily employed in industry than formerly and especially so if partially disabled by degenerative disease The medical care, the rehabilitation and the productive employment of the aging and the aged is already a serious medical and social problem How often we see a widow alone in her room, with no one to mother or mend for, depressed that she is no longer needed, her children long since busy with their own young families How often we see the once competent man, now retired, depressed and becoming decayed in person, irritable and contentious in minor affairs or, saddest of all the prey of chance delusions — professional, political or amorous To live on indefinitely and idly with old-age assistance may be more cruel than to be allowed an earlier and peaceful terminal illness

Geriatrics is not a medical specialty but is a field of human endeavor with medical and sociologic aspects and with many potential resources of manpower In its medical aspect geriatrics, like pediatrics, refers to general medicine applied to a particular age group Cosin\* has made some pertinent suggestions for organizing a geriatric department in the hospital system providing for acute geriatric wards for investigation and treatment, long-stay

\*Cosin L Organizing geriatric department. *Brit M J* 2 1044-1046 1947

associated with increased rates of nucleoprotein turnover. The literature contains at least 25 cases of polycythemia vera and gout, in addition to the 25 or more cases of leukemia and gout. There have been reported at least 11 cases of hemolytic anemia and gout, 9 cases of pernicious anemia and gout, many cases in which gout followed the hematoietic stimulus of blood loss and many more in which lead intoxication was the responsible factor. In pernicious anemia, the attacks tend to occur during the reticulocyte crisis induced by liver extract, at a time when nucleoprotein turnover is at its peak, and at least nine authors have reported induction of gout attacks by the injection of potent liver extract, not always in patients with pernicious anemia.

The most important observation suggesting that accelerated nucleoprotein turnover may be quite directly concerned in the production of gouty symptoms has been made in several cases of gout associated with hemolytic anemia. A number of these patients who have been submitted to splenectomy have been relieved of the symptoms of both diseases for follow-up periods up to ten years.

There appears to have been no study of the proportion of joint pains in leukemia that are actually referable to gout. Nevertheless, from a therapeutic point of view, recognition of this possibility appears desirable for the comfort of the patient, since gout attacks occurring during leukemia have responded to the judicious use of colchicine, the specific for the ordinary gout attack.

WILLIAM QUITMAN WOLFSON, M D

Michael Reese Hospital  
Chicago, Illinois

Dr Wolfson's letter was referred to Dr Mark Aisner, whose reply is as follows:

To the Editor Doctor Wolfson's letter brings up the interesting and, at the present time, highly controversial and speculative problems of nucleoprotein metabolism, hyperuricemia and gout, the inter-relations of which are still far from clear.

The commonest type of joint pain in the acute leukemias is polyarticular, often migratory, and clinically resembles most closely rheumatic fever and, in some cases rheumatoid arthritis. Although some patients present hyperuricemia, they do not show the typical features of gout. The fact that in many of the acute leukemias various changes in the bones and periarticular structures are demonstrated both roentgenologically and pathologically, none of which are seen in gout, may explain, in part at least, the symptoms of bone and joint pain in such cases. The age and sex distributions in the acute leukemias are quite different from those in gout.

The mere presence of hyperuricemia does not necessarily establish a diagnosis of gout. However, this finding, along with studies on uric acid excretion, has for years led to speculation regarding the relation between leukemia and its associated nucleoprotein breakdown and gout. Forkner, in his monograph *Leukemia and Allied Disorders* (333 pp New York Macmillan Company, 1938), comments that the "simultaneous occurrences of the two conditions is so rare that any real relationship seems doubtful." Statistically, the number of cases of true gout associated with the various disorders mentioned by Dr Wolfson is insignificant. Disturbances in nucleoprotein metabolism and hyperuricemia have been demonstrated in renal failure, toxemias of pregnancy, liver disease, lobar pneumonia, bronchopneumonia, arteriosclerosis with hypertension, cardiac failure, fatal methyl alcohol poisoning, chronic eczema and allied dermatoses and so forth. Yet gout remains a relatively rare disease so far as the frequency with which one encounters the disorders listed above is concerned. From a therapeutic standpoint the beneficial effects of colchicine do not help to clarify the relation between nucleoprotein breakdown and gout, since this drug has no apparent influence upon uric acid metabolism.

Although I agree that occasional cases of leukemia are associated with gout, I cannot subscribe to the idea that an appreciable number of them are.

In conclusion I should like to quote the statement of Peters and Van Slyke, that "when all is said and done the determination of uric acid in blood and urine still offers little aid to the clinician."

MARK AISNER, M D

375 Commonwealth Avenue  
Boston

## BOOK REVIEW

*The Diagnosis and Treatment of Diarrheal Diseases* By William Z. Fradkin, M D 8°, cloth, 254 pp, with 114 illustrations New York Grune and Stratton, 1947 \$6.00

This is a small, useful, clearly written and very well illustrated book, by a man with large experience in diarrhea as physician in charge of the Colitis Clinic and associate bacteriologist, Colitis Division, of the Jewish Hospital of Brooklyn.

It aims at being a short, practical presentation of laboratory and clinical features in the diagnosis and treatment of diarrhea. It has real value but might perhaps be compared to a hook on vomiting or headache. It is evidently addressed to the general practitioner as well as to the specialist in gastroenterology. Many of the methods of examination are too elaborate for the practitioner, and the book as a whole is much too short for the specialist. The value of a careful history is stressed, but one is not told how to use these data in differential diagnosis. The limitations and delay in stool cultures might be emphasized more. The chapter on intestinal parasites is excellent. In the excellent x-ray illustrations of ulcerative colitis, it is surprising to find the cecum sometimes on the right side and sometimes on the left side of the prints.

The general chapter on treatment is very good, but more detail could be given in some of the individual diseases. The results of treatment in cancer of the bowel are evidently considered beyond the scope of the book, being dismissed with half a line. The chapter on nervous diarrhea (four and a half pages) might be larger, since no organic cause is found in more than half the cases of diarrhea.

The author is evidently an individualist, and some of his statements might be misunderstood—for example, in ulcerative colitis, "surgery—is never indicated even as a partial aid in the management of this disease," "pregnancy should be interrupted in all patients" and "specialized psychotherapy is not indicated." Colectomy is not mentioned for this disease.

There is much that is good in the book, but much has been omitted because of the large field covered in a small volume.

## BOOK RECEIVED

The receipt of the following book is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

*Mental Health A practical guide to disorders of the mind* By John H. Ewen, F R C P E, D P M, physician and lecturer in psychologic medicine, Westminster Hospital, and medical superintendent, Springfield Mental Hospital, London. With a chapter on special treatments and their practical technique by C. Friedman, M D (Vienna), L R C P and S E d, registrar and tutor, Department of Psychological Medicine, St. Thomas's Hospital, psychotherapist, the Tavistock Clinic, and medical officer, Insulin Therapy Clinic, Springfield Mental Hospital. 8°, cloth, 270 pp. Baltimore: The Williams and Wilkins Company, 1947 \$4.00.

In Great Britain during the past few years, owing to the problems brought about by national planning and organization of mental health services, a knowledge of mental illness has become necessary to the general practitioner and social worker. This manual has been written to fill this need. Particular attention has been given to the requirements of students studying for a diploma in psychologic medicine. The text is divided into five sections. The first, which is general in character, deals with etiology, diagnosis and classification. The following sections in order consider the psychoneuroses, psychoses, mental deficiency and psychopathic states, and the legal aspects of mental disorder and mental-hospital practice from the British viewpoint. The material is well organized, and the volume well published. The printing was done in Great Britain. The manual should prove useful to those persons for whom it was written.

## MASSACHUSETTS MEDICAL SOCIETY

## IMPORTANT NOTICE

It is imperative that all fellows of the Society be properly classified as to their availability for military service when and if the occasion arises. The armed forces of the United States and the Council on Emergency Medical Service have requested that this be accomplished as soon as possible.

A return postal card has been sent to each fellow asking for certain pertinent information. This should be returned to the headquarters of the Society immediately.

H QUIMBY GALLUPE, M D, *Secretary*

## MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

## DIRECTOR OF DIVISION OF HOSPITALS

Dr Richard P MacKnight, former state director of hospital inspection, has been appointed director of the new division of hospitals of the Massachusetts Department of Public Health, Dr Vlado Getting, Massachusetts Public Health Commissioner, announced recently.

Dr MacKnight will direct the new division's activities, which include the inspection and licensing of hospitals, sanatoriums, convalescent and nursing homes, and boarding homes for the aged, as well as the administration of hospital survey and construction under Public Law 725 — the Hospital Survey and Construction Act.

Dr MacKnight has had a long and creditable career in public-health work, especially in relation to hospitals. After his graduation from Jefferson Medical College in Philadelphia in 1914, he served as rotating intern for twenty-eight months, and then entered the Army Medical Corps. He served for twenty-six months in World War I and attained the rank of Captain. After the war, Dr MacKnight went into private practice until 1923, when he was appointed assistant superintendent of the Bristol County Tuberculosis Hospital in Attleboro.

In December, 1924, Dr MacKnight became a district health officer for the Massachusetts Department of Public Health, and served in that capacity until 1938. He was appointed assistant director of the Division of Cancer and Other Chronic Diseases in 1939.

Dr MacKnight became supervisor of hospital inspection in 1942, he held this position until October, 1947, when he was further promoted to director of hospital inspection for the Massachusetts Department of Public Health. All this experience makes Dr MacKnight an excellent choice for the important work of the new division.

Until recently, hospital licensing and inspection had been handled by the Bureau of Hospital Licensing, under Dr MacKnight. The licensing of convalescent and nursing homes and of boarding homes

for the aged is a new function assigned to the Massachusetts Department of Public Health by the Legislature in 1948.

## MISCELLANY

## WATER POLLUTION CONTROL ACT

The Water Pollution Control Act (Public Law 84) has been signed by President Truman. Under the terms of this act a scientific program will be developed with federal loans to any state, municipality or interstate body for the purpose of pollution abatement and control. The program will be administered by the United States Public Health Service and the Federal Works Agency. The sum of \$112,000,000 will become immediately available for the first five year period.

## CORRESPONDENCE

## VETERANS ADMINISTRATION APPROVAL OF FOREIGN MEDICAL SCHOOLS

To the Editor: Dr J L Lochner, Jr, secretary of the Board of Registration for the state of New York, in his article in the May 1, 1948, issue of the *Journal of the American Medical Association*, entitled, "Licensure Evaluation of European Medical Graduates," calls attention to the fact that the Veterans Administration in Washington is advising veterans that they may attend any medical school in Europe at the expense of the Government. The veterans are furnished with a list of European medical schools that have been approved by the Veterans Administration, and, so far as Dr Lochner was able to ascertain, "named every single medical school abroad."

A committee on foreign medical credentials, consisting of representatives from the Association of American Medical Colleges, Federation of State Medical Boards, National Board of Medical Examiners, United States Office of Education, United States State Department and the New York State Education Department, is at work and is collecting valuable information about foreign medical schools and education. It is regrettable that the Veterans Administration has not consulted this committee and recommended to veterans schools that have been certified by the Committee.

It seems pertinent that the Massachusetts Medical Society should protest against the present policy of the Veterans Administration and that the Committee on Veterans' Affairs of the Massachusetts Medical Society should be requested to take up the implications of this policy with the Veterans Administration.

A J A CAMPBELL

520 Commonwealth Avenue  
Boston 15

## BONE AND JOINT PAIN IN LEUKEMIA

To the Editor: The interesting discussion of bone and joint pain in leukemia by Drs Aisner and Hoxie in the May 20 issue of the *Journal* leaves the reader with the impression that most of these pains are nonspecific rheumatoid affairs. Actually, although it is not possible to obtain quantitative estimates, a review of the literature suggests that an appreciable number of joint pains occurring in leukemia may well be due to gout. Drs Aisner and Hoxie, for example, present data on a patient whose history of foot pain, acute arthritis in the elbow and a circulating urate level of 18.5 mg per 100 cc. is most suggestive of gout.

The rate of nucleoprotein turnover is known to be greatly accelerated in leukemia, as pointed out by Fortunato (11 *metabolismo dei nucleoproteidi nei leucemia Studi* 21 221-230, 1931) and by Wolfson et al (Transport and excretion of uric acid in man *J Clin Investigation* 26 995-1001, 1947). Although, on occasion, it has been suggested that an hereditary tendency is a prerequisite for the occurrence of gout in leukemia, most of the reported cases are sporadic. There is, in fact, considerable experimental and clinical evidence that the increased rate of nucleoprotein turnover is more than a mere inciting factor in cases of gout associated with leukemia. Gout may, for example, occur in other disturbances of hematopoiesis

## NOTICES (Concluded from page 158)

JULY 26-30 Biology Conference Brookhaven National Laboratory  
 JULY 21, issue of July 15  
 AUGUST 11-21 International Congress on Mental Health Page 344  
 issue of March 4  
 AUGUST 23-26. International Society of Hematology Page 419 issue  
 March 18  
 AUGUST 26-28 American Association of Blood Banks Page 420 issue  
 March 18.  
 SEPTEMBER 7-11 American Congress of Physical Medicine Page 582  
 issue of April 15  
 SEPTEMBER 7-11 American Occupational Therapy Association Page  
 issue of July 8  
 SEPTEMBER 9 Some of the Advances in Surgery Dr Frank H Lahey  
 -ntucker Association of Physicians 8 30 p.m. Haverhill  
 SEPTEMBER 13-15 American Academy of Pediatrics Olympic Hotel,  
 atle Washington.  
 SEPTEMBER 16-18 Vermont State Medical Society Annual Meeting  
 urington  
 SEPTEMBER 20-23 American Hospital Association Page 310 issue of  
 ebruary 26  
 SEPTEMBER 29 Mississippi Valley Medical Editors' Association.  
 age 170 issue of January 29  
 OCTOBER 6-9 American Board of Ophthalmology Page 170 issue of  
 anuary 29  
 OCTOBER 18-22 American College of Surgeons Page 34 issue of  
 uly 1  
 OCTOBER 27 New England Obstetrical and Gynecological Society  
 nnnal Meeting Hotel Somerset, Boston  
 NOVEMBER 1-3 American Clinical and Climatological Association.  
 age 582 issue of April 15  
 NOVEMBER 8-12 American Public Health Association Page 420 issue  
 f March 18.  
 NOVEMBER 10-13 Association of Military Surgeons of the United  
 states Page 722 issue of May 13  
 NOVEMBER 20-23 American Academy of Pediatrics Annual Meeting  
 hallfonte-Haddon Hall Hotel, Atlanuc City New Jersey  
 DECEMBER 7-9 Southern Surgical Association Annual Meeting  
 Page 543 issue of April 8  
 DECEMBER 9 and 10 New York State Society of Anesthesiologists.  
 Page 34 issue of July 1  
 MARCH 28-APRIL 1, 1949 American College of Physicians Page 158  
 NOVEMBER 11-17 1949 Third Inter-American Congress of Radiology  
 Page 158

**Washingtonian Hospital**

41-43 WALTHAM STREET, BOSTON, MASS

Incorporated 1859

Conditioned Reflex, Psychotherapy, Semi-Hospitalization  
 For Rehabilitation of Male AlcoholicsTreatment of Acute Intoxication and Alcoholic Psychoses  
 IncludedOutpatient Clinic and Social-Service Department for  
 Male and Female PatientsJOSEPH THIMANN, M D, *Medical Director*Visiting Psychiatric and Neurologic Staff  
 Consultants in Medicine, Surgery and the Other Specialties  
 Telephone HA 6-1750**Valleyhead Hospital**

CONCORD, MASSACHUSETTS

For the treatment of psychoneuroses, alcoholism, mild  
 mental disorders and chronic diseases Pleasant pastoral  
 setting near historic Concord. Accepted modern therapies  
 used Complete occupational and recreational facilities  
 available including outdoor swimming pool and tennis  
 court.

S GAGNON M D  
*Superintendent*J BUTLER TOMPKINS, M D  
*Director of Clinical Psychiatry*J P THORNTON, M D  
*Consultant in Neuro-  
 psychiatry*IRVING KAUFMAN, M D  
*Psychiatrist*

Post Office, Box 151, Concord, Mass Tel Concord 1600

**HARVARD MEDICAL SCHOOL**

Courses for Graduates

**SURGICAL ANATOMY**By DR EDWARD A EDWARDS and ASSOCIATES  
 at the Harvard Medical School

September 7-October 30, 1948

(Five afternoons a week)

**MODERN TREATMENT OF FRACTURES  
 AND OTHER TRAUMATIC CONDITIONS**By DR EDWIN F CAVE and ASSOCIATES  
 at the Massachusetts General Hospital

September 20-30, 1948

For further information and application write to

ASSISTANT DEAN COURSES FOR GRADUATES  
 Harvard Medical School Boston 15 Massachusetts**Tablets Ferglate-B with C**High in vitamin B complex content to quicken hemo-  
 globin response to iron therapy

## EACH TABLET CONTAINS

Ferrous Gluconate (5 grains)	0.375 gm	Pyridoxine HCl	0.15 mg
Thiamin HCl	3 mg	Calcium Pantothenate	0.5 mg
Riboflavin	2 mg	Ascorbic Acid	30 mg
Niacinamide	20 mg	Yeast-Liver Base	q.s.

## INDICATIONS

Iron deficiency and nutritional anemias as a source of iron and  
 B complex factorsWrite Department N12 for Professional  
 Sample and Literature**KENMORE PHARMACAL CO.**500 COMMONWEALTH AVENUE  
 BOSTON 15, MASS**Firm, Natural Support Need Never  
 Be Sacrificed for ANY Fashion**

A functional garment, properly fitted, will mold  
 a figure to the fashion's new requirements with-  
 out causing displacement of organs

**EVYLYN L. WEIGEL**

25 HUNTINGTON AVE.	MASSACHUSETTS AVE., ROUTE 111
BOSTON 16, MASS	WEST ACTON, MASS.
KENMORE 6-2718	ACTON 504-3

## NOTICES

## AMERICAN COLLEGE OF PHYSICIANS

The American College of Physicians will conduct its thirtieth annual session in New York City from March 28 through April 1, 1949. Secretaries of medical societies are especially asked to note these dates and, in arranging meeting dates of their societies, to avoid conflicts with the meeting, for obvious mutual benefits.

AMERICAN COLLEGE OF PHYSICIANS  
RESEARCH FELLOWSHIPS

The American College of Physicians announces that a limited number of fellowships in medicine are available from July 1, 1949, to June 30, 1950. These fellowships are designed to provide an opportunity for research training either in the basic medical sciences or in the application of these sciences to clinical investigation. They are for the benefit of physicians who are in the early stages of their preparation for a teaching and investigative career in internal medicine. Assurance must be provided that the applicant will be acceptable in the laboratory or clinic of his choice and that he will be provided with the facilities necessary for the proper pursuit of his work. The stipend will be from \$2200 to \$3200.

Application forms will be supplied on request to The American College of Physicians, 4200 Pine Street, Philadelphia 4, Pennsylvania, and must be submitted in duplicate not later than November 1, 1948. Announcement of the awards will be made as promptly as is possible.

EXAMINATION FOR MEDICAL-OFFICER  
POSITIONS

The United States Civil Service Commission has announced an examination for filling medical-officer (rotating intern and psychiatric resident) positions in St. Elizabeths Hospital, Washington, D. C.

Medical officers (rotating intern) are paid \$2200 for the first year and \$2400 for the second year. Medical officers (psychiatric resident) are paid from \$2400 to \$4100 a year, depending upon the amount of approved postgraduate training the applicant has completed. Appointments are open for July 1, 1949. Internships consist of two years of rotating service, and psychiatric residencies consist of one to three years in psychiatry. To qualify for internships applicants must be third-year or fourth-year students in an approved medical school, however, they may not enter on duty until they have successfully completed the full course of study. Applicants for psychiatric residencies must be graduates of an approved medical school, with the degree of doctor of medicine, and, in addition, they must have completed an approved internship or must be serving such an internship. No written test is required for the medical-officer positions. Details about the requirements are given in the examination announcement.

Interested persons may obtain information and application forms from the United States Civil Service Commission, Washington 25, D. C., from most first-class and second-class post offices and from Civil Service regional offices. Applications will be accepted until further notice in the Commission's Washington office.

THIRD INTER-AMERICAN CONGRESS OF  
RADIOLOGY

The third Inter-American Congress of Radiology will be held in Santiago, Chile, on November 11, 1949.

UNITED STATES NAVY MEDICAL  
TRAINING PROGRAM

The Surgeon General of the Navy has announced the expansion of the professional training program of the Bureau of Medicine and Surgery for reserve and regular medical officers, which is similar to the recently expanded Army medical training program. The object is to permit more Navy doctors to meet the requirements for certification by

the various American specialty boards and to enable the young doctor to serve his internship under the auspices of the Navy.

Graduates of Class A medical schools who have been accepted for internship by a hospital approved for such training by the Council on Medical Education and Hospitals of the American Medical Association may be commissioned as lieutenants (junior grade), MC, U. S. N. R., and permitted to continue their intern training. They will receive all the pay and allowance of the rank while so serving. After completing their internships, the medical officers must remain on active duty for a period of one year. If they meet the professional, physical and moral requirements, they will be given every encouragement to transfer to the regular Navy.

Interns who have completed the one year of obligated service, and who have transferred to the regular Navy, may be considered for residency training on a competitive basis with other officer personnel of the regular Medical Corps.

Resident physicians now in civilian hospitals, or those accepted for approved residency training, are eligible for commissions in the regular Navy. Those so commissioned will be assigned to duty, with full pay and allowances, in the hospital in which they are already a resident, or to which they have been accepted for residency training. Every attempt will be made to permit residents holding commissions in the regular Navy to complete their training in event of an emergency.

The Navy has at the present time 400 approved residencies and fellowships in the various specialties recognized by the American Specialty Boards in Navy and civilian hospitals. This educational training involving the 400 residencies is divided into 2 programs.

**Program A** One hundred of the above mentioned residencies, courses and fellowships will be made available for civilian physicians accepting a commission in the United States Navy. An additional 100 civilian physicians will be commissioned in the Navy and permitted to pursue their course, fellowship or residency, provided it is approved by the Council on Medical Education and Hospitals of the American Medical Association with concurrence of the specialty board. Upon acceptance of the designated training, they will be required to agree to remain in the Navy for a certain obligated time.

If on original appointment a candidate has not been approved for more than one year of training, during his first year of residency training (Program A) he may compete for one of the 300 residencies (Program B) available to the regular Navy medical officers, and if he obtains such training he will obligate himself to remain on active duty for an additional period depending upon the amount of time spent in training.

**Program B** Three hundred residencies, fellowships or courses, will be reserved for continuing the training program as presently organized for regular medical officers.

The obligated service following graduate medical training (courses, fellowships and residencies) in Navy hospitals is one year for each year of training received.

Information concerning any part of the program may be obtained by application to the Chief of the Bureau of Medicine and Surgery, Navy Department, Washington 25, D. C.

## SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING  
THURSDAY, JULY 29

## FRIDAY, JULY 30

\*10:00 a. m. - 12:00 p. m. Medical Staff Rounds. Peter Bent Brigham Hospital.

## TUESDAY, AUGUST 3

\*12:00 p. m. X-ray Conference. Margaret Jewett Hall. Mt. Auburn Hospital, Cambridge.

\*12:15-1:15 p. m. Clinicorontgenological Conference. Peter Bent Brigham Hospital.

\*1:30-2:30 p. m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.

## WEDNESDAY, AUGUST 4

\*12:00 p. m. - 1:00 p. m. Clinical Conference (Children's Hospital). Amphitheater. Peter Bent Brigham Hospital.

\*Open to the medical profession.

(Notices concluded on page xix)

# The New England Journal of Medicine

Copyright 1948 by the Massachusetts Medical Society

Volume 239

JULY 29, 1948

Number 5

## A REPORT TO THE NEW ENGLAND SURGICAL SOCIETY CONCERNING THE AMERICAN BOARD OF SURGERY\*

SAMUEL C HARVEY, M D †

NEW HAVEN, CONNECTICUT

THE American Board of Surgery, established in 1937, has completed the first ten years of its activities. It seems appropriate that the present representative on the Board of the New England Surgical Society should report upon its accomplishments and the lessons learned during this time.

It is best, perhaps, to start with the reasons for its establishment. These were in general two: the chaotic situation regarding the qualifications that might reasonably be expected of a surgeon, and the inadequacy, both in quantity and in quality, of opportunities for obtaining the experience necessary to prepare one to meet these qualifications.

It was generally recognized at that time by those competent to judge that a large component of surgery was done by inadequately trained physicians devoting only a part of their time to this specialty. It was well nigh impossible to ascertain except by personal knowledge, not generally available and frequently unreliable, who was in fact a competent surgeon and who was not. In the *Directory of the American Medical Association* surgeons were authenticated on their own statements that they were practicing surgery and therefore presumably competent. In fact, it was generally known that a great many physicians in general practice were doing their own surgery even in communities where competent surgeons, confining their practice to surgery alone, were available.

This situation had been recognized and discussed for many years, and several solutions had been proposed and some attempted. Governmental licensure of specialists had been repeatedly suggested but was obviously impracticable if not undesirable, for this could only be accomplished by legislation in each of the states, a procedure that has not been satisfactory enough, when applied to the basic requirements for the practice of medicine in general, to encourage its application to the specialties.

Membership in surgical societies was, with the exception of the surgical section of the American Medical Association and the American College of Surgeons, a mark of distinction too limited in its coverage. In the former one joined on signifying an interest in surgery, and in the latter the requirements were on a level pitched at initiating men actually doing surgery with the hope of improving their competency through postgraduate education.

The pattern of the boards for certification has become well established in other specialties, and that of surgery, a latecomer in the field, was set up along the same lines, being approved on the recommendation of the Advisory Board for Medical Specialties, by the Council on Medical Education and Hospitals of the American Medical Association. It should be made clear that, while recognized in this fashion, the American Board of Surgery was the result of the thought and action of many informed surgeons recognized by their colleagues as such, and approved by the major representative surgical associations, this has been evident in the continuing organization and functioning of the Board.

The objectives of the Board were and are to examine applicants and certify those meeting its requirements and — a purpose inextricably interwoven with this — to improve the opportunities for the training of surgeons by establishing the qualifications necessary for examination.

As in other specialty boards, the first certificates granted were to members of the founders' group "who had already amply demonstrated their fitness as trained specialists in surgery," 1152 surgeons being so certified. These were the senior surgeons to whom it would have been a hardship, if not an impossibility, to take the examinations. This method of admission could not be continued indefinitely without vitiating the purposes of the Board, and therefore it was announced at the start through suitable channels that the founders' group would be closed as of January 9, 1940. Unfortunately, for one reason or another, a number of sur-

\*Presented at a meeting of the New England Surgical Society, Providence, Rhode Island, October 4, 1947.  
From the Department of Surgery, Yale University School of Medicine.

†Professor of surgery (oncology), Yale University School of Medicine; under grant from the National Cancer Institute of the National Institute of Health, United States Public Health Service; associate surgeon, New Haven Hospital.



I WANT MORE PABLUM!

COPYRIGHT, 1945, MEAD JOHNSON & CO.  
EVANSVILLE, INDIANA, U.S.A.

aspect — and they are by no means immune to the charge of exploitation of professional personnel at his level — can be more adequately and readily done, for they are fewer in number and more susceptible to investigation both in potentiality and in performance

This screening of the applications is, then, the first step in the process for examination and a very necessary one, not only for the purposes of the Board but also for the best interests of many candidates. Some say that all who wish should be admitted to the examination without further ado. The result of this would be that either a large number of candidates would be failed or so many would pass that the Board would be discredited as an examining agency. To avoid the latter it would then tighten up its examination, failing some men who do not do well on the examinations, but have had good training, and passing others skilled in taking examinations, but who have had little or no experience. Less important perhaps is the number who would take a "flyer" at the examination on the chance of slipping through and would make it almost impossible to handle the load. Lastly, a major purpose of the Board, that of encouraging the development of adequate training programs, would be under these circumstances completely vitiated. This suggestion of relying completely upon examination is advanced by those who have not thought the question through or who suppose that this procedure is or can be made one of great accuracy. The methodology of examination has been thoroughly studied by experienced workers in the field of education and it has been well established that as the sole source of reference it has a considerable degree of error — approximately 20 per cent. The expression of results in precise mathematical terms gives an appearance of absolute and accurate value that is fictitious. It is at best only an approximation and must be reinforced in every way to reduce the error so far as possible, one of these is to evaluate the opportunity that the candidate has had for learning in the field of surgery.

This evaluation is made in the first instance by the secretary of the Board, whose long experience and sympathetic insight into the problems of the prospective surgeon are invaluable. In instances in which the problem is at all complicated, or in which his decision is questioned, the matter is carried before a special committee of the Board for further consideration and adjudication. Although the interests of the applicant concerned are viewed sympathetically and in detail, the paramount responsibility of the Board is to the public and its decisions must be so governed.

Another knotty problem concerned in the screening process is that of the ethical and moral standards of the candidate or, as I should prefer to put it, the pattern of behavior that may be expected of him in his future professional life. This has no reference

to economic and social classification, race, creed, color or sex, because the pattern of behavior is not conditioned by these, per se, although as in all persons, adversity and misfortune may have a warping effect. It is the right of one in our form of civilization to be considered an individual rather than to be submerged in invidious categories. The record of the Board in this respect is one of which all surgeons may well be proud.

This "pattern of behavior" is unpredictable to a considerable degree even with adequate information. The usual letters of recommendation are perfunctory, sometimes even mendacious, and these sources of information are, on the whole, not reliable. They are worth obtaining, however, because of the occasional enlightening response, which may lead to further investigation. When there is any cause for suspicion certain persons whose reliability is beyond question are queried confidentially. This necessity may arise when a man has shifted about for no apparent reason. Without evidence to the contrary, it may be assumed that the behavior of a person who completes his training in one institution, or in several, with a sense of responsibility has been above reproach, at least up to that time. In spite of these precautions it is not only possible but probable that there are a certain number of certificated surgeons whose practice will be tagged "unethical." Occasionally this complaint comes to the Board, and it is taken most seriously. When the evidence justifies such a step, certification is recalled, but it is necessary to be certain that it will stand up in court, for it is likely that legal action for damages will be taken against the Board. In the majority of cases on detailed inquiry it is found that there is an internecine situation — one of those professional quarrels arising from jealousy, clash of personalities and so forth and giving rise to charges of "unethical conduct" that even locally are never taken so seriously that they are brought before a board of censors of the county or state society. Frequently it is a stab in the back of which the victim is unaware, for the informer insists on remaining anonymous. I dwell on this not to establish a thesis that the Board makes no errors in the evaluation of the future behavior of men accredited by it, but to call attention to the inherent difficulties in this problem. If the New England Surgical Society or any other organization can see its way clear to being of assistance to the Board in this matter it will be welcomed.

The examination having taken place, every effort is made to obtain a fair evaluation of the results. In the written examination (Part I) the papers of all failures or near failures are reviewed by two additional members after the initial reading by a member of the Board, and the mark primarily given confirmed or revalued. Papers that are still doubtful are brought before the Board as a whole and fully discussed with the additional information concern-

geons at the time presumably qualified, did not see fit to take advantage of this opportunity. Even more unfortunate, in spite of ample publicity concerning the requirements of the Board for examination, a group of younger men were unable or at least did not make any attempt to fit themselves to meet its basic requirements. To lower these requirements now to meet the desires of these men would be unfair to those who have spent the necessary time and energy to prepare themselves properly and would encourage others to attempt a similar short cut to certification.

Meanwhile, during the first ten years of activity of the Board, 1752 surgeons were certified by examination, making with the founders' group a total of 2904. As of January 1, 1948, there were 2062 and 3214, respectively, 310 having been certified by examination during the past year.

It is of interest to you, I am sure, to get some idea of the activity that is involved in this examination process. During the year 1946 the Board had about two thousand letters of inquiry. There were 789 completed applications, of which 40 per cent were at once acceptable for examination. Others may have become so with further information or preparation, the general experience is that only about 20 per cent of the completed applications are finally rejected. Out of some 700 men taking Part I of the examination, of whom 100 were repeaters, 25 per cent failed. Of 362 taking Part II approximately the same percentage also failed. It should be borne in mind that these data for Part II comprise numerous partial failures and that the actual number of final failures is somewhat lower because of success when the candidate repeats the examination.

The criteria that are used for the process are relatively simple, and at the same time reasonably rigorous. The candidate must demonstrate that he has a sound knowledge and understanding of the field of general surgery as of today. This is in part contained in the more detailed texts of general surgery, and in the surgical literature of the last ten years, which may not yet have arrived at this distinction. He must also give evidence that he is capable of employing this knowledge with judgment and skill in the care of the patient. The question always asked in summation is, "Is this potentially a safe and sound surgeon?" Such values are, of course, relative, as is the process of examination. Thus, it must be considered as a screening mechanism in which the sound and unsound grain, together with a considerable amount of chaff, go into the original hopper.

The review of the application is the first screen, and is concerned with whether the candidate has had a fair opportunity to learn through study and experience what the surgeon entering upon practice today should know, a matter requiring adequate exposure to both time and environment. This cannot be and is not rigidly defined and enforced, but one must bear in mind that no matter at what level

the bar is set there will always be some who will insist upon attempting to crawl under it, even if the same amount of exertion expended properly would enable them to clear the obstacle without difficulty. The judgment of the Board has always been that a minimum of three years of institutional training is necessary, supplemented by two years of further experience. Recently, this has been modified upon the basis of experience indicating that one year of additional institutional training is usually equivalent to two years of supplementary experience gained otherwise. Therefore, four years of continuous, graded, institutional training is now recognized as adequate for admission to examination. It is the opinion that this represents the more desirable approach, but the number of opportunities for this intensive training are limited, and quite aside from the question of desirability it will be necessary for some time to continue also the requirements as established previously — namely, three years of institutional training with two years of supplementary program. There are thus two plans in effect by which a man can obtain the necessary preparation before taking the examination of the American Board of Surgery, one requiring five years, and the other four.

One may well ask whether the former is not quite satisfactory and what experience of the Board has led it to an adverse conclusion. The two supplementary years are almost as difficult to obtain as the additional year of institutional experience and often amount to little more than a waiting period, the educational value being only that which the prospective surgeon may vicariously gain in the first two years of practice. It is becoming increasingly difficult for him to obtain the hospital facilities necessary for surgical practice until he is at least eligible for examination. This fact, as well as the necessary requirement of the Board that he show evidence of further experience under suitable conditions, forces him into the hands of a preceptor. This relation may, when the preceptor is himself competent and also interested in the active and progressive training of the man, be highly desirable. Unfortunately it is altogether too frequently the subject of abuse, and the young surgeon becomes the preceptor's assistant with inadequate remuneration and the experience that is acquired in doing the "scut" work for the older man. He may then find, having completed his period of service, that any attempt to establish himself in practice is blocked at every turn by the very man who has been his preceptor. I cannot conceive that any surgeon will in principle condone conscienceless exploitation, and certainly the American Board of Surgery cannot be a party to any such business. Yet, under present conditions and despite the exercise of the greatest possible caution, this situation may inadvertently arise in occasional cases. On the other hand the evaluation of institutions in this

ive been established. These are particularly important as "pilot plants" for working out and demonstrating the proper approach. There are, however, by no means enough of these hospitals to train an adequate number of surgeons to replace those daily dropping by the wayside. Unfortunately, the idea has developed that without the facilities of a school of medicine it is impossible to carry out such training programs. This is not the case, and if the objectives projected in the formation of the Board of Surgery are to be achieved, many hospitals that are potentially capable of undertaking this training must do so. If the hospital is situated so that it is possible to do this under the guidance and with the assistance of a school of medicine, it may be the more readily accomplished, but this is not essential. There are now a sufficient number of younger surgeons who have been through this process of examination and training and who are therefore familiar with the concept and the application of it, so that given the opportunity this conversion of many hospitals quite away from schools of medicine and institutions for formal graduate instruction can be accomplished.

There are some who question the need or appropriateness of this method for the training of surgeons. To some it may seem an "academic" approach directed at the provision of the future teacher, rather than a "practical" method for obtaining practicing surgeons. If this is true, it has failed completely, for much more is required of the professional teacher than is provided in this program. More time and greater breadth of experience, particularly in the technics of teaching and investigation, are necessary for him. The requirements of the present training program, I must repeat, are directed at training competent, sound surgeons.

Another question that may be proposed is, Has the Board been reasonably successful in attaining its objectives? I think that there can be no question of the answer. The degree of recognition that has been accorded its diplomates has even proved embarrassing. The armed forces and the Veterans Administration, without the previous knowledge of the boards, recognized the qualifications of those physicians and surgeons who were diplomates, not only of the American Board of Surgery but of all the other specialty boards. That they were justified in so doing was proved by the experience during the war, for when these men were given appropriate assignments they performed superbly. In the Veterans Administration at the moment they are the core and foundation of the hope for improved professional care. Again, I wish to emphasize that the preferential position that these diplomates hold is not by any action of the boards, but is a voluntary and unsolicited recognition of their superior qualifications.

A similar situation for which the Board is not responsible is the special recognition of the diplo-

mates accorded by many hospitals. This is not the concern of the American Board of Surgery except so far as the indiscreet, injudicious and arbitrary action of many of these institutions has served to throw discredit upon it. It has officially and in all honesty disclaimed any responsibility for this. Many hospitals have made a very laudable effort to elevate the level of professional services and have considered a blanket and complete restriction of facilities to certified specialists the simplest and most effective way of doing so. They have overlooked in many cases the fact that such an abrupt transition cannot be made. There may be on their staffs men who are known to be incompetent and whom they justifiably wish to dispossess. The easiest way, instead of deciding and acting in the individual case, is a blanket ruling requiring certification for staff membership and thus relieving themselves of the personal antagonism aroused by direct action. Unfortunately, this also dispossesses many surgeons who in their services have long since proved their competence, but who because of age fall in the intermediate group caught in this transitional period without certification. In doing this, the hospital "throws out the baby with the bath." In all fairness, although the ultimate transition in many hospitals may well end in making their facilities available for the most part only to those certified, such a regulation is at present premature. In fact, in some situations it may be a long time before this can be done, for there is still an inadequate number of diplomates to fill the needs, and in many of the smaller communities it would be an economic impossibility to support these specialists were they available. The objective, although it may be admirable, cannot be reached at once and in all cases, but must be approached by a period of transition and adjustment.

It is my impression, and that of many others, I am sure, that the success of the Board's activities has been well beyond what the originators of it might reasonably have expected. It has by no stretch of the imagination resolved the problem of providing a high grade of surgery for all, and there still remains a very great and disgraceful amount of incompetent, dangerous and unnecessary surgery. Recently, at a meeting in New York of the American College of Surgeons, Dr. Harold L. Foss pointed out what all of us know but rarely confess. This has received considerable publicity and will intensify the pressure upon the hospitals for restricting the specialists within them to those who are diplomates of their respective boards. This is a problem that the members of the New England Surgical Society might well study, for it is to them that the public should look for a proper answer. The Board cannot do this, it can only assist in the carrying on of its specific functions. It is not in any sense responsible for the development of a postgraduate plan of education, or of surveying and making

ing the candidate that may be pertinent, and the Secretary is directed regarding suitable action.

In the oral examination (Part II) held in clinical surgery on patients, in anatomy on the cadaver and in pathology on gross surgical specimens and microscopical sections carefully selected, approximately half the examiners are surgeons other than members of the Board and competent for this purpose. In clinical surgery teams are made up of a Board member and an accessory examiner who query together and separately grade the results. Since the candidate has two cases for examination, he is evaluated by two teams, a total of four surgeons, two of whom are Board members. This part of the examination is rated heavily, but there is also insistence that he demonstrate a knowledge of anatomy and pathology, adequate for sound surgery. This requires intensive study or review by most candidates, for it is the experience of the Board that men otherwise competent are frequently distressingly lacking in these subjects, which are fundamental to surgery.

The evaluations so obtained are assembled and gone over in a conference of all examiners in which questions and discussion are most welcome. With the failures and in doubtful cases, the information available in the secretary's files is brought to bear before a decision is reached, and then the Secretary is instructed concerning the action to be taken. It should be noted that in this conference, which is the last and most important step leading to certification, while the members of the Board bear the responsibility, they are assisted by an equal number of surgeons who are not Board members. This has the advantage of relieving it of any implication of bias and bringing into its activities at the most significant point a considerable number of surgeons who not only contribute materially to its deliberations but also learn at first hand the way in which the Board approaches this problem of examination and certification.

The second purpose is the improvement of the training of surgeons who may wish to qualify for the certificate of the Board. As pointed out above, the first and, as has been confirmed by experience, the most important step was taken when the general plan of training was outlined. This was made sufficiently rigorous in the over-all requirement to ensure the necessary time and application for the learning of surgery, but elastic in detail so that the candidates' individual ability and opportunity would not be forcibly compressed into a standard form. Unfortunately, as educators are well aware, the majority of students "jell" into a pattern if there is the slightest opportunity to do so, and it is almost traditional, as well as being consistent with human nature, that some will attempt to find some way of "beating the game." There is too much of the idea that the awarding of a certificate makes a surgeon, a fallacious concept that is by no means limited to the experience of the American Boards of Surgery.

For these candidates, the requirements must be rigorous, and vigilance must be constantly employed to see that in one place or another the standards are not evaded. For others, and fortunately there are many of these whose primary and fixed interest is in becoming sound and competent surgeons, great elasticity is allowable. The touchstone is whether the primary interest lies in the certificate or in the antecedent training. This can be ascertained fairly readily in most instances by the plan that the candidate submits for review, if he does not submit such a plan to the Board, it must assume that he is content with the customary pattern and is not concerned with its being adapted to his particular desires or opportunities.

A problem that remains a distressing one is the lack of suitable institutions both in quality and quantity capable of providing the opportunity for learning to be a surgeon. This has always been apparent and was recognized in 1936 by the American College of Surgeons when the regents adopted a policy directed toward increasing suitable residencies. So far as physical facilities, proper administration and organization, number of patients and competent surgeons on the staff are concerned, there are plenty of hospitals that could and should undertake the responsibility for training surgeons. But there is more to it than this, and this centers about a willingness of the professional staff to modify certain prerogatives and to divert a modicum of time and energy to a program directed at training surgeons. There must be a continuity of effort and maintenance of its operation at a constant high level, which requires that one person—a surgeon—must have the responsibility and the authority for carrying this on. When there is already an authoritative chief surgeon, he must in addition be competent, familiar with the literature, soundly educated and have a great interest in teaching in the broadest sense. To do this, he and the staff will have to sacrifice some of their customary activities, however, if a sound residency system is established, any concessions made by the staff will be more than compensated for by the assistance and stimulation of these younger men. Lastly, there comes a time when direct responsibility for the complete care, including operative procedures of an adequate number of patients, under supervision, of course, provides the final step in training. This seems to involve the greatest difficulty in the organization of the complete training program, particularly today when private patients are consuming bed capacity, leaving but few in the ward category. If one thinks of the resident at this stage of his development, at least four years out of medical school and with three years of surgical training, as a "junior attending" surgeon who is incidentally living in the hospital, the transition is less difficult.

In many hospitals connected with the schools of medicine such residency-training programs

low include all lots used during the past twelve months, but the similarity of their composition, spite several minor changes, makes a statistical valuation valid. In Table 1 the composition of a representative lot of the solution of amino acids with respect to the eight amino acids essential for man\* and for arginine and histidine is shown and is compared with that of casein. The results are based on analyses by microbiologic assay.<sup>7-9</sup>

All subjects selected were carefully followed each day. Many of the infusions early in this study, as well as subsequent ones, were given to subjects in the metabolic ward for more detailed study. Since this product had previously been shown to be well tolerated in dogs at very rapid rates of in-

tients received this product postoperatively as the sole source of protein, as did the newborn infants with infectious diarrhea. The patients with malnutrition and liver disease usually received the amino acid solution as a parenteral protein

TABLE 2 *Diagnostic Classification of Subjects*

CLASSIFICATION	NO OF SUBJECTS
Normal volunteers	11
Convalescent medical patients	5
Postoperative surgical patients	10
Partial gastrectomy	6
Esophagectomy	2
Bowel resection	2
Malnutrition	16
Obstructive lesions of gastrointestinal tract	8
Chronic medical illnesses	8
Liver disease	15
Cirrhosis acute severe	11
Acute yellow atrophy	1
Wells disease	1
Infectious diarrhea of newborn	7
Total	62

TABLE 1 *Comparison of the Composition of the 10 Per Cent Solution of Amino Acids with Casein*

AMINO ACID	AMINO ACID SOLUTION* (1 FORM) gm. per liter of 10% solution	CASEIN		
		†	‡	§
		gm.	per 100 gm.	
Soleucine	9.2	5.6	6.4	8.6
Leucine	17.7	9.9	9.9	10.5
Lysine	9.9	7.7	8.5	6.7
Methionine	4.0	2.6	2.6	3.1
Phenylalanine	4.2	5.9	5.2	4.8
Threonine	2.0	4.2	4.2	4.6
Tryptophane	0.9	1.1	1.2	1.4
Valine	7.2	6.7	6.2	5.8
Arginine	2.5	3.9	3.6	3.7
Histidine	4.5	2.8	2.6	3.0

\*Also contains: 0.9 gm. of D-tryptophane, 22.6 gm. of glycine, 0.2-0.5 gm. of glutamic acid, less than 0.05 gm. of aspartic acid and 0.2 gm. of tyrosine per liter of 10 per cent solution (microbiological assay).

†Stokes et al.<sup>7</sup>

‡Hodson and Krueger.<sup>8</sup>

§Pearce et al.<sup>9</sup>

fusion,<sup>1,2</sup> it was planned to administer it at rates exceeding those possible with the commercial protein hydrolysates that had previously been employed. In no case was the rate of infusion slowed to avoid or diminish a reaction. The following data were obtained: the diagnosis and body weight, quantity of material infused, quantity of other substances (glucose, vitamins and so forth) simultaneously infused, time required for infusion, and all untoward reactions, both immediate and delayed, no matter how mild or transient.

## RESULTS

### Classification of Subjects

The subjects were classified by diagnosis (Table 2). We were able to observe the most minute untoward effects in the normal volunteers (medical students and interns) even at extremely rapid rates of infusion (50 gm. of amino acids injected intravenously in ten minutes). Similar data were obtained from the convalescent patients. All other subjects were infused for therapeutic reasons as well as for data concerning tolerance. Most of the surgical pa-

supplement. Many of the patients were critically ill.

### Quantity of Material Administered

The quantity of the 10 per cent solution of amino acids administered with each injection is shown in Table 3. Dosages of 30 cc (3 gm. of amino acids) of the solution were given twice daily with an equal volume of 10 per cent dextrose to newborn infants with infectious diarrhea. This actually amounts to over 0.5 gm. of protein per kilogram of body weight at each injection and is roughly comparable to the injection of 500 cc (50 gm. of amino acids) to a 70-kg adult subject. All the 342 injections in this study were given in thera-

TABLE 3 *Quantity of Amino Acid Solution Administered*

QUANTITY	NO OF INJECTIONS
cc	
30 (3 gm.)	90
500 (50 gm.)	162
1000 (100 gm.)	88
100 (10 gm.)	2
Total	342

peutic amounts — that is, they supplied at least 0.5 gm. of protein per kilogram of body weight, and many were larger.

### Composition of Material Administered

When administered for therapeutic purposes on the hospital wards, particularly when employed as the sole source of protein nutrient, the 10 per cent solution of amino acids was frequently given with 5 to 15 per cent dextrose in water or physi-

recommendations to hospitals regarding the organization of their staffs. It is not a continuing organization. When the man receives his certificate he does not become a member of a group such as this, or the American College of Surgeons. There is a place, however, for the postgraduate continuing education of the surgeon, a function that surgical organizations may perform and, particularly on a national scale, the American College of Surgeons is splendidly organized to carry out.

Quite aside from this, the New England Surgical Society can assist the American Board of Surgery in its objectives of improving the training of surgeons and of examining those who have had adequate training. Beyond this there are certain needs apparent from the previous discussion. The necessity for more hospitals that can give acceptable

residency training is great, and the members of the society should take the initiative and responsibility in developing their institutions to this end. Information—candid and dependable—regarding hospital staffs in respect to teaching programs and applicants who may apply for admission to the examination is sorely needed and could be provided in New England by the members of this society. Thoughtful criticisms and suggestions are always welcome to the Board and can be readily presented through representatives of the Society. Above all is needed the moral support of the members if the Board is believed to be doing reasonably well while the Society endorsed in the beginning and what its representatives have attempted to carry out in conformity with its wishes.

789 Howard Avenue

## THE RAPID INJECTION OF A SOLUTION OF AMINO ACIDS

### A Note on Its Clinical Tolerance in Man\*

RICHARD D. ECKHARDT, M.D.,† AND CHARLES S. DAVIDSON, M.D.‡

BOSTON

**E**XPERIENCE with the parenteral administration of protein hydrolysates of five varieties (four acid and one enzymatically hydrolyzed) has led us to establish certain criteria for an ideal solution. In the first place, it must be shown to be nutritionally adequate by maintaining weight and nitrogen balance in the normal person when used as a sole source of nitrogen, and, in addition, positive nitrogen balance, weight gain and regeneration of serum albumin should be observed in persons depleted of protein. Secondly, side effects—that is, pyrogenic reactions, nausea, vomiting, venous thrombosis and anorexia—should be minimal. Thirdly, the solution must be nonantigenic. Finally, only small amounts of the material injected should appear in the urine, even with rapid infusion. Although the available hydrolysates have been shown to be nutritionally adequate as measured by nitrogen balance, unpleasant side effects occur frequently enough to limit their clinical usefulness.

Observations of the clinical tolerance to a 10 per cent solution of amino acids§ prepared by the re-

combination of fractions of an acid hydrolysate of casein are reported below. The solution is essentially devoid of glutamic and aspartic acids, and supplemented with dl-tryptophane and glycine.<sup>1</sup> The results of 342 injections in 62 subjects over the past year indicate that the present solution of amino acids is better tolerated in man than the previously employed. The nutritional adequacy of the material and the urinary loss following infusion will be reported subsequently.

### MATERIALS AND METHODS

The product under investigation is a complete acid hydrolysate of casein, contains no peptides, is essentially devoid of the dicarboxylic amino acids (glutamic and aspartic) and is supplemented with dl-tryptophane and glycine so that it contains the eight amino acids essential for man.<sup>2</sup> Additional dl-methionine was added to the product employed in our early studies, but is no longer supplied since excess methionine in man does not contribute nutritional advantage to a protein containing adequate quantities of this amino acid.<sup>3,4</sup> The solution of amino acids now regularly contains adequate phenylalanine, although some of the early lots contained an insufficient amount of this essential amino acid.<sup>5</sup> The product is now neutralized with lactic acid to a pH of 7.2 to 7.4, whereas hydrochloric acid was previously used. Observations of the clinical tolerance of the 10 per cent solution of amino acids in man reported

\*From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital and the Department of Medicine, Harvard Medical School.

The expenses of this investigation were defrayed in part by a grant from Merck and Company Inc., Rahway, New Jersey to Harvard University.

†Research fellow in medicine, Harvard Medical School; chief research fellow, Thorndike Memorial Laboratory; and assistant in medicine, Boston City Hospital.

‡Associate in medicine and Francis Weld Peabody Fellow, Harvard Medical School; junior visiting physician and assistant director, Second and Fourth Medical Services, Boston City Hospital; assistant physician, Thorndike Memorial Laboratory, Boston City Hospital.

§Developed and distributed by Merck and Company Inc., Rahway, New Jersey, who supplied the material used in this investigation.

was more apparent in individual cases. Some subjects tolerated 50-gm amounts but became nauseated with 100 gm, even at a slower rate of infusion. Although nausea was noted in 27.4 per cent of the subjects at one time or another during the period of therapy, it occurred in but 9.4 per cent of all injections. Of the 17 subjects who became nauseated during this study, 9 (53 per cent) accounted for 75 per cent, and 3 (18 per cent) for 37.5 per cent of all cases of nausea observed. It appears, therefore, that the nausea that followed this solution of amino acids was not definitely related to the speed of the infusion (and thus the height of the blood amino acid level) but, to some degree, to the quantity of material infused (apparently a "saturation" phenomenon), and, most of all, it appeared to be an individual reaction most frequently observed in a few subjects.

Since no infusions were slowed down to lessen reactions, the severity of the nausea can be judged by the end point of vomiting. In only 2.6 per cent of all infusions did vomiting occur. In 4 of the 9 cases it followed an attempt at forced feeding, and in another it followed the ingestion of brewer's yeast immediately after the infusion.

The true incidence of anorexia is probably higher than the 9.1 per cent observed, since this phenomenon was not always inquired about and some patients were tube fed or too ill to be aware of such a subtle subjective reaction. It is our impression, arrived at mainly from normal subjects, that a transient diminution of appetite usually occurs but is of very short duration and rarely persists for more than one or two hours. Two subjects studied on our metabolic ward received the solution of amino acids parenterally for nineteen and twenty days, respectively, and consumed at least 3000 calories of food by mouth at regular meal hours. Thus, with the infusion speeds readily attained with this product, proper spacing of the infusions between feedings allows for normal food consumption at the regular mealtimes.

In approximately 7.6 per cent of all injections, and in 21.0 per cent of all subjects, a transient sense of "flushing" or "warmth" without temperature change was noted. There was no significant change in the blood pressure in several subjects in whom this observation was made. In 3 of the 62 subjects (4.1 per cent) and in 5 of the 342 injections (1.5 per cent) an urge to move the bowels immediately after the infusion was noted, occurring only with rapid rates of infusion. A few subjects complained of a mild frontal headache. On careful questioning, several subjects were aware of the ability to "taste" and to a lesser extent to "smell" the infusion immediately after it had entered the vein. This sensation was transient. A very few subjects noted mild formication of the extremities.

The veins of all subjects infused with this solution were carefully watched. No cases of venous

spasm, as has been reported with amino acid infusions,<sup>10</sup> were noted even with the rapid rates of infusion. Of the 342 infusions, thickening of the vein wall occurred in 8 (2.3 per cent). In 2 subjects the thrombotic process appeared to be inflammatory, the redness appearing about one day after the infusion and subsiding after about twenty-four hours. In these cases there was complete occlusion of the vein. Although glucose (even in hypertonic solutions) was frequently given with the 10 per cent solution of amino acids, no in-

TABLE 7 *Relation between Incidence of Nausea and Quantity of Material Administered*

QUANTITY ADMINISTERED IN EACH INJECTION	NO OF INJECTIONS	CASES OF NAUSEA	
		NO	PERCENTAGE
30 (3 gm)*	90	3	3
50 (50 gm.)	162	17	10.5
100 (100 gm.)	88	13	14.8
150 (150 gm.)	2	2	100.0
Totals	342	32	
Average			9.4

\*No objective reactions were observed in the 90 injections in the newborn infants with infectious diarrhea.

creased incidence of thrombosis could be attributed to its use. Many subjects received multiple injections of this solution in the same vein, and thrombotic processes developed in only 4 of the entire group.

When a diuresis occurred it could be related to the quantity of fluid infused. One patient with rheumatic heart disease with mitral stenosis and another patient with multiple pulmonary and mediastinal metastases from an osteogenic sarcoma became short of breath during the infusion, but to no greater degree than when an equivalent quantity of fluid containing dextrose and water was given. Obviously one must employ discretion whenever solutions are administered parenterally to patients with diminished cardiac reserve. No anaphylactic reactions of any type were noted — and, indeed, none were anticipated since the product is a complete hydrolysate and does not contain peptides. Clinical acidosis was not apparent, even on repeated daily injections. No untoward reactions were observed in the 90 injections in 7 infants with infectious diarrhea of the newborn. Finally, no serious reactions or deaths due to these 342 injections in 62 subjects were observed.

## DISCUSSION

The 10 per cent solution of amino acids employed in this study had previously been shown by others to maintain weight and nitrogen balance in normal dogs<sup>11</sup> and to achieve positive nitrogen balance with regeneration of hemoglobin and plasma proteins in the doubly depleted Whipple dog.<sup>12</sup> The results obtained in the present study of the clinical

ologic saline solution. Vitamins prepared for parenteral use (B complex, C and K) were often added. Many of the malnourished group and patients with cirrhosis of the liver received 10 to 20 cc of

TABLE 4 Number of Injections per Subject

NO OF INJECTIONS	NO OF SUBJECTS
1	19
2-5	24
6-10	6
11-15	7
16 or more*	6
Total	62

\*Two subjects received 16 injections. 1 received 18. 1 received 19, 1 received 20 and 1 received 21.

crude liver extract\* in the infusion mixture. Sodium lactate was occasionally added. On three occasions the solution of amino acids (50 gm) was given

ing the solution diluted to a large volume administered by constant intravenous drip. Over 70 per cent of the 342 infusions administered to our 62 subjects were given rapidly—that is, at rates corresponding to the infusion of 50 gm of amino acids to a 70-kg subject in less than an hour. Seventy-one per cent of these 242 rapid infusions were given at the rate of 50 gm of amino acids to a 70-kg subject in thirty minutes or less, and 41 per cent similarly in a quarter of an hour or less. These rates of infusion were far more rapid than could be attained with any of the protein hydrolysates previously employed, and at least four times faster than is usually recommended that they be given—that is, 50 gm of amino acids to a 70-kg adult in two hours.

### Reactions

The incidence of reactions at varying rates of infusion is presented in Table 5, and that of reactions

TABLE 5 Rate of Infusion and Incidence of Reactions of the 10 Per Cent Solution of Amino Acids

RATE OF ADMINISTRATION	CORRESPONDING TIME REQUIRED FOR INJECTION*	NO OF INJECTIONS	THROMBOSIS OF VEINS		ANOREXIA		NAUSEA		VOMITING		FREQUENCY OF NAUSEA AND VOMITING FROM PROTEIN HYDROLYSATES PREVIOUSLY EMPLOYED
			NO†	PER-CENT-AGE‡	NO†	PER-CENT-AGE‡	NO†	PER-CENT-AGE‡	NO†	PER-CENT-AGE‡	
gm/kg/hr	hr										
<0.36	>2	23	0	—	1	4.3	2	8.7	1	4.3	Infrequent
0.36-0.71	1-2	77	2	2.6	2	2.6	5	6.5	1	1.3	Frequent
>0.71	<1	242	6	2.5	18	11.6	25	10.3	7	2.9	Very frequent
<0.55->0.71	<1->2	342	8	2.3	31	9.1	32	9.4	9	2.6	Administration usually impossible

\*50 gm of amino acid, injected in a 70 kg subject.

†Cases of reaction for each rate period.

‡Percentage of reaction for each rate period.

together with 75 gm of human serum albumin (300 cc of a 25 per cent solution). Although 240 of the 342 injections were "mixed," there was no apparent difference in the clinical tolerance whether the solution of amino acids was given alone or with these other substances. The only noticeable effect of the addition of other substances to the solution of amino acids was the decrease in the infusion rate necessitated by the increased fluid volume.

### Number of Injections per Subject

Although many of the subjects received multiple injections (Table 4), no apparent increased incidence of untoward reactions was observed with subsequent infusions.

### Rate of Infusion

In Table 5 are presented the rates of infusion of the solution of amino acids employed during this study. Only 7 per cent of all injections were given slowly, and most of these were in patients receiv-

ing the solution diluted to a large volume administered by constant intravenous drip. Over 70 per cent of the 342 infusions administered to our 62 subjects were given rapidly—that is, at rates corresponding to the infusion of 50 gm of amino acids to a 70-kg subject in less than an hour.

Seventy-one per cent of these 242 rapid infusions were given at the rate of 50 gm of amino acids to a 70-kg subject in thirty minutes or less, and 41 per cent similarly in a quarter of an hour or less. These rates of infusion were far more rapid than could be attained with any of the protein hydrolysates previously employed, and at least four times faster than is usually recommended that they be given—that is, 50 gm of amino acids to a 70-kg adult in two hours.

TABLE 6 Reactions Occurring One or More Times in All Subjects at All Rates of Infusion

NO OF SUBJECTS	THROMBOSIS OF VEINS		ANOREXIA		NAUSEA		VOMITING	
	NO	PER-CENT-AGE	NO	PER-CENT-AGE	NO	PER-CENT-AGE	NO	PER-CENT-AGE
62	4	6.5	7	11.3	17	27.4	5	8.1

should have anticipated from the infusion bottle and sets employed.

Nausea was observed in 9.4 per cent of all injections, and did not greatly vary in incidence with the rates of infusion. There does seem to be a greater incidence of nausea, however, the larger the quantity of material injected (Table 7). The increased incidence of nausea with larger infusions

\* "Intrasheptol" furnished by Lederle Laboratories Inc., Pearl River, New York.

- 8 Hodson A. Z. and Krueger G. M. Essential amino acid content of casein and fresh and processed cow's milk as determined microbiologically on hydrolysates *Arch Biochem.* 10:55-64 1946.
- 9 Pearce E. L., Sanberlich H. E. and Baumann C. A. Amino acids excreted by mice fed incomplete proteins *J Biol. Chem.* 168: 271-282, 1947
- 10 Werner S. C. Use of mixture of pure amino acids in surgical nutrition certain pharmacologic considerations *Ann Surg* 126:169-194 1947
- 11 Silber R. H. Clark I., Howe, E. E. and Porter C. C. Maintenance of dogs on diet containing amino acids as source of nitrogen *Federation Proc* 6:290 1947
- 11 Rohsheit-Robbins F. S. Personal communication
- 13 Smyth C. J. Laschak A. G. and Levey S. Effect of orally and intravenously administered amino acid mixtures on voluntary food consumption in normal men *J Clin Investigation* 26:459-446 1947
- 14 Bassett S. H. Woods R. R. Shull F. W. and Madden S. C. Parenterally administered amino acids as source of protein in man *New Eng J Med* 230:106-108 1944
- 15 Madden S. C., Woods R. R. Shull F. W. Remington, J. H. and Whipple G. H. Tolerance to amino acid mixtures and casein digests given intravenously glutamic acid responsible for reactions. *J Exper Med* 81:439-448 1945
- 16 Unna K. and Howe E. E. Toxic effects of glutamic and aspartic acid *Federation Proc* 4:1-8 1945

## THE AGE DISTRIBUTION OF POLIOMYELITIS IN MASSACHUSETTS

R. J. M. HORTON, M.D.,\* AND A. DANIEL RUBENSTEIN, M.D.†

BOSTON

DATA concerning the incidence of poliomyelitis in Massachusetts have been collected by the Department of Public Health since 1907. This material had been studied statistically by Forsbeck and Luther<sup>1</sup> in 1930, and it was thought that a review of these older records, combined with the

consideration of the age distribution. The material on the geographical aspects will be published elsewhere.

In the earlier study of Forsbeck and Luther,<sup>1</sup> it was noted that the percentage age distribution of the reported cases of poliomyelitis had been undergoing considerable variation. This change,

TABLE 1 Age Distribution of Poliomyelitis in Massachusetts (1907-1945)

YEAR	PATIENTS 0-4 Yr. of AGE		PATIENTS 5-9 Yr. of AGE		PATIENTS 10-14 Yr. of AGE		PATIENTS 15-19 Yr. of AGE		PATIENTS OVER 20 Yr. of AGE		KNOWN AGES	UNKNOWN AGES	ALL CASES
	NO.	PER- CENTAGE	NO.	PER- CENTAGE	NO.	PER- CENTAGE	NO.	PER- CENTAGE	NO.	PER- CENTAGE	NO.	NO.	NO.
1907	—	—	—	—	—	—	—	—	—	—	—	234	234
1908	37	53.7	15	21.7	6	8.7	7	10.1	4	5.8	69	67	136
1909	408	66.3	115	18.7	44	7.2	15	2.4	33	5.4	615	308	923
1910	345	57.4	—	—	—	—	—	—	—	—	601	244	845
1911	—	(64.2)	—	—	—	—	—	—	—	—	—	260	260
1912	60	66.7	15	16.7	—	—	—	—	7	7.7	90	79	169
1913	181	62.0	58	19.9	—	—	—	—	9	3.0	292	69	361
1914	62	64.6	15	15.6	—	—	—	—	9	9.4	96	55	151
1915	76	62.3	24	19.7	—	—	—	—	5	4.1	122	13	135
1916	1289	69.7	366	19.8	—	—	—	—	85	4.6	1850	77	1927
1917	—	(64.0)	—	(19.8)	—	—	—	—	—	(4.4)	—	174	174
1918	63	66.3	13	13.7	7	7.4	5	5.2	7	7.4	95	4	99
1919	39	61.9	13	20.6	6	9.5	3	4.8	2	3.2	63	3	66
1920	347	53.2	165	25.5	67	10.3	34	5.2	39	6.0	632	44	696
1921	98	43.6	53	23.5	30	13.3	13	5.8	31	13.8	225	8	233
1922	103	49.8	52	25.1	27	13.0	15	7.3	10	4.8	207	10	217
1923	126	59.4	46	21.7	20	9.4	8	3.8	12	5.7	212	11	223
1924	126	47.0	65	24.2	39	14.6	15	5.6	23	8.6	268	9	277
1925	81	50.3	27	16.8	23	17.4	8	5.0	17	10.5	161	6	167
1926	107	44.8	70	29.3	23	9.6	15	6.3	24	10.0	239	6	245
1927	536	45.9	361	30.9	135	11.4	70	6.0	67	5.8	1167	22	1189
1928	160	36.9	137	31.6	70	16.1	30	6.9	37	8.3	434	—	434
1929	32	27.8	38	33.1	19	16.5	15	1.0	11	9.6	115	4	119
1930	191	38.0	197	39.1	62	12.5	24	4.8	28	5.6	503	—	503
1931	398	27.9	579	40.5	230	16.1	113	7.9	108	7.6	1428	—	1428
1932	15	24.7	19	31.1	13	21.3	8	13.1	6	9.8	61	—	61
1933	98	27.8	151	37.1	61	17.3	24	6.8	39	11.0	353	—	353
1934	15	19.7	26	34.3	15	19.7	11	14.5	9	11.8	76	—	76
1935	448	32.2	461	33.2	298	21.4	98	7.1	55	6.1	1390	—	1390
1936	13	25.5	6	11.8	12	23.5	16	31.4	4	7.8	51	—	51
1937	74	21.1	116	33.0	85	24.2	40	11.4	36	10.3	351	—	351
1938	8	44.4	3	16.7	4	22.2	2	11.1	1	5.6	18	—	18
1939	17	22.4	27	35.5	14	18.4	10	13.2	5	10.5	76	—	76
1940	9	20.0	15	33.3	12	26.7	5	17.8	1	2.2	45	—	45
1941	43	23.6	62	34.1	33	18.1	16	8.8	28	15.4	182	—	182
1942	7	19.4	15	41.7	4	11.1	2	5.6	8	22.2	36	—	36
1943	71	28.1	83	33.0	43	17.1	25	9.9	30	11.9	252	—	252
1944	62	14.5	166	39.0	115	27.0	39	9.2	44	10.3	426	10	436
1945	103	19.8	181	34.6	119	23.0	49	9.4	69	13.2	521	6	527

data accumulated during the past fifteen years would yield additional information on this subject.

In the present analysis particular attention has been given to the age distribution and the geographical behavior of poliomyelitis in Massachusetts since 1907. This discussion is limited to a con-

sideration of the age distribution. The material on the geographical aspects will be published elsewhere. In the earlier study of Forsbeck and Luther,<sup>1</sup> it was noted that the percentage age distribution of the reported cases of poliomyelitis had been undergoing considerable variation. This change,

first noted about 1918, was still active in 1930. The same gradual alteration had been noted in other states by various authors.<sup>2</sup> To our knowledge, no satisfactory explanation of this phenomenon has yet been presented.

The age distribution of poliomyelitis in Massachusetts for the period during which records are available (1910-1947) is given in Table 1. The figures for the years 1907, 1911 and 1917 are

\*County health officer, Board of Health, Lahui, Kawai, Hawaii

†Assistant professor of epidemiology, Harvard School of Public Health, director of hospital survey and construction, Massachusetts Department of Public Health

tolerance to rapid intravenous infusions of the solution of amino acids indicate that the present solution is better tolerated in man than those previously employed in this clinic. On several occasions the present product was satisfactorily employed, even though infused more rapidly, in persons in whom other hydrolysates had been discontinued because of nausea, vomiting or venous thrombosis. Over 70 per cent of the infusions were given at rates of administration more rapid than is usually possible with the available commercial hydrolysates. Because of the length of time previously required to infuse 50 to 100 gm of amino acids and the frequency of nausea and vomiting, parenteral protein therapy has unfortunately been limited, because of both inconvenience and discomfort to the patient and the constant vigilance required by the physician. Since these disadvantages are minimized by the present product, parenteral protein hydrolysate therapy is more practical, and the physician may, if necessary, provide optimum protein feeding entirely by the intravenous route.

When employed as a parenteral protein supplement, the available protein hydrolysates may greatly diminish the voluntary oral food consumption, their apparent benefits being thus negated.<sup>13</sup> The present solution of amino acids appears to have marked superiority in this respect. Because of the rapidity of infusion attainable as well as the short duration of the anorexia that may ensue, the proper spacing of the injection between feedings allows for normal food consumption at regular mealtimes.

Although mixtures of synthetic amino acids are extremely well tolerated in man at rapid rates of infusion,<sup>10, 14</sup> have no significant effect on the oral food consumption<sup>13</sup> and can maintain nitrogen balance,<sup>10, 14</sup> their practical use is greatly limited because of both their excessive cost and the inefficiency due to the nonnutritive value and urinary loss of many of the unnatural amino acid isomers that they contain. Their value has been mainly as an investigative tool from which knowledge concerning the amino acids required by man, the tolerance of individual and mixtures of amino acids, the loss of these substances in the urine and the utilization of the unnatural isomer of the amino acids has been obtained.

An ideal product is not yet available. Although the dicarboxylic amino acids (glutamic and aspartic) contribute to the production of nausea and vomiting,<sup>15, 16</sup> their virtual removal from this product has not entirely eliminated these undesirable responses. The greater incidence of nausea when larger quantities of amino acids are infused (even at slower rates of infusion) suggests that a "saturation point" may be reached. Infusions of 50 gm of amino acids twice daily (instead of a single 100-gm infusion) might be ex-

pected to diminish reactions. As mentioned above, many cases of nausea appeared to be due to a lowered individual tolerance.

The relative freedom from venous thrombosis with the enzymatic casein hydrolysate previously employed ("amigen") is comparable to that of the present product, whereas most other hydrolysates caused a much higher incidence.

The solution of amino acids was well tolerated by the patients with the various illnesses reported in this paper, including those with severe acute cirrhosis of the liver, and infants with infectious diarrhea of the newborn.

## SUMMARY

A 10 per cent solution of amino acids prepared by the complete acid hydrolysis of casein, devoid of peptides, largely freed of glutamic and aspartic acids and supplemented with dl-tryptophane and glycine, was administered 342 times to 62 subjects.

Over 70 per cent of all infusions were administered at rates usually unattainable with the previously available protein hydrolysates (50 gm of amino acids in 70-kg subject in less than an hour). All injections supplied at least 0.5 gm of protein per kilogram of body weight, and many were larger.

The clinical tolerance of the solution of amino acids was evaluated in normal subjects as well as in patients with a variety of illnesses requiring parenteral protein therapy. There was no apparent difference in the clinical tolerance of the amino acid solution whether it was given with glucose, saline, lactate or vitamins, or when it was given repeatedly.

The incidence of pyrogenic reactions was 0.3 per cent, nausea 9.4 per cent, vomiting 2.6 per cent, venous thrombosis 2.3 per cent, and transient anorexia 9.1 per cent.

Because of the rapid rates of infusion attainable with but few untoward reactions, it is concluded that the solution of amino acids employed in this study was better tolerated in man than the protein hydrolysates previously used in this clinic.

## REFERENCES

1. Howe E. E., Unna K., Richards G. and Seeler A. O. Comparative tolerance to mixtures of natural and racemic amino acids in intravenous infusion in dog. *J Biol Chem.* 162:395-401 1946.
2. Silber R. H., Seeler A. O. and Howe E. E. Urinary excretion of amino acids following intravenous administration of amino acid mixtures. *J Biol Chem.* 164:639-649 1946.
3. Rose W. C. *Progress in Conquest of Malnutrition by Amino Acids*. 52 pp. New York: American Pharmaceutical Manufacturers Association 1944. P. 18.
4. Johnson R. M., Deuel H. J. Jr., Morehouse M. G. and Mehl J. W. Effect of methionine upon urinary nitrogen in men at normal and low levels of protein intake. *J Nutrition* 33:371-387 1947.
5. Cox W. V. et al. Nitrogen retention studies on rats, dogs and man: effect of adding methionine to enzymatic casein hydrolysate. *J Nutrition* 33:437-457 1947.
6. Ehardt R. D. and Davidson C. S. Oral and parenteral phenylalanine requirements for nitrogen equilibrium in man. *J Clin Investigation* 27:165-170 1948.
7. Stokes J. L., Gunness M., Dwyer I. M. and Caswell M. C. Microbiological methods for determination of amino acids. II. Colorimetric assay for the ten essential amino acids. *J Biol Chem.* 160:35-49 1945.

17 per cent of the cases of poliomyelitis reported during that year were nonparalytic. Data for certain other years also indicate that in general, nonparalytic cases constituted less than 10 per cent of the total number reported through 1917 and less than 50 per cent until 1920.

Reporting of nonparalytic cases became routine in 1935. During the succeeding eleven years nonparalytic cases have been recorded at an average rate of 37.0 per cent of the total for any one year. Partially complete data for 1931 show that 35.0 per cent of the cases were nonparalytic. There has been no apparent tendency for nonparalytic poliomyelitis either to increase or to decrease during the past decade. There is evidence, therefore, of an increase in the reporting of nonparalytic poliomyelitis from about 10 per cent to approximately 33.3 per cent of the total number of cases.

Since the rate of reporting of nonparalytic cases has been relatively steady since 1935, this increase in reported cases of nonparalytic poliomyelitis occurred in the period between 1918 and 1931. The significant factors responsible were greater knowledge of the disease as a result of the studies made during the great New York epidemic of 1916 and the introduction of convalescent serum for the treatment of paralytic cases. The reporting of nonparalytic cases was also stimulated to a great extent by the difficulties encountered in differentiating paralytic from nonparalytic cases. Apparently, once the habit of reporting such cases had been established, it continued to the present.

#### AGE DISTRIBUTION OF PARALYTIC AND NON-PARALYTIC POLIOMYELITIS

Although paralytic and nonparalytic poliomyelitis in Massachusetts are alike so far as the seasonal, geographic and sex distribution is concerned, the

TABLE 3 Percentage Age Distribution of Nonparalytic Poliomyelitis in Massachusetts (1935-1945)

AGE	NO OF CASES	PERCENTAGE
0-4	221	18.2
5-9	489	40.3
10-14	702	56.9
15-19	110	9.1
20	9	0.6
Total	1,215	

age distribution of the two varieties is dissimilar. The greatest number of nonparalytic cases occurs in the patients five to nine years of age, the second greatest in those ten to fifteen years of age, and the least in those under four years of age, the latter being the group in which the greatest number of paralytic cases are found. Difficulties in diagnosing nonparalytic poliomyelitis in infants and very young children may be the most significant factor

in this observed difference. The age distribution of the nonparalytic cases has remained relatively unchanged since 1935 (Table 3). Although the data concerning nonparalytic cases in the years prior to 1935 are less complete, there is no evidence from

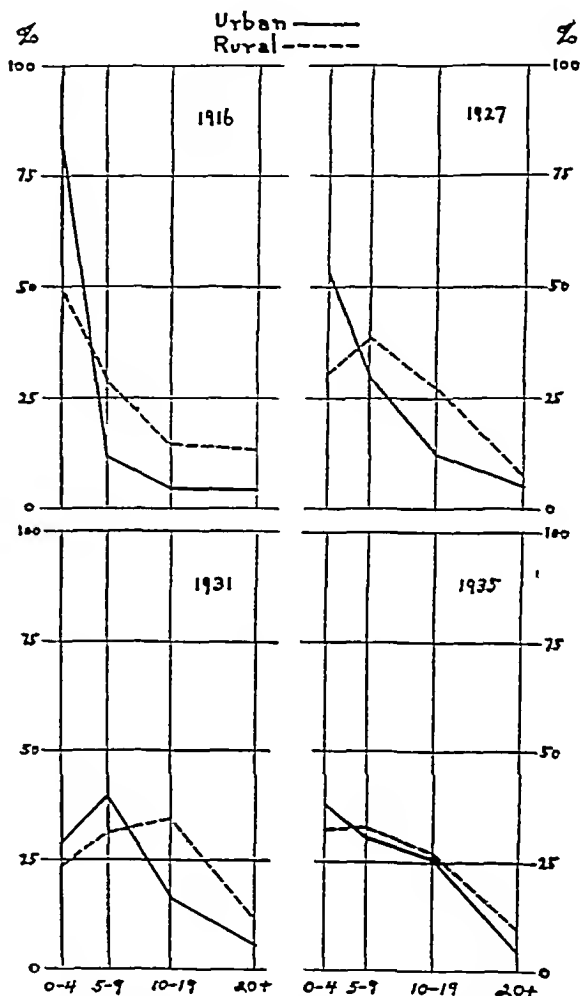


FIGURE 2. Urban (Cities with Populations of More Than 100,000) and Rural (Towns with Populations of Less Than 2500) Age Distribution of Poliomyelitis in Massachusetts for Epidemic Years

the available information that the age distribution of this disease has been different for these periods.

Since the age distribution of the nonparalytic cases, as noted above, differs from that of the paralytic, it would be expected that the addition of a gradually increasing proportion of nonparalytic cases would alter considerably the age distribution of the total. The more marked changes would be a decrease in number of nonparalytic cases in the patients under four years of age and increases in those five to nine and ten to fourteen years of age. The change would be most striking between 1927

lacking, and those for 1910 to 1916 are not available in all age groups

These data, presented graphically in Figure 1, differ from those used by Forsbeck and Luther<sup>1</sup> in that the figures for the various age groups are here shown as five-year moving medians. By this method trends become more apparent. It is noted that the decrease in the group of patients under four years of age from 1918 to 1920 seems somewhat exaggerated when compared with the actual percentages as given in Table 1.

The missing values for the years 1911 and 1917 have been obtained by interpolating a figure mid-

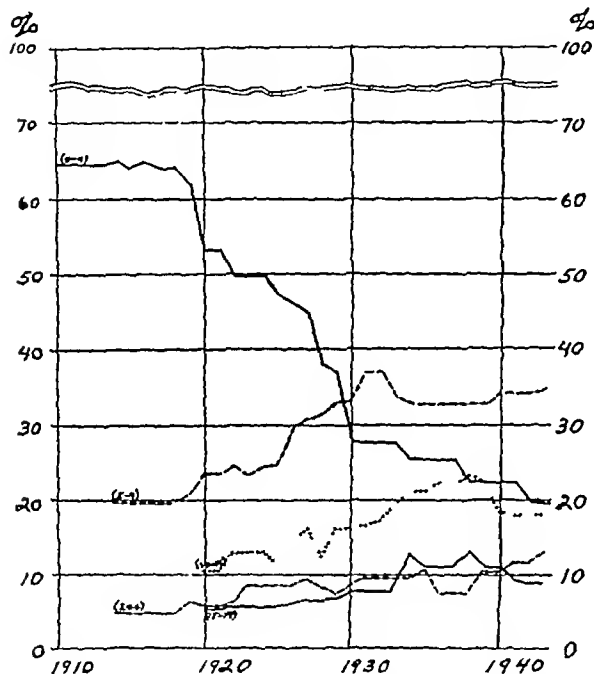


FIGURE 1 Age Distribution of Poliomyelitis in Massachusetts, 1910-1943 (Five-Year Moving Medians)

way between the middle values of the two years immediately preceding and following the year for which the value is lacking. The figures so obtained have been inserted in parentheses in Table 1.

Although the data are incomplete in the first decade (1910-1920), it is apparent that the age distribution during this period remained relatively constant. In the last two years of this period — namely, 1918 and 1919 — a decline occurred in the patients under four years of age, with a compensatory increase in the group from five to nine years of age. During the next decade (1920-1930) a continuation of this trend is noted, with the greatest decrease between 1927 and 1930 in the patients under four years of age. The compensating increases are most striking during this decade in the patients from five to nine and those from ten to fourteen years of age, with small increases in the

two remaining categories. From 1930 to 1943 the decrease in the patients under four years of age is still apparent, although less marked, and the increases in other age groups are much less spectacular.

#### CHANGES IN AGE OF THE POPULATION

In 1900, 1910 and 1920 persons under four years of age constituted respectively 10.1, 9.8 and 10.0 per cent of the total population in Massachusetts. This period of stability in the population corresponds with a period in which the age distribution of poliomyelitis remained stationary. In 1930 the same age group comprised 8.2 per cent of the entire population of the Commonwealth, and in 1940 it decreased by about a third — to 6.5 per cent. The decrease in the incidence of poliomyelitis in this age group, however, for the same period was over two thirds and therefore cannot be explained totally on the basis of aging population. The change in

TABLE 2 Ratios of Rates under Five Years of Age to Total Rates for Paralytic and All Cases

YEAR	ALL PATIENTS			PARALYZED PATIENTS		
	UNDER 5	ALL AGES	RATIO	UNDER 5	ALL AGES	RATIO
1910	147.47	25.10	5.87	147.47	25.10	5.87
1920	96.00	18.07	5.31	96.00	18.07	5.31
1935	141.90	32.24	4.39	101.90	19.37	5.27
1940	5.19	1.04	3.05	2.13	0.59	3.61

population age distribution has undoubtedly been a significant factor, but that it is not the only factor is apparent from Table 2, from which the influence of the variation in annual incidence of poliomyelitis and the aging population has been removed by the use of a ratio between specific and total morbidity rates. From this table it is apparent that the ratio is lower for the more recent years (1935-1940) and this would not have occurred had the change in age distribution of the population been the only factor concerned.

During the period between 1930 and 1940 it was found as previously noted that the decrease in the incidence of poliomyelitis among children under four years of age was much less than that in the previous decades. The reduction is, however, proportionate to the decrease in that age group of the population during the same period and may therefore be considered as having been caused by it. However, the marked change that occurred between 1920 and 1930 must have been caused by some factor or factors in addition to that of alteration in age of the population. This factor would have to be one that was most marked between 1918 and 1930, particularly between 1927 and 1930, and one that remained active after 1930.

#### REPORTING OF NONPARALYTIC POLIOMYELITIS

The annual report of the Massachusetts Department of Public Health for 1909<sup>2</sup> states that

## SPLENIC RUPTURE IN INFECTIOUS MONONUCLEOSIS\*

JOSEPH J TIMMES, M.D.,† JAMES H AVERILL, M.D.,‡ AND JAMES METCALFE, M.D.§

NEWPORT, RHODE ISLAND

**R**UPTURE of the spleen in infectious mononucleosis is a rare complication of a rather common disease. King,<sup>1</sup> in 1941, presented the first authenticated case. Since then 13 additional cases have been reported.<sup>2-8</sup>

It is the purpose of this paper to present 2 additional cases of infectious mononucleosis complicated by splenic rupture. In 1 of these the primary pathologic process was unsuspected preoperatively. In the other the diagnosis had been established before operation was undertaken. Subsequent to splenectomy both patients recovered full health, and microscopical changes consistent with those described as occurring in infectious mononucleosis were found in both the removed spleens. In one of these cases rupture apparently followed slight trauma to the abdomen. In the other, spontaneous rupture appears to have occurred.

Previously reported cases include only two in which splenic rupture followed definite abdominal trauma.<sup>5,6</sup> It must therefore be emphasized that rupture of the spleen in infectious mononucleosis may occur spontaneously or as the result of such trauma as that involved in defecation or in palpation of the abdomen in the course of physical examination.

Smith and Custer<sup>6</sup> first called attention to the time element of pre-existing symptoms in relation to splenic rupture. Table 1 includes an estimate of this time factor in the reported cases. In only 1 case (reported below) did splenic rupture occur less than two weeks after the onset of symptoms. This tends to support the statement made by Smith and Custer<sup>6</sup> that not until the third week have the capsular and trabecular changes progressed sufficiently to permit rupture, either spontaneously or as the result of slight trauma.

Consideration of the data summarized in Table 1 leads to the impression that a preoperative diagnosis of infectious mononucleosis was made in only 7 of the 16 cases. It is interesting to note that in the 7 cases in which a diagnosis of infectious mononucleosis had been made there was only 1 subsequent death, in that case no operation was performed because the diagnosis of ruptured spleen was not made. In the 9 undiagnosed cases 3

patients died without benefit of operation, and 2 died postoperatively. The over-all mortality in the 16 cases was 30 per cent. Although this series is too small to draw statistical conclusions it seems reasonable to hope that with increasing awareness of the fact that spontaneous rupture of the spleen may occur in infectious mononucleosis, more prompt and decisive operation will result, with subsequent improvement of the survival rate in this dangerous complication of an otherwise benign disease.

## CASE REPORTS

Case 1. R. E. M., a 19-year-old seaman second class, entered the hospital on September 8, 1947, with the chief complaint of pain in the left upper abdomen of 48 hours' duration. One month before admission he had developed swollen cervical lymph nodes and fever associated with malaise and anorexia. He had no sore throat or infection about the head or neck at that time to account for the lymphadenopathy. He was treated with penicillin, and apparently his symptoms subsided in several days. On September 4, while roughhousing, he was struck a light blow in the epigastrium, which was not severe enough to knock him down. Upon arising on September 6 he noted mild left-upper-quadrant pain which suddenly became severe and doubled him up. This pain remained constant until entry, except for periods of increased severity when it radiated to his left shoulder. His symptoms were aggravated by coughing or deep breathing and relieved partially when he sat upright. On the day of admission feverishness and generalized abdominal pain were present. Nausea, vomiting, diarrhea and headache were denied.

Physical examination revealed a hot, flushed, somewhat dehydrated patient, there was a questionable icteric tint to the sclerae. There was limitation of expansion of the left side of the chest because of the abdominal pain, but the lungs were clear. Examination of the heart was not remarkable. The abdomen was diffusely tender, but most tender in the left upper quadrant, where there was a sense of fullness and a questionable mass. Throughout the abdomen there was "a doughy type of rigidity."

The temperature was 100°F, the pulse 108, and the blood pressure 124/72.

Examination of the blood disclosed a red-cell count of 5,400,000, with a hemoglobin of 9.5 gm., and a white-cell count of 7200. A differential white-cell count was not done at that time.

The patient was taken directly to the operating room. A high, left-rectus-muscle-splitting incision was made under nitrous oxide, oxygen and ether endotracheal anesthesia. Blood clots and free old blood were found in the peritoneal cavity. An enlarged spleen was encountered with a large hematoma on its lateral surface. The spleen was not adherent, but in freeing the superior pole by blunt dissection, it was further ruptured into several fragments. The fragments were manually removed, and the pedicle ligated en masse. During manipulation of the spleen the patient went into profound circulatory collapse, which responded to the intravenous infusion of 1500 cc of whole blood. The abdominal wall was closed in layers without drainage.

The postoperative course was remarkably smooth, without any evidence of a pulmonary complication. He became ambulatory on the 3rd postoperative day.

On September 25 heterophil-antibody agglutination was positive in dilutions up to 1:1792, and a blood smear showed 63 per cent neutrophils, 34 per cent lymphocytes, 1 per cent

\*The opinions or assertions contained herein are the private ones of the authors and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

†Acting chief of surgery, United States Naval Hospital.

‡Member, Department of Medicine, United States Naval Hospital formerly medical house officer, Massachusetts General Hospital, Boston.

§Member, Department of Medicine, United States Naval Hospital formerly medical house officer, Peter Bent Brigham Hospital.

and 1931, when the stimulus to increased reporting of nonparalytic cases was most dominant. This is precisely the pattern of the change in the age distribution of the disease from 1918 to 1930 that was not wholly explained by the variation in the population as mentioned above.

If the change in age of the population and increased reporting of nonparalytic cases were responsible for the major portion of the alteration in percentage age distribution, and if only paralyzed cases were considered, the relation between the morbidity rates for poliomyelitis in the whole population and in the group under five years of age should show no marked change during the period under observation. In Table 2 such a relation is presented for sample years. Census years have been used except for 1935. This table suggests a relatively constant ratio of approximately 5 cases in the patients under five years of age, to each 1 in the general population for the four sample years. It may therefore be concluded that there has been no essential change in the epidemiologic behavior of poliomyelitis in Massachusetts and that the apparent variation in its age distribution has been due almost entirely to two factors: a change in the age distribution of the population, and an increase in the reporting of nonparalytic cases.

#### URBAN-RURAL AGE DISTRIBUTION

Figure 2 represents the urban and rural percentage age distribution of poliomyelitis in Massachusetts for epidemic years. The age grouping ten to nineteen only is used because the data for 1916 are available only in this form. The distribution shows the same changes previously discussed — namely, a decrease in the patients under four years of age and increases in the older age groups. In addition, the marked difference between urban

and rural distributions that existed in 1916 has gradually decreased until in 1935, although still apparent, it is less striking. Similar differences between urban and rural age distributions are found in other communicable diseases, particularly the virus infections of childhood. It is generally accepted that these changes are due to the greater dispersion of the population in rural areas, resulting in relatively fewer cases at early ages and more among older persons. In Massachusetts there are comparatively few isolated communities at the present time, whereas in 1916 there was a larger number of truly rural areas. The great increase in automobile travel, the expansion of cities and changes in rural school systems have tended to increase the opportunities for exposure of rural populations to infectious diseases.

#### SUMMARY

Changes in the percentage age distribution of poliomyelitis in Massachusetts since 1907 are presented.

It is concluded that there has been no essential change in the epidemiologic behavior of the disease, and that the apparent change in its age distribution has been caused by an alteration in the age of the population and an increase in the reporting of nonparalytic cases.

The difference between urban and rural age distributions of poliomyelitis in Massachusetts is rapidly disappearing.

#### REFERENCES

1. Forsbeck, F. C. and Luther, E. H. Anterior poliomyelitis in Massachusetts, 1907-1929. *New Eng. J. Med.* 203: 1115-1121, 1930.
2. International Committee for the Study of Infantile Paralysis. *Poliomyelitis*. 562 pp. Baltimore: Williams & Wilkins, 1923. P. 383.
3. Massachusetts Department of Public Health. *Annual Report* 1930.

Physical examination revealed an acutely ill, toxic, dehydrated and hyperpeptic patient. Bilateral enlargement of the axillary lymph nodes was noted, and a few coarse rhonchi were heard throughout both lung fields.

The temperature was 104°F, the pulse 112, and the respirations 26. The blood pressure was 125/80.

A plain film of the abdomen revealed gaseous distention of the small bowel and a large left-upper-quadrant mass (Fig 1).

Examination of the blood disclosed a red-cell count of 4,100,000, with a hemoglobin of 12.5 gm., and a white-cell count of 9600, with 13 per cent neutrophils, 64 per cent lymphocytes and 3 per cent monocytes. Many of the lymphocytes were large and immature, and were very suggestive of infectious mononucleosis. A blood Kahn test was negative. Initially, examination of the urine showed the presence of acetone bodies, which subsequently cleared with rehydration.

A Miller-Abbott tube was passed. The patient was started on penicillin therapy, 100,000 units every 3 hours, and given intravenous fluids.

On December 15 a heterophil-antibody agglutination was positive in dilutions up to 1:3584. With persistence of abdominal findings and the probability of infectious mononucleosis, a tentative diagnosis of a subcapsular splenic hemorrhage was made.

Under nitrous oxide, oxygen and ether endotracheal anesthesia a left subcostal incision was made, with transverse sectioning of the left rectus muscle. When the peritoneal cavity was entered blood clots and free, dark blood were encountered, estimated at 500 cc. in amount. The spleen was enlarged and exhibited a ragged laceration of the capsule measuring 4 by 6 cm. on the anterior surface of the lower pole and a few small lacerations of the capsule over the lateral surface. The splenic pulp lay exposed through the capsular rents, did not appear ruptured and was not bleeding. As the spleen was not adherent it was easily separated by blunt dissection from its diaphragmatic and renal attachments and manipulated to a position outside the abdomen. Segmental ligation of the pedicle was carried out, and after all free blood had been aspirated from the peritoneal cavity the abdominal wall was closed in layers.

The postoperative course was essentially uneventful. The feared atelectasis, pneumonia and pleural effusion frequently seen after splenectomy were avoided, it is believed, by frequent inspiratory exercises, turning maneuvers, carbon dioxide inhalations and the prophylactic use of penicillin.

The gross specimen consisted of a spleen weighing 250 gm. when fixed. It was markedly abnormal, containing a large amount of clotted blood beneath the capsule, and appeared more friable than normal when handled. On microscopical examination the sections were those of a spleen with slight to moderate distortion of the architecture. The capsule was of average thickness throughout. The parenchyma was made up for the most part of large mononuclear endothelial-type cells, with round to oval vesicular nuclei. They were indistinguishable from the large, swollen endothelial cells lining the sinusoids. The malpighian corpuscles were moderately obliterated, with no distinguishable central arterioles. There were many subcapsular dilated sinusoids filled with red cells and atypical mononuclear leukocytes.

The pathological diagnoses were acute splenitis and infectious mononucleosis.

## Discussion

Rupture of the spleen in infectious mononucleosis, although rare, does occur. Furthermore, its apparent rarity may be due in some part to lack of awareness of the syndrome among those who are called upon for emergency removal of the ruptured spleens. With more general appreciation of the fact that in infectious mononucleosis splenic rupture may occur either spontaneously or as the result of minimal abdominal trauma three things may be accomplished. The performance of diagnostic tests for infectious mononucleosis in patients suspected of splenic rupture, and in the postoperative

study of those from whom a ruptured spleen has been removed, may lead to a revision of the present estimate of the rarity of the condition discussed. Secondly, such simple prophylactic measures as avoidance of heavy exertion during the phase of infectious mononucleosis in which the spleen is enlarged and avoidance of repeated palpation of an enlarged spleen in patients with infectious mononucleosis, as emphasized by Smith and Custer,<sup>6</sup> may lower the incidence of this complication (this consideration assumes increased importance when it is realized that although infectious mononucleosis is a benign disease splenic rupture carries a high mortality). Finally, careful observation of patients with infectious mononucleosis for evidence of abdominal pain or acute blood loss may lead to more prompt and definitive surgical action, with resultant improvement in the mortality figures of this complication. Awareness of the syndrome certainly played an important role in the decision to operate on the second case reported above when the diagnosis of infectious mononucleosis had been established.

In neither of the cases reported did the total white-cell count rise above 10,000 after splenic rupture. This is at variance with the usual findings in splenic rupture and with the majority of the reported cases of the syndrome under discussion.

Smith and Custer<sup>6</sup> were the first to state that rupture of the spleen seldom occurs prior to the third week in the course of infectious mononucleosis. A review of the literature appears to support this statement.

## SUMMARY

Fourteen cases of splenic rupture in infectious mononucleosis reported in the literature are reviewed, and 2 additional cases are presented.

Careful consideration of the reported cases suggests that awareness of the syndrome leads to more decisive action, with a consequent decrease in mortality.

Since splenic rupture occurs in infectious mononucleosis after minimal trauma, repeated abdominal palpation and strenuous exertion while the spleen is enlarged are contraindicated.

## REFERENCES

1. King R. B. Spontaneous rupture of spleen in infectious mononucleosis. report of case. *New Eng J Med* 224:1058-1060 1941.
2. Ziegler E. E. Infectious mononucleosis: report of fatal case with autopsy. *Arch. Path.* 37:196-201 1944.
3. Darley, W. Black, W. C., Smith C., and Good F. A. Spontaneous splenic rupture in infectious mononucleosis: case and pathologic report. *Am. J. M. Sc.* 208:381-384 1944.
4. Davis J. S., MacFee, W. Wright, M. and Allyn R. Rupture of spleen in infectious mononucleosis. *Lancet* 2:72, 1945.
5. Vidne J. Infectious mononucleosis. *New Eng J Med* 233:727-731 1945.
6. Smith E. B., and Custer R. P. Rupture of spleen in infectious mononucleosis: clinicopathologic report of 7 cases. *Blood* 1:317-333 1946.
7. Vaughan S. L., Regan J. S. and Terplan K. Infectious mononucleosis complicated by spontaneous rupture of spleen and central nervous system involvement. *Blood* 1:334-338 1946.
8. Spence W. O. Spontaneous rupture of spleen associated with infective mononucleosis. *Brit M J* 2:910 1947.
9. Editorial. Infectious mononucleosis. *J A M A* 134:1545 1947.

monocytes, 1 per cent basophils and 1 per cent eosinophils. A few young lymphocytes were noted.

The gross specimen consisted of a spleen weighing 444 gm in the fixed state and of usual shape. The capsule was

the pulse 88, and the respirations 20. The pharynx was injected, and the tonsils enlarged and inflamed. The abdomen was soft and slightly distended, and there was generalized abdominal tenderness. Peristalsis was hyper-

TABLE 1 Data Concerning Rupture of the Spleen in Infectious Mononucleosis

AUTHOR	PREOPERATIVE DIAGNOSIS OF INFECTIOUS MONONUCLEOSIS	OUTCOME*	POSTOPERATIVE COMPLICATIONS	DURATION OF SYMPTOMS BEFORE SPLENIC RUPTURE days
King <sup>1</sup>	Doubtful	Recovery	None	17
Ziegler <sup>2</sup>	Made	Death	—†	Doubtful
Darley et al. <sup>3</sup>	Made	Recovery	None	15
Davis <sup>4</sup>	Made	Recovery	None	15
Milne <sup>5</sup>	Doubtful	Recovery	Atelectasis and pneumonia	Doubtful
Smith and Custer <sup>6</sup>				
Case 1	Not made	Death after operation	Pneumonia and pulmonary embolism	21
Case 2	Made	Recovery	None	15
Case 3	Not made	Death	—†	Doubtful
Case 4	Made	Recovery	None	18
Case 5	Made	Recovery	Pneumonia	Doubtful
Case 6	Not made	Death after operation	Pulmonary embolism	30
Case 7	Not made	Death	—†	14
Vaughan et al. <sup>7</sup>	Not made	Recovery	? pneumonia	30
Spence <sup>8</sup>	Not made	Recovery	Pleural effusion	Doubtful
Timmes, Averill and Metcalfe				
Case 1	Not made	Recovery	None	30
Case 2	Made	Recovery	None	7

\*In all cases in which the outcome is reported as "recovery" splenectomy was performed.

†No operation performed.

ruptured, and the surface was covered with clotted blood. The cut surface revealed many areas of hemorrhage and clotted blood within the spleen itself. These areas varied from pin-point size up to several centimeters in diameter. The splenic pulp appeared homogeneous and grayish. On microscopical examination, performed at the United States Naval Medical School, section of the spleen showed several areas of extensive hemorrhage, with disruption of the tissue in these areas. Elsewhere the splenic structure demonstrated a normal number of malpighian bodies. In many of them the germinal cells were enlarged and disclosed rather marked reticuloendothelial hyperplasia. Throughout, the red pulp and sinusoids were somewhat dilated, and the reticuloendothelial cells lining the sinusoids had markedly enlarged, somewhat irregular, oval to round nuclei, which were very vesicular. There was rather marked hyperplasia of these cells throughout the tissue. Many polymorphonuclear leukocytes were found scattered throughout the tissue. Many of the sinusoids contained rather bizarre atypical cells. The cellular detail was rather distorted, and a definitive diagnosis of infectious mononucleosis could not be made. However, the histologic appearance was compatible with such a diagnosis.

The pathological diagnosis was probable infectious mononucleosis, with rupture of the spleen.\*

The diagnosis in this case was not suspected preoperatively. However, the history of lymphadenopathy, the strongly positive heterophil-antibody agglutination and the splenic disease made the diagnosis extremely probable.<sup>9</sup>

Case 2 C K, a 19-year-old seaman first class, was admitted to the hospital on December 14, 1947, complaining of nausea and vomiting of 4 days' duration and abdominal pain of 24 hours' duration. The patient had been perfectly well until 1 week before admission, when he developed a "cold" characterized by coryza, a moderately severe sore throat, slight cough and malaise. He had no headache and did not feel sick enough to report to his doctor. Four days before admission he became nauseated and began vomiting. In the course of the next 4 days he vomited frequently and took only fluids by mouth. His bowel movements were normal. On the day prior to admission, while retching, he suddenly developed a severe, sharp pain in the left upper quadrant, which radiated to the left shoulder, and he reported to the sick bay. Shortly thereafter the pain became generalized. Physical examination at that time revealed a pale young man in moderately acute distress. The temperature was 99.4°F,

active. The patient was given intravenous fluids, Was genstein suction and was placed under observation. On the following day extreme tenderness below the left costal



FIGURE 1 Plain Film of the Abdomen in Case 2, Showing the Large Mass in the Left Upper Quadrant

margin and rebound tenderness in the hypochondrium were present, a questionable mass in the left upper quadrant was felt, and he was transferred to the hospital.)

\*Dr. Charles F. Geschickter, who reviewed the slides, concurred in the diagnosis.

tion must be considered as one of the important regions where a special circulation significantly conditions general hemodynamics

Comparing hepatic blood flows as estimated above in normal nonpregnant women with those in normal pregnant women at various stages of gestation, and with blood flows in pregnant women with toxemia, Munnell and Taylor<sup>118</sup> found that pregnancy was without influence on hepatic circulation. In 6 toxemic women one exceedingly high rate of 4070 cc per millimeter was found — almost exactly twice the highest value found in the normal pregnant group. Whereas no more than suggestive of a change in liver circulation in toxemia of pregnancy, the finding deserves further elucidation.

Another method of assessment of liver circulation has been devised by Lipscomb and Crandall.<sup>119</sup> Urea excretion is measured by urine collection, and this quantity divided by the portal-hepatic venous difference in urea, assuming that urea is produced in the liver and quantitatively excreted by the kidneys. Despite certain inherent difficulties that magnify the error in analysis of urea concentration (the portal-hepatic urea difference is small, averaging close to 10 mg per 100 cc) the procedure was found to check reasonably well with the bromsulphalein method. Myers<sup>120</sup> estimated hepatic flow by the urea method in 10 subjects and obtained an average of 1.0 liter per square meter of body surface per minute. With the bromsulphalein method he produced an average flow of 0.8 liter per square millimeter per minute, comparing well with Bradley's value of 0.9 liter.

#### *Other Special Circulations*

Catheterization of the renal vein has permitted studies of the extraction of oxygen and sodium para-amino hippurate by the kidneys for validation of other methods<sup>121</sup> and makes possible the assessment of the influence of intra-abdominal and venous pressure upon kidney function.<sup>122</sup> Studying the renin content of blood obtained by catheterization from the renal vein of 12 hypertensive patients and in comparable samples from 12 normal subjects, Haynes, Dexter and Seibel<sup>123</sup> found small but detectable amounts of renin in 7 of the 12 in each group. Superficially considered at least, this finding does not support the hypothesis that renin is the hormone responsible for human hypertension.<sup>123</sup> The observation that the Cournand catheter sometimes passes into the coronary venous sinus, as shown by its radiologic position and by the low oxygen content found in blood samples obtained when it is in that position, has encouraged attempts to measure the coronary blood flow in man.<sup>124, 125</sup> These have been based on Kety and Schmidt's<sup>126</sup> method for measurement of cerebral blood flow. When low concentrations of nitrous oxide are rebreathed for a few minutes and serial samples of arterial blood and internal jugular blood are

obtained, a rising curve of the concentration of nitrous oxide in the arterial blood flow is inscribed, leveling off as equilibrium is reached. The curve of internal jugular blood concentration reaches the same maximum but at a later time and along a less steep curve, because of the loss of nitrous oxide to the brain by simple solution therein. If the nitrous oxide tension at the point of equilibrium is known, the total amount of the gas dissolved in a given weight of brain can be calculated from previously determined solubility curves. The arteriovenous nitrous oxide difference can be calculated from the area of the difference between the two curves of arterial and venous concentrations or by means of acceptable simplifications. Again the basic Fick calculation gives the cerebral blood flow in terms of unit volume of brain tissue. Measurement in monkeys checks reasonably well with determination by direct flowmeters.<sup>127</sup> Once the blood flow has been determined, it becomes possible to reverse the usual Fick calculation, and from this value and from direct determinations of arterial and internal jugular blood oxygen levels, to calculate the oxygen consumption of the brain.<sup>128</sup>

#### *The Lungs*

In the calculation of pulmonary blood flow by Vandam, Bing and Gray<sup>129</sup> it is assumed that blood returns from the lungs almost fully saturated (95 per cent). At operation these authors have had several opportunities to obtain pulmonary venous blood samples that proved as fully saturated as was expected, and Dr Arnold Johnson, at the Children's Memorial Hospital, Montreal, has passed a catheter through an interventricular septal defect into the left auricle and there obtained arterialized blood 95 per cent saturated with oxygen. By inserting the catheter far enough into a branch of the pulmonary artery to obstruct it, Dexter and his co-workers<sup>94</sup> withdrew blood that was 95 to 100 per cent saturated with oxygen. They drew the logical conclusion that pulmonary capillary blood had been drawn backward into the catheter.<sup>94</sup> This is not the opinion of Taussig and Blalock,<sup>129</sup> however, who conclude as follows:

We do not mean to imply that the lack of circulation to the lungs is the sole cause for the production of cyanosis and polycythemia, or that in the presence of polycythemia all of the blood which passes through the lungs is in effective contact with the oxygen in the alveolae (*sic*). On the contrary, the change in the patient's color when he is anesthetized and is receiving high concentrations of oxygen, offers clear evidence that without any fundamental alteration in the course of the circulation the oxygen saturation of the arterial blood may be greatly increased. In an attempt to analyze these factors, samples of arterial blood have been obtained prior to operation but after the patient was anesthetized and was receiving oxygen in high concentration. These samples have shown a striking increase in the oxygen saturation due to an increase in the oxygen content of the arterial blood, but, as is to be expected, there was no change in the oxygen capacity. These samples are truly basal, a condition which it is virtually impossible to obtain during an arterial puncture made when a child is

## MEDICAL PROGRESS

## PHYSIOLOGY (Concluded)\*

HEBBEL E. HOFF, M.D.,† AND H. J. SCOTT, M.D.‡

MONTREAL, CANADA

## SPECIAL CIRCULATIONS

*The Liver*

The unusual nature of the hepatic circulation has been emphasized by recently acquired evidence<sup>103</sup> that the oxygen supply to the liver may constitute the dominant factor determining whether shock becomes irreversible. It has been stated that the liver depends in large measure on portal blood for its oxygen,<sup>104</sup> and that increasing the oxygen content of portal blood by transfusion of arterial blood into the portal circulation protects the recipient against death from shock.<sup>105</sup> This view is in keeping with the classic anatomic opinion that the portal circulation is the major source of blood for the liver sinusoids. There can be no doubt, however, on anatomic grounds alone, that the hepatic artery also supplies the sinusoids, through anastomoses via the bile capillaries, direct arteriportal venous anastomoses and intralobular anastomoses.<sup>106-109</sup> Pathologically, the variable results of occlusion of portal or arterial vessels suggest that the relative contribution of the two vessels indeed varies. Grindlay, Herrick and Mann<sup>110</sup> measured portal inflow and hepatic venous outflow by the thermostromuhr method and found total flows averaging 100 cc per 100 gm of liver per minute, the hepatic artery flows constituting from 10 to 30 per cent of the total flow in the nonanesthetized animal. In anesthetized animals it was significantly higher, at times even exceeding the contribution of the portal vein.

This concept of dynamic variability of the portal circulation has much other evidence to support it. Rein and his co-workers<sup>111</sup> obtained flows of 62 to 75 cc per 100 gm per minute by the thermostromuhr method, with much the same partition between arterial and portal venous contributions. They also noted that, when adrenalin was given, more blood left the liver than entered it, so that the liver discharged as much as 60 per cent of its weight in blood. Bauer et al.<sup>112</sup> confirmed this finding in perfused livers and concluded that in the dog liver outflow is controlled by a variable sluice mechanism at the hepatic venous side of the circulation that could be closed by histamine or opened

by epinephrine or sympathetic-nerve stimulation. In much the same kind of study McMichael<sup>113</sup> found that a portal venous hypertension followed administration of epinephrine, presumably by vasoconstriction in the ramifications of the portal system in the liver. Wakim<sup>109</sup> saw on microscopical examination of the liver in situ an intermittence in the activity of lobular sinusoids, which could remain relaxed and engorged with stagnant blood only to expel it later. All the foregoing evidence points strongly to a storage function in the operation of liver circulation.

Employing an ingenious adaptation of the Fick principle combined with catheterization of the hepatic vein in man, Bradley<sup>114-116</sup> has estimated the minute volume of the hepatic circulation. Assuming that the dye bromsulfalein is removed from the blood stream by the liver and no other organ, one can calculate liver blood flow by dividing the total quantity of the dye removed from the circulation in a given time by the difference in the concentration of the dye in systemic and hepatic blood. The total amount removed Bradley determined by the quantity of the dye injected in a given time when the rate of injection was balanced against the rate of removal in the liver to give a constant concentration in the blood. Values so calculated ranged from 1085 to 1845 cc per minute in the adult human subject, with an average figure close to 1500 cc per minute. Considering the average human liver to weigh 1500 gm, flows of 100 cc per 100 gm per minute were thus found, just as in the dog. After sympathectomy for hypertension in man, liver flow as measured in this manner rises markedly, provided blood pressure is maintained, indicating that in man as well as in animals the liver circulation is under sympathetic control.<sup>116</sup> Since cardiac output in man averages about 5.4 liters per minute in the basal state, it is apparent that hepatic circulation constitutes a significant proportion of the whole, equaling in fact the total renal blood flow. The two together make up very close to half the total cardiac output. Even if it is admitted that the liver is, by virtue of its portal supply, out of the main circulatory channel and thus unable to contribute greatly to the peripheral resistance by which systemic blood pressure is regulated and that its circulation must be subject to significant passive or secondary changes resulting from gastrointestinal circulatory regulation,<sup>117</sup> the liver circula-

\*From the Department of Physiology, McGill University Faculty of Medicine.

†Joseph Morley Drake Professor of Physiology, McGill University Faculty of Medicine.

‡Research assistant, Department of Physiology, McGill University Faculty of Medicine.

blackwater fever, in which there is intravascular hemolysis, was noted. They also drew attention to the fact that the crush syndrome was not a new condition as they had previously thought but had been recognized by German clinicians and pathologists in World War I. A review of these cases was published by Minami<sup>135</sup> in 1923. De Navasquez<sup>136</sup> reported 3 fatal cases of transfusion reaction and pointed out that 2 of these patients had had alkaline urine, experimentally, when hemoglobin was injected into rabbits, animals with acid urine actually excreted more iron in their urine than those with alkaline urine. He also found insufficient tubular blockage to account for the anuria. Hence he concluded that mere hemoglobinuria was not the sole cause of anuria and that hemoglobin was not precipitated in undue amounts owing to the acidity of the urine, he suggested that diminished glomerular circulation might be the cause of the anuria. In 1942 Yuile<sup>137</sup> reviewed the literature on hemoglobinuria and concluded that hemoglobin was able to pass into the glomerular filtrate only after damage to the glomeruli, possibly because of anoxia. He also noted that not all cases of "transfusion kidney" at autopsy had pigment casts. Foy and his associates<sup>138</sup> suggested that the anuria in all hemoglobinurias, sulfonamide reactions, favism, crush injuries and so forth fell into a common category, pointing out the rather similar pathological findings and suggesting that the lesion was caused by dehydration with diminished blood volume and renal circulation, in their opinion the pigment casts were only an aggravating factor.

Meanwhile in 1942 Barnes and Trueta<sup>139</sup> had been investigating the effects on the circulation of the rabbit's hind leg produced by a rubber-covered wire tourniquet applied to the thigh for four and a half hours. They found that this produced a severe spasm of the vessels of the affected limb for periods up to seventy-two hours (well beyond the period of shock and hemoconcentration), as well as a spasm of the arteries of the opposite limb. This was demonstrated by arteriography, thorotrast being injected into the abdominal aorta. During the laparotomy to expose the aorta, it was noted that the kidneys were pale and blanched on their surfaces but the authors were unable to pursue this observation at that time. Trueta et al.<sup>140, 141</sup> returned to this investigation in 1945. The subjects of the experiment were rabbits, and a variety of experiments were carried out. Serial radiography using thorotrast as the radiopaque material, revealed, after release of the tourniquet on the left hind limb in the intact animal, that the calibers of the renal artery and the femoral artery of the left side were greatly reduced, whereas there was some dilatation of the superior mesenteric artery. At laparotomy they noticed that the renal cortex was pallid, although the renal vein was redder than normal, often containing bright-red central stream-

lines and showing pulsations almost like an artery, suggesting a rapid circulation through part of the kidney at the expense of the cortex. This was confirmed by study of cineradiographs, which showed that the circuit time of the radiopaque mass through the affected kidney might be half that of the normal and the size of the renal artery was reduced to a quarter its normal size. The cortex of the affected kidney was less opaque than the medulla during the phase of the renal circulation when one would expect the cortex to be more opaque, furthermore, in the left kidney at that time it was noticed that although the thorotrast appeared in the renal vein sooner than normal, it took a longer time for the renal artery to be completely emptied. These observations suggested some sort of circulatory by-pass through the medulla of the affected kidney. To study this more fully dyes and particulate matter were injected into the arterial side of the circulation during the period of cortical ischemia, these substances stained and filled the medulla completely and yet did not appear in the cortex or stain the surface as in the normal kidney. Histologic examination of the kidneys after injection of the India ink localized the pigment in the vasa recta of the medulla and in subcortical vessels of considerable size. These changes in the renal circulation could also be evoked by the intravenous injection of adrenalin, pitressin or staphylococcus toxin, with the injection of the last substance an extreme degree of cortical ischemia was produced, resulting in a pathologic lesion identical with that found in bilateral cortical necrosis. Similar but less extensive cortical ischemia was found in animals that had been bled sufficiently to produce shock. Stimulation of the central end of the divided left sciatic nerve or the distal end of the divided splanchnic nerves also caused renal cortical pallor and medullary circulatory by-pass. When, however, the splanchnic nerves were previously divided the renal circulation in the tourniquet of otherwise stimulated animals remained relatively unchanged, although the femoral artery of the affected limb and the mesenteric vessels showed some constriction.

From these experiments it was concluded that a similar mechanism producing cortical ischemia could be the cause of the azotemia and oliguria seen in renal injury due to sulfonamides and transfusion of incompatible blood, Weil's disease, cholera, crush syndrome, hysterical anuria and so forth. In support of this theory a considerable body of experimental, clinical and pathological evidence has been presented in recent years. In 1944 Richards<sup>142</sup> found in studies of the circulation in traumatic shock in man that when cardiac output dropped to about half normal renal blood flow fell to a tenth or twentieth of normal, and simultaneously that the urine output fell, he saw renal failure only once in these cases, however. Selkurt<sup>143</sup> cannulated the renal vein via the jugular to avoid local trauma and

conscious. These values are probably influenced both by inhalation of a high concentration of oxygen and by the basal condition associated with anesthesia, and possibly by the anesthetic agent. The relative importance of these factors is not easy to determine. Nevertheless, the fact that there is a rise in the oxygen saturation of the arterial blood when the patient is given a high concentration of oxygen is in accord with the existence of pulmonary factors emphasized by Lundsgaard and Van Slyke in their classical studies on cyanosis.

Such a difference of opinion emphasizes how limited knowledge of the precise details of the pulmonary circulation, especially in man, has been, and shows how the new technics will prove of value, both by raising problems and by providing their solution.

The technic of catheterization has been combined with pressure recording by means of the Hamilton or other manometers, to make possible, for the first time in man, a direct quantitative study of the pressure relations of the pulmonary circulation.<sup>120</sup> In 77 catheterizations in 70 subjects, mean right arterial pressures varying between  $-2$  to  $+2$  mm of mercury were found in recumbent normal subjects. Pulse pressures ranged from 4 to 8 mm of mercury. Curves showed peaks of pressure associated with auricular systole, closure of the auriculoventricular valves and accumulation of blood in the auricle during ventricular systole. The second peak is followed by an abrupt fall in pressure with descent of the ventricular base, after the third peak of pressure there is a rapid fall as interventricular pressure falls, and the phase of early diastolic filling of the ventricle begins. In the right ventricle maximum systolic pressures in normal subjects range between 18 and 30 mm of mercury, averaging 25 mm. Among patients with lung disease, increased systolic pressures were found in the right ventricle in 14 out of 19 patients with chronic pulmonary fibrosis in the absence of failure of the right side of the heart and without elevation of diastolic pressures in the right auricle or ventricle. Patients after pneumonectomy or pneumothorax had normal pressures. A marked elevation in right ventricular pressure was found in a single patient with mitral-valve disease without evidence of right ventricular failure.

In the presence, however, of venous congestion coincident with right ventricular failure, diastolic pressures in the auricle and ventricle rose (7 to 9 mm of mercury in 1 case), diminishing markedly the normal gradient of pressure between the peripheral veins and the right auricle. The intraventricular pressure curves showed characteristic alterations in contour, one of the most constant being an accentuation of the early diastolic "dip" in the ventricular and auricular pressure curves due to the sudden relaxation of the ventricle.

These findings have significance when considered from the standpoint of pulmonary cardiodynamics since the outputs of the right and left ventricles are equal over long periods, the pulmonary circu-

lation in general equals the systemic, which means in turn that pulmonary resistance must be very low indeed to permit such a large flow at such low pulmonary pressure, whereas under most circumstances there is equal output from the two ventricles, the capacity and flexibility of the small vessels of the lungs are such that considerable variations in the quantity of blood in the lungs can occur, so that during accumulation or discharge of this stored blood, right ventricular output may temporarily exceed or be less than left ventricular output. Quite the reverse, alterations of right or left ventricular output can influence the quantity of blood in circuit through the lungs.<sup>121</sup>

Whether the lung vessels have a clear-cut vasomotor regulation was still left in doubt by these studies, but Cournand et al.<sup>122</sup> have recently found evidence of another type of some kind of active regulation of peripheral resistance in the lungs. When normal adult males breathed mixtures of 10 per cent oxygen in nitrogen instead of room air, mean pulmonary artery pressure rose from 13 to 23 mm of mercury, diastolic from 6 to 13, and systolic from 22 to 35. Calculated pulmonary resistance doubled. The maximum increase in pressure was reached within two to four minutes, the elevation of pressure remained as long as the subject breathed the low oxygen mixture, and fell rapidly back to normal as room air was readmitted to the subject. Cardiac output fell as much as 20 per cent. Animal experiments by other workers suggest that the phenomenon is an expression of a direct sensitivity of the pulmonary arterioles to oxygen lack, which serves to direct blood from nonaerated portions into regions of better oxygenation, where arterioles are in consequence relaxed.

#### RENAL DISEASE IN THE LIGHT OF RECENT STUDIES ON THE RENAL CIRCULATION

With the report by Bywaters and Beall,<sup>123</sup> in 1941, of 4 cases of azotemia, oliguria and finally fatal anuria following crushing injury to the extremities sustained in the bombing of London, numerous workers began to investigate the clinical and pathological features of many different conditions that give rise to renal shutdown. Bywaters and Dible<sup>124</sup> described the typical pathological features of crush syndrome in which there is pallor of the renal cortex and degeneration of the convoluted tubules, which are often filled with desquamated debris and pigment-containing casts, the pigment was identified as myoglobin, a substance related to hemoglobin and presumably liberated by the crushing injury to large amounts of muscle. They speculated on the part played by the pigment casts in the production of oliguria by mechanical obstruction or by toxic effect on the kidney, and came to the conclusion that it was probably an aggravating factor but not necessarily the entire cause, the similarity of this lesion to that seen in

rendered ischemic by some hours of binding with a tourniquet, which depressed creatinine clearance in the kidney, it was also observed in muscles of dead animals between four and ten hours post mortem, after which time it disappeared. This substance was unstable and could not be dialyzed. If injected slowly through the portal vein it produced no effect suggesting that it was detoxified by the liver. Lucké<sup>152</sup> postulated that this explained the occurrence of hepatorenal syndrome after operation on the biliary tract when there is presumed to be some alteration of liver function. That nervous inhibition of urine function can occur is shown by the experiments of O'Connor and Verney<sup>158, 159</sup> in 1942 in which they demonstrated two types of emotional inhibition of water diuresis in dogs produced by sounding a horn or faradic stimulation of the skin, one being rapid and the other slow and delayed. The rapid type is abolished by sympathectomy, and the authors suggest it is due to renal ischemia produced by impulses traveling in the splanchnic nerves, the second is due to the antidiuretic hormone of the pituitary body. Similarly, Charcot<sup>160</sup> reported cases of hysterical anuria in 1877. On the other hand Smith,<sup>161</sup> using clearance studies of renal circulation, showed that increased sympathetic tone induced by elevating a previously supine man on a tilt table caused renal vasoconstriction primarily in the afferent arterioles, a similar effect was produced by psychomotor stimuli.

Having found that such a medullary by-pass existed Trueta and his co-workers<sup>141</sup> investigated the anatomy of the renal circulation by means of neoprene casts, some being made in rabbit's kidneys and others in those of human subjects. To show the side of this by-pass they injected the renal arteries of rabbits after producing cortical ischemia experimentally. At times this still did not enable them to demonstrate fully the flow into the vasa recta of the medulla, so that they first injected large quantities of thorotrast into the rabbit's arterial system, which they found completely blocked the cortical glomeruli. Using these techniques in the rabbit's kidneys and by straight injection techniques in human kidneys they found that the by-pass in circulation occurred through what Heggie<sup>162, 163</sup> called the juxtamedullary glomeruli. In these glomeruli the circulation of the nephron is somewhat different to that which occurs in the cortical glomeruli. In the latter, as originally described by Bowman<sup>164</sup> in 1842, the blood travels through the interlobular arteries and thence to the afferent arterioles and the capillaries of the glomerulus from which emerges the efferent arteriole, which then breaks up into the capillaries surrounding the convoluted tubules, and after following the descending and ascending limbs they reunite to join the venous side of the circulation. In the juxtamedullary glomeruli the following differences were noted. First of all it was found that the efferent

arteriole—unlike that in the cortical glomeruli—was larger than the afferent arteriole. Secondly, the efferent arteriole does not break up into the usual capillaries that surround the convoluted tubules, but immediately forms large vessels which descend into the medulla as the vasa recta. These vessels, the vasa recta, were always poorly described anatomically before this, since they were difficult to inject. Trueta et al<sup>141</sup> found that after descending for varying distances into the medulla they hook back upon themselves, forming curious "H" and "Y" forms, and that when they reach the juxtamedullary region they reunite to join the venous system. These vessels form very extensive thin-walled channels about the ascending and descending limbs of the tubules descending into the renal medulla. In this connection it was pointed out by Trueta et al<sup>141</sup> that Peter<sup>165</sup> showed in 1909 that the tubules of the cortical region only descended into the outer fringes of the medullary zone of the kidney, whereas those from the juxtamedullary-zone glomeruli were much larger, descending deeply into the medulla, and had a much longer loop of Henle. Hence these tubules are surrounded by the vasa recta through which the entire circulation of the kidney passes during the periods of cortical ischemia. Thus, there is further support for the theory that greater tubular reabsorption is a partial cause of traumatic anuria.

In their anatomic studies of the renal circulation in man Trueta et al<sup>141</sup> noted in many cases in these juxtamedullary glomeruli that there was marked degeneration of the glomerular capillaries, which at times was so extreme that there remained only a direct connecting channel, with a muscular coat, between the afferent and the efferent arteriole, the site of the degenerated glomerulus being marked only by a slight curve in the vessel. The vessels were only found in kidneys in which there was some degenerative process, and had been previously reported by MacCallum<sup>166</sup> in 1939. In all probability these vessels were what caused all the dispute between the earlier anatomists regarding whether or not Ludwig's arteriole, or the arteriae verae rectae, existed. They found no evidence of any other types of nonglomerular circulation.

Oliver<sup>167</sup> observed these degenerated glomeruli with a direct continuity between the afferent and efferent arteriole to be especially prevalent in cases of chronic Bright's disease. From this fact, and considering the role of renal ischemia in the experimental production of hypertension as shown by Goldblatt<sup>168</sup> and numerous subsequent workers, Trueta et al<sup>141</sup> suggest that there is some connection between this by-pass of normal renal circulation and the etiology of essential hypertension. They postulate that in normal persons, owing to varying stimuli, there is frequent re-routing of the renal circulation through the juxtamedullary glomeruli. When this mechanism is called into being too

spasm, and then made simultaneous recordings of renal clearance and blood flow during shock produced by hemorrhage. He found that when the pressure had fallen to 40 mm of mercury the renal circulation had dropped to 11 per cent of normal, but clearances of para-aminohippuric acid and creatinine were zero. However, when the blood pressure was raised by transfusion to about 80 mm of mercury and the renal blood flow was 80 per cent of normal, the clearance of para-aminohippuric acid and creatinine was not restored to normal but still remained nearly at zero. Selkurt could not explain this to his satisfaction, but it now seems that it was due to the re-routing of the renal circulation as described by Trueta et al.<sup>141</sup> Pathologically the kidneys of these dogs showed cloudy swelling and early degenerative changes in the tubular cells. Scarff and Keele<sup>144</sup> found in 1943 that clamping the renal artery in rabbits for an hour after the other kidney had been removed resulted in azotemia and oliguria, frequently going on to fatal uremia, and produced degeneration of the tubules, not unlike that found in crush syndrome and so forth, although it principally affected the proximal convoluted tubules rather than the lower part of the nephron. Corcoran and Page,<sup>145</sup> reviewing their experimental work on dogs in relation to post-traumatic anuria in 1936, reported that injection of hemoglobin or myoglobin into dogs and rats caused variable damage, which was frequently not serious even when the urine was acid, however, if this were accompanied by shock to produce renal ischemia, most of the animals died of anuria. From this they concluded that renal ischemia was the important factor in the pathogenesis of this condition. Lauson, Bradley and Cournand<sup>146</sup> found by studies of inulin and diodrast clearance in shocked men that there was a fall of renal blood flow out of all proportion to the fall of systemic blood pressure, which, they calculated from estimated renal artery and vein blood pressure and renal blood flow, was due to increased resistance in the kidney. Darmady et al.<sup>147</sup> and Darmady<sup>148</sup> analyzed a total of 17 cases of traumatic anuria occurring in the British forces in France in 1944-1945. All showed a clinical picture, developing about five or six days after injury, distinguished by azotemia, oliguria, elevated serum potassium and occasionally mild hypertension. Most of these patients had received blood transfusions at some time, but no reactions were recorded. In the 12 fatal cases the authors found the typical pathological features of degenerated convoluted tubules and frequent pigment casts in the tubules, whereas the cortices were pale and ghastening and the glomeruli rather avascular. They suggested that the lesion was due to renal anoxia, and noted that in 2 patients who recovered there was dramatic improvement after splanchnic block. Maegraith, Havard and Parsons<sup>149</sup> came to similar conclusions in 1945, after comparing the

pathological features of blackwater fever, incompatible transfusion, bilateral cortical necrosis, Weil's disease, hepatorenal syndrome, renal injury due to sulfonamides, crush injury and cholera. Duff and More<sup>150</sup> analyzed 71 cases of bilateral cortical necrosis of the kidney that came to autopsy, ascribing the pathogenesis to renal ischemia of unknown origin, which is possibly an individual idiosyncrasy to some stimulus or toxin. Mallory,<sup>151</sup> in 1947, and Lucké,<sup>152</sup> in 1946, after extensive analyses of over 500 cases of renal shutdown occurring in the American forces during the war, ascribed the renal lesion primarily to anoxia, although Mallory believed that the factor of mechanical blockage of the tubules could not be completely excluded and was certainly an aggravating factor.

Trueta et al.<sup>141</sup> ascribed the oliguria to reduced glomerular circulation and consequent low filtrate formation, and also to increased reabsorption in an unselective fashion from the tubules due to the increased blood flow in the vasa recta and the fact that the tubules are damaged. In support of the latter theory they cited the work of Dunn and Polson<sup>153</sup> in 1926 and Richards<sup>154</sup> in 1929, who found that in tubules damaged by uric acid or bichloride of mercury there is increased reabsorption of water with oliguria and with loss of normal impermeability to phenolsulfonephthalein. By this process Lucké<sup>152</sup> accounted for the presence of tubular casts, which he considered a result rather than a cause of oliguria, owing to excessive reabsorption of water. Brun, Knudsen and Raaschou<sup>155</sup> studied the effect of syncope on renal clearance of inulin and diodrast in man and noted that although renal plasma flow returned to normal within a few minutes, there was oliguria lasting for about sixty to ninety minutes. They concluded that this was due to increased tubular reabsorption and suggested that it was induced by the antidiuretic hormone of the posterior portion of the pituitary body, for blood withdrawn from these men during the period of oliguria produced oliguria in normal controls. There was also increased chloride excretion similar to that produced by the antidiuretic hormone, and in 2 men with diabetes insipidus the postsyncope oliguria was less marked than normal. Trueta and his co-workers<sup>141</sup> were undecided whether the cause of the ischemia was toxic or neurogenic, or both. Page<sup>156</sup> found a vasoconstrictor substance in blood during shock produced in dogs by trauma, hemorrhage or burns that caused vasoconstriction in the perfused vessels of a rabbit's ear, he decided that it was not histamine or angiotonin because when the vessels of the perfused ear were fatigued by repeated injections of this substance they still constricted with histamine or hypertensive plasma, and the converse was also found. This substance could be obtained in the blood after removal of the kidneys, adrenal glands and spinal cord. Eggleston<sup>157</sup> found a substance in muscles of dog's legs

# MASSACHUSETTS MEDICAL SOCIETY

## PROCEEDINGS OF THE ONE HUNDRED AND SIXTY-SEVENTH ANNIVERSARY

May 25, 26 and 27, 1948

THE one hundred and sixty-seventh anniversary of the Massachusetts Medical Society was observed at the Hotel Statler in Boston on May 25, 26 and 27, 1948

Seventeen hundred and forty-one physicians, 219 ladies and 495 exhibitors were registered

The Committee on Membership met in Parlor C at 4 30 p m on the afternoon of May 24 The Supervising Censors met in Parlor C at 5 00 p m This meeting was followed by the Cotting Supper in Parlors A and B, which was attended by 236 councilors The annual meeting of the Council was held in the Georgian Room at 7 00 p m with 235 councilors in attendance, as recorded in the attendance books

### TUESDAY, MAY 25

The first general session opened at 9 00 a m in the Georgian Room under the co-chairmanship of Dr Dwight O'Hara and Dr Frederick S Hopkins

The one hundred and sixty-seventh annual meeting of the Society was held in the Georgian Room at 11 00 a m, President Edward P Bagg presiding The attendance was about 400 Dr Bagg spoke on "The State of the Society," after which the annual oration, "The Responsibility of Medicine in the Propagation of Poor Protoplasm," was delivered by Dr Allen S Johnson (This lecture appeared in the May 27 issue of the *Journal*) The annual luncheon was served in Parlors A, B and C to 104 fellows

The second general session was held in the Georgian Room at 2 00 p m under the co-chairmanship of Dr W Richard Ohler and Dr Lewis M Hurxthal The Shattuck Lecture was delivered at 8 00 p m by Dr C Stuart Welch, of Boston, on the subject "Surgery in the Aged" (This lecture appeared in the June 10, 1948, issue of the *Journal*)

### WEDNESDAY, MAY 26

The third general session was held at 9 00 a m under the co-chairmanship of Dr Charles J Kickham and Dr Roy J Heffernan

At noon certain of the sections held their luncheons, followed by their annual meetings The Section of Medicine, under the chairmanship of Dr Francis C Hall, met in Parlor A The attendance was 142 The Section of Pediatrics, under the chairmanship of Dr Lewis W Hill, met in Parlor B, with 60 members in attendance at the luncheon and 75 at the scientific meeting following The Section of Radiology, under the chairmanship of Dr Hugh F Hare, met in Parlor C,

with 52 in attendance at the luncheon and 75 at the meeting The Section of Physiotherapy met in the Hancock Room under the chairmanship of Dr William D McFee, with 15 members present

At 2 00 p m the fourth general session was held in the Georgian Room, under the co-chairmanship of Dr William B Castle and Dr Stanley J G Nowak

The annual dinner was held in the Georgian Room at 7 00 p m with 456 in attendance The speaker of the evening was Mary Ellen Chase, Professor of English Language and Literature at Smith College, who delivered an address entitled "The Country Doctor on the Maine Coast"

### THURSDAY, MAY 27

The fifth general session was held in the Georgian Room at 9 00 a m under the joint chairmanship of Dr John J Poutas and Dr Claude E Welch

At noon the remaining scientific sections held their luncheons and meetings The Section of Surgery, under the chairmanship of Dr George S Reynolds, met in the Salle Moderne, with 140 in attendance The Section of Obstetrics and Gynecology met in Parlor A under the chairmanship of Dr Arthur T Hertig, with 50 in attendance The Section of Dermatology and Syphilology met in Parlor C under the chairmanship of Dr Austin W Cheever, with 38 in attendance The Section of Anesthesiology, under the chairmanship of Dr Urban H Eversole, met in Parlor B with 53 members attending

The sixth general session was held at 2 00 p m under the joint chairmanship of Dr John Fallon and Dr George S Reynolds

An exhibition of works of art by members of the Massachusetts Physicians' Art Association was on view throughout the meeting

The special list of officers, standing and special committees, councilors, censors, admissions and deaths is appended

H QUIMBY GALLUPE, *Secretary*

### ANNUAL MEETING OF THE SOCIETY

The one hundred and sixty-seventh annual meeting of the Massachusetts Medical Society was called to order by the president, Dr Edward P Bagg, in the Georgian Room of the Hotel Statler, Boston, at 11 00 a m, on May 25, 1948 Approximately 400 fellows were present

The Secretary submitted the record of the 1947 annual meeting, held on May 20, 1947, and pub-

frequently it may ultimately lead to glomerular degeneration, a constant by-pass of the cortical glomeruli with resulting ischemia and hypertension. Whereas the studies of Smith and his collaborators have made it difficult to maintain any theory of essential hypertension based on gross glomerular ischemia of any persistence, the possibility, of course, remains that circulation through specialized vessels not included or lost sight of in the usual clearance methods of measuring renal blood flow is the crucial factor in the origin of essential hypertension.

## REFERENCES

- 103 Hoff H E. Physiology. *New Eng J Med* 235 826-830 and 855-862 1946.
- 104 McMichael J. Oxygen supply of liver. *Quart J Exper Physiol* 27 73-87 1937.
- 105 Frank H A, Seligman A M, and Fine J. Traumatic shock VIII. Prevention of irreversibility in hemorrhagic shock by viviperfusion of liver. *J Clin Investigation* 25 22-29 1946.
- 106 Olds J M and Stafford S S. On manner of anastomosis of hepatic and portal circulations. *Bull Johns Hopkins Hosp* 47 176-185 1930.
- 107 Freerkens E. Sondereinrichtungen am Organkreislauf der Leber. *Klin Wchnschr* 22 733-735 1943.
- 108 Wakim K G and Mann F C. Intrahepatic circulation of blood. *Anat Rec* 82 233-253 1942.
- 109 Wakim K G. Effect of certain substances on intrahepatic circulation of blood in intact animal. *Am Heart J* 27 289-300 1944.
- 110 Grindlay, J H., Herrick J F and Mann F C. Measurement of blood flow of liver. *Am J Physiol* 132 489-496 1941.
- 111 Grab W, Janssen S., and Rein H. Die Leber als Blutdepot. *Klin Wchnschr* 8 1539 1929.
- 112 Bauer W, Dale H H, Paulsson L T and Richards D W. Control of circulation through liver. *J Physiol* 74 343-374 1932.
- 113 McMichael J. Portal circulation I. Action of adrenaline and pituitary pressor extract. *J Physiol* 75 241-263 1932.
- 114 Bradley E S. Hepatic blood flow in man. *Bull New Eng M Center* 1 224-228 1945.
- 115 Bradley E S, Ingelfinger F J, Bradley G P., and Curry J J. Estimation of hepatic blood flow in man. *J Clin Investigation* 24 890-897 1945.
- 116 Wilkins R W., Culbertson J W and Ingelfinger F J. Effects of splanchnicectomy upon hepatic function and blood flow in hypertensive patients. *J Clin Investigation* 26 1200 1947.
- 117 Culbertson, J W, Wilkins R W, Ingelfinger F and Bradley S E. Effect of upright posture upon hepatic blood flow in normal and hypertensive human subjects. *J Clin Investigation* 26 1178 1947.
- 118 Munnell E. W and Taylor H C Jr. Liver flow in pregnancy hepatic vein catheterization. *J Clin Investigation* 26 952-956 1947.
- 119 Lipscomb A and Crandall L A Jr. Hepatic blood flow and glucose in normal unanesthetized dogs. *Am J Physiol* 148 302-311 1947.
- 120 Myers J D. Hepatic blood flow and splanchnic oxygen consumption of man—their estimation from urea production or bromsulphalein excretion during catheterization of hepatic veins. *J Clin Investigation* 26 1130-1137 1947.
- 121 Warren J V, Brannon, E S and Merrill, A G. Method for obtaining renal venous blood in unanesthetized persons with observations on extraction of oxygen and sodium para-amino hippurate. *Science* 100 108-110 1944.
- 122 Bradley S E. and Bradley G P. Effect of increased intra-abdominal pressure on renal function in man. *J Clin Investigation* 26 1010-1022 1947.
- 123 Haynes F W, Dexter L., and Seibel R E. Renin content of renal venous blood of normal and hypertensive patients at rest. *Am J Physiol* 150 198-201 1947.
- 124 Bing R J et al. Catheterization of coronary sinus and middle cardiac vein in man. *Proc Soc Exper Biol & Med* 66 239 1947.
- 125 Goodale W T et al. Coronary sinus catheterization technique for studying coronary blood flow and myocardial metabolism in vivo. *Proc Soc Exper Biol & Med* 66 571-573 1947.
- 126 Kety S S and Schmidt, C F. Determination of cerebral blood flow in man by use of nitrous oxide in low concentrations. *Am J Physiol* 143 53-66 1945.
- 127 Dumke P R., and Schmidt, C F. Quantitative measurements of cerebral blood flow in macaque monkey. *Am J Physiol* 138 421-431 1942.
- 128 Schmidt C F, Kety, S S and Pennes H H. Gaseous metabolism of brain of monkey. *Am J Physiol* 143 33-52 1945.
- 129 Taussing H and Blalock, A. Observations on volume of pulmonary circulation and its importance in production of cyanosis and polycythemia. *Am Heart J* 33 413-419 1947.
- 130 Bloomfield R A, Lawson, H D, Courmand A, Breed, E S, and Richards D W Jr. Recording of right heart pressures in normal subjects and in patients with chronic pulmonary disease in various types of cardiorespiratory disease. *J Clin Investigation* 25 639-664, 1946.
- 131 Courmand A. Recent observations on dynamics of pulmonary circulation. *Bull New York Acad Med* 23 27-30 1947.
- 132 Motley, H L, Courmand A, Werks L, Himmelstein, A., and Goodale D. Influence of short periods of induced acute or chronic pulmonary artery pressures in man. *Am J Physiol* 150 115-120 1947.
- 133 Bywaters E G L and Beall D. Crush injuries with impairment of renal function. *Brit M J* 1 427-432 1941.
- 134 Bywaters E G L and Dible J H. Renal lesion in traumatic anuria. *J Path & Bact* 54 111-120 1942.
- 135 Minami S. Über Nierenveränderungen nach Verschluss der Harnleiter. *Arch. J Path. Anat* 245 247-267 1933.
- 136 De Navasquez S. Excretion of haemoglobin with special reference to "transfusion" kidney. *J Path. & Bact.* 51 415-425 1940.
- 137 Yule C L. Hemoglobinuria. *Physiol Rev* 22 19-31 1942.
- 138 Foy H, Altmann, A., Barnes H D, and Kouda A. A special reference to renal failure in blackwater fever in malarial transfusions and crush injuries. *Tr Roy Soc Trop Med & Hyg* 36 197-238 1943.
- 139 Barnes J M and Trueta J. Arterial spasm experimental. *Brit J Surg* 30 74-79 1942.
- 140 Trueta J, Barclay, A. E., Daniel P M., Franklin K J., and Pritchard M M L. Renal pathology in light of recent experimental studies. *Lancet* 2 237 1946.
- 141 *Idem*. Studies of the Renal Circulation 187 pp Oxford Blackwell Scientific Publications 1947.
- 142 Richards, D W Jr. Circulation in traumatic shock in man. *Bull New York Acad Med* 20 363-393 1944.
- 143 Sellert E E. Renal blood flow and renal clearance during hemorrhagic shock. *Am J Physiol* 145 699-709, 1946.
- 144 Scarff R W and Keele C A. Effects of temporary occlusion of renal circulation in rabbit. *Brit J Exper Path.* 24 149 1943.
- 145 Corcoran, A. C. and Page I H. Crush syndrome, post-traumatic anuria, observations on genesis and treatment. *JAMA* 134 436-441 1947.
- 146 Lawson H D, Bradley S E and Courmand A. Renal circulation in shock. *J Clin Investigation* 23 381-402 1944.
- 147 Darmady E. M et al. Traumatic uraemia reports on eight cases. *Lancet* 2 809-812 1944.
- 148 Darmady E M. Renal anoxia and traumatic uraemia syndrome. *Brit J Surg* 34 262-271 1947.
- 149 Macgraith B G, Havad R E., and Parsons D S. Renal syndrome of wide distribution induced possibly by renal anoxia. *Lancet* 2 293-296 1945.
- 150 Duff G L and More R H. Bilateral cortical necrosis of kidneys. *Am J Med Sci* 201 428-450 1941.
- 151 Mallory T B. Hemoglobinuric nephrosis in traumatic shock. *Am J Clin Path.* 17 427-443, 1947.
- 152 Lucke B. Lower nephron nephrosis renal lesions of crush syndrome of burns transfusions and other conditions affecting lower segments of nephrons. *Mil Surgeon* 99 371-396, 1946.
- 153 Dunn J S., and Polson C J. Experimental uric acid nephritis. *J Path. & Bact* 29 337-351 1926.
- 154 Richards A N. Direct observations of change in function of renal tubule caused by certain poisons. *Tr Am Physicians* 44-64 1929.
- 155 Brun C, Knudsen E O E. and Raaschou F. Kidney function and circulatory collapse post-syncope oliguria. *J Clin Investigation* 25 568-574, 1946.
- 156 Page, I H. Occurrence of vasoconstrictor substance in blood during shock induced by trauma hemorrhage and burns. *Am J Physiol* 139 386-398 1943.
- 157 Eggleston M G. Crush syndrome in cat. *Lancet* 2 208-210 1946.
- 158 O'Connor W J and Verney, E. B. Effect of removal of posterior lobe of pituitary on inhibition of water diuresis by emotional stress. *Quart J Exper Physiol* 31 393-408, 1942.
- 159 *Idem*. Effect of increased activity of sympathetic system in inhibition of water diuresis by emotional stress. *Quart J Exper Physiol* 33 77-90 1945.
- 160 Charcot Cited by Trueta et al.
- 161 Smith H W. Physiology of renal circulation. *Harey Lectures* 35 166-222 1939-40.
- 162 Heggie, J F. Circulation in kidney. *Lancet* 2 436 1946.
- 163 *Idem*. Lesser circulation in kidney. *Lancet* 1 385 1946.
- 164 Bowman W. On structure and use of malpighian bodies of kidney with observations on circulation through that gland. *Phil Tr Roy Soc Lond (B)* 132.57-80 1842.
- 165 Peter, K. Untersuchungen über Bau und Entwicklung der Niere 446 pp Jena Gustav Fischer 1909.
- 166 MacCallum D B. Bearing of degenerating glomeruli on problem of vascular supply of mammalian kidney. *Am J Anat* 65 69-103 1939.
- 167 Oliver J. Architecture of the Kidney in Chronic Bright's Disease 25 pp New York Paul B Hoeber Inc., 1939.
- 168 Goldblatt, H. Experimental hypertension induced by renal ischemia. *Harey Lectures* 33 237-275 1938.

team of collaborators. Letters and queries are answered promptly, and there has been excellent co-operation with the other officers of the Society.

One of the epochal features of the transition stems from the change in by-laws that places the secretaryship on a full-time basis and in the scribe's hands responsibility for the work of his associates, the Director of Medical Information and Education and the Executive Secretary who pulls more than his own weight as office and business manager for the Society. In addition, Miss Gaston's Information Bureau, which has served such a useful purpose, has come under the Secretary's wing. Hereafter, all committee meetings will be cleared through him so as to prevent duplication in dating and accommodations.

In this manner, a continuity of policies and a proper regard for essential details not only will be attained but also will no longer depend upon officials who change from year to year. The presidency from now on should be a less demanding office, particularly when that officer is domiciled out of Boston. Both the Society and the incumbents thereby will gain. The Secretary will sit with practically all the Society's many committees to give advice when asked and to keep track of the proceedings. However, he will have the right to vote at only a few of them so that his power cannot become too great and thereby reduce the Society to just another example of eastern democracy such as Tito vouchsafes to the Serbs, the Croats and the Slovenes.

On July 1, 1947, the staid old Massachusetts Medical Society definitely broke with the past for the sake of improving public relations. The swift advance and dissemination of new facts in science during the twentieth century had effected a partial eclipse in the prestige of the medical practitioner. He himself was so busy meeting the demands of ailing fellow citizens and attempting to keep abreast of discoveries that cults and professional social workers were usurping his prerogative of preserving the health of the nation. Press relations were poor and legislators often were not much impressed with the doctor or what they conceived to be his motives. Smaller groups with more efficient organization were getting the attention and the votes.

In less than one year, I am glad to report, thanks to our energetic Director of Medical Information and Education, the situation, if not completely reversed, is greatly improved. The press now has ready access to facts and can check news items with authority before publication, and columns are open to us with unaccustomed liberality. The ink was scarcely dry on John Conlin's public-health diploma before he was in full swing in his new office. In less than six months he so hedged himself in with files, clippings and telephone calls than an expert stenographer, a press assistant and a sound scriber that could function at all hours were rushed to the rescue. His inspired management of the "pound law" campaign need not be re-told here, but the public as well as the legislators have once more come to understand that the medical profession, as a whole, is not venal or self-centered, and that the Massachusetts Medical Society's chief purpose is to further medical education and so to improve the standards of practice and to further the prevention of disease for one and all. Proud as I am of John's beginning, I have reminded him that the flesh has limitations and asked him hereafter not to spread himself too thin for efficiency in attacking important issues.

It is a pleasure to acknowledge the large debt of gratitude that we all owe to the ever-willing, always agreeable and yet astute Bob Boyd, who reserves the accommodations, satisfies hotel managers or hires perfect office girls all in his day's work. He has dealt so fairly with exhibitors that our display space is always oversubscribed by representatives who declare that they will come to Boston by preference so long as they can do business with our Robert. The balance sheet of the New England Postgraduate Assembly always shows black figures because we lend our business manager. More power to him, say I, and sometime soon more pay!

Those of you who have had occasion to sample the work of our stenographers know how well the officers and the interests of the Society have been served by the Misses Biggs, Kelly and Adler. They have outdone themselves in speed and accuracy during this transition period

with a most commendable spirit of friendly co-operation in spite of many new faces, new problems and new equipment. With their help also, the excellent 1947 *Directory* was compiled in the midst of the turmoil.

Such, then, is the state of the Society at the present writing. The sedate mid-Victorian styling has been replaced with the "New Look" of the mid-twentieth Century. Heaven forefend that coming modes should drive her again to straight lacing and waspishness. Naturally, it costs more today to keep our Alma Medica as she should be kept. Our dues, as you know full well, have more than doubled. To what ends, you may ask with justice, and with what results?

Of course, quite a number of resignations were prompted by the receipt of this year's bills. But most of these fellows already had reached retirement age and most of the others were residents outside Massachusetts. It is a sad commentary on the assiduity with which the *New England Journal of Medicine* is read to report that the Treasurer received not a few irate queries regarding his authority, his intentions and why in blazes he should need more pay. In spite of all this, our membership continues to grow, having surpassed 6500, and more members had paid their assessments before the March 1 deadline than did so in 1947. Thanks to this splendid record, more than \$22,000 has been turned over to the Boston Medical Library to assist in making more accessible one of the world's choicest collections of medical information. The new directors representing the Massachusetts Medical Society are already aiding in allocating this much-needed fund to best advantage.

A special committee is looking into the question of how we may assist the widows and dependents of fellows who have come upon hard times, as was originally recommended in partial justification of higher dues. Furthermore, in accordance with instructions, twice as much money was returned to the district societies this year.

Advances in pay for the employees in our office, together with retirement policies, have been put into effect according to previous authorization. The result was a considerable increase in our overhead expenses.

To cap the climax, the Commonwealth of Massachusetts now insists that we must pay the employment security tax on our own employees and those of the *Journal* retroactive to the middle of 1944, so that the financial status of the Massachusetts Medical Society may not prove to be so roseate as anticipated with the January 1 increase. The Treasurer may still find himself "standing in the need of prayer," if not of monies.

The reports of the numerous committees speak for themselves, but I should like to reiterate my admiration for the committeemen whose patience, ability and ready co-operation have opened my eyes during this enlightening year. Friendships formed in sharing assignments have more than compensated for the inevitable sacrifices and for geographic and meteorologic aggravations that impeded our efforts.

It is regrettable that the solution of the special services' problem was thwarted by economic considerations and the widespread lack of up-to-date hospital cost accounting. At least the definitions have been made clear and are widely distributed. Fellows who serve on individual hospital staffs must implement them locally wherever possible.

Judging from latest reports, there is small likelihood of the passage of compulsory health legislation in the current session of Congress, but this too is a problem that must continue under constant scrutiny.

Perhaps the most urgent item of unfinished business is that of our new headquarters, made more so by the need of the Medical Library for larger space. All year long Chairman Frank Ober has verged on but actually never achieved the gladsome report of a real-estate transfer that would provide us with a more suitable meeting place and rooms in which committees may function. If we do not acquire better accommodations soon, the proportion of district representation must be reduced. Otherwise, councilors will not have room to masticate the Cotting lunches, let alone hold rational converse with one another.

To these few admonitions, I join the best of wishes for the success of the incoming regime. The new officers

lished in the August 28, 1947, issue of the *New England Journal of Medicine*, and moved its acceptance. The motion was seconded and so voted.

President Bagge brought up the matter of the amendments to the by-laws and stated that in the printed form mailed to the fellows two mistakes had been noted at the Council meeting on the previous day—namely, the use of "Inc" following the two appearances of "The Massachusetts Medical Service"—and that these should be omitted. He also noted the omission of the Vice-President in the list of officers.

Dr. Bagge then read Article II of the Articles of Incorporation of the Society.

The Fellows of said Society shall have full power and authority to make and enact such rules and by-laws for the better government of the said Society as are not repugnant to the laws of this Commonwealth, and to annex reasonable fines and penalties, etc. The Fellows at their Annual Meeting, whenever such a number shall be present as the regulations of the Society may require [being 100, and there are 100 present] may revise, alter, enlarge, and repeal the by-laws of the said Society as the major part of the Fellows present may see fit, and not otherwise.

He then urged the adoption of these amendments (Appendix No. 1), that the work of the Society might be carried on more successfully.

The Secretary moved that the amendments to the by-laws, with the corrections already noted and made, be adopted. The motion was seconded.

Dr. Carl Bearse, Norfolk, then noted two more omissions as follows: Chapter VI, Section 4 under duties of the Secretary, "he shall perform such other duties as the Society or the Council may require," and again under Chapter VI, Section 7, under duties of the Executive Secretary, "he shall hold office at the pleasure of the Executive Committee."

Stressing the point that a committee should screen by-law changes and that the proposed changes were not urgent, Dr. Bearse moved that they be tabled until the next annual meeting. The motion was seconded. Dr. Bagge said that the motion was not debatable and asked for a show of hands. The Secretary counted and reported the motion carried.

Dr. Bagge registered his disapproval of the action and said he wished that the by-law changes could have been adopted.

Dr. Elmer S. Bagnall, Essex North, said that he believed that the fellows did not realize, when they voted, what the conditions would be and moved reconsideration. The motion was seconded and on a show of hands the motion was carried.

Dr. Albert A. Hornor, Suffolk, then asked for a reading of the motion to be re-considered. (The motion was read.)

Dr. Dwight O'Hara, Middlesex South, moved the adoption of the by-laws as amended. The motion was seconded.

Dr. Bagge then asked for the inclusion of the omissions as related by Dr. Bearse above. It was moved and seconded that these inclusions be made. It was so voted.

The Secretary reported on the membership of the Society as follows:

In May, 1947, the membership of this Society was 6256. There was a gain of 403 new members, and 9 re-instatements, making a total of 6668. Our losses consisted of 88 deaths, 35 resignations and 7 deprivations. The total membership in the Society, as of May 22, 1947, is 6538.

The Secretary then commented upon the *Directory* of the Society as follows:

The *directory* now in use was published last year and is correct as of July, 1947. It has in it all the information concerning the membership of the Society that the Society deems essential, and is issued under the direction of the Committee on Publications. The *directory* is available to members of the Society on request, and extra copies may be obtained by purchase from the office of the Society.

At the request of the President, the vice-president, Dr. Charles J. Kichham, Norfolk, assumed the chair and Dr. Bagge gave the following address:

The twelve months just completed undoubtedly will be judged in historical perspective as a period of transition for the Massachusetts Medical Society. In the loss just previously of our exceptionally able secretary, Michael A. Tighe, a severe handicap was imposed upon the efficient conduct of the Society's business, because he carried so many of the important details in his head. Coincidentally, the office assistant on whom he in turn had leaned was compelled by ill health to leave our employ.

However, President Dwight O'Hara, as his parting contribution, furnished the Society and the incoming regime with a capable new Secretary, Joseph Garland. The latter was courageous enough to accept the challenge to do what he could to put our affairs in order. You yourselves know how well he succeeded at no small sacrifice to himself. But I can assure you, from the point of view of harassed presidential inexperience, that his willingness and patience were exceeded only by his good nature and all-around reliability. Somehow we survived that first council meeting, though the margin was slim.

And then in September a second severe blow again deprived the Society of a highly esteemed fellow, the able editor of the *Journal*, Robert N. Nye. Once more the secretaryship fell vacant when the Committee on Publications elected Joseph Garland to succeed him as editor-in-chief. The latter long had been interested and associated in the editing of the *Journal* and naturally chose to devote his full time to publishing rather than recording the minutes and managing presidents for the Society. There really was no question in his mind or in mine about how the interests of the Massachusetts Medical Society would best be served, so that genial Joseph was released unconditionally to reactivate the blue pencil.

In behalf of the entire membership, hearty thanks are hereby extended to our new editor and erstwhile secretary for his prompt and loyal endeavors to help us in whatever role that was assigned to him.

When the availability of H. Quimby, Gallupe became known, his fine record in rectifying the disordered affairs of the Board of Registration in Medicine as secretary, and his wide acquaintance with medical practitioners of Massachusetts both in and out of the Society gained in this way, prompted his appointment early in December as secretary *pro tempore*. His nomination last month for the position of full-time secretary bears witness to the satisfactory character of his temporary ministrations. Under his supervision, the routine business of the Society now is handled with a minimum of friction by a superior

## APPENDIX NO 1

## AMENDMENT TO BY-LAWS

To be approved by Annual Meeting of Council on May 24, 1948

To be presented to the Massachusetts Medical Society at Annual Meeting to be held on May 25, 1948

## CHAPTER IV, Section 1

The Council shall consist of councilors chosen by the district societies, the president, vice-president, ex-presidents, president-elect, vice-presidents ex-officio, secretary, treasurer, and assistant treasurer of the Society, the secretaries of the district societies, the chairmen of all standing committees, the editor of the *New England Journal of Medicine*, the president of the Massachusetts Medical Service, if he be a physician and a member of this Society and the medical director of the Massachusetts Medical Service, if he be a member of this Society

## CHAPTER IV

## APPOINTMENT OF DIRECTOR OF MEDICAL INFORMATION AND EDUCATION

Section 8 The Council may appoint and dismiss a Director of Medical Information and Education

## SALARIES AND APPROPRIATIONS

Section 9 The Council shall vote the salaries of its officers and employees, shall determine the tenure they may respectively have in their offices, the appropriations for its officers, employees, and committees, and such other appropriations as it deems suitable

No officer, employee, or committee shall exceed the voted appropriation

No salary to any officer or employee and no regular appropriation shall be increased except on recommendation of the Committee on Finance and by vote of the Council

The Treasurer is authorized, on recommendation of the Committee on Finance, to pay such monies as may be necessary in the event of emergency, the existence of which shall be determined by the President.

## CHAPTER VI OFFICERS

## DUTIES OF SECRETARY

Section 4 The Secretary shall attend all meetings of the Society, the Council and the Executive Committee, and shall record their respective proceedings in separate volumes

He shall cause to be engrossed and shall sign the diplomas of new fellows, if satisfied that they have met the requirements of Chapter I, and shall issue all diplomas and certificates of fellowship

He shall notify fellows of votes by the Council or Executive Committee granting permission to retire, to resign, to transfer district membership or to have dues remitted, and of votes depriving them of or reinstating them in the privileges of fellowship

He shall be *ex officio* secretary of all boards of trial, the Board of Supervising Censors, the Committee on Publications, the Committee on Ethics and Discipline, and the Committee on Membership, and shall keep the records of each in separate volumes. He shall be a member *ex officio* of all other committees without power of vote

He shall notify members of committees of their appointment and of the duties assigned them. On advice of their chairman or secretary he shall give due notice of the time and place of their several meetings

He shall have custody of the seal of the Society and of all books, papers, manuscripts, prints and paintings belonging to the Society, except such as are in charge of the Treasurer

He shall issue notices of the meetings of the Council according to such rules as the Council may adopt. He shall issue to every fellow one month before the annual meeting of the Society a program, listing the time and place of that meeting and of the stated meetings of the

Council, the boards of censors for that year, and information concerning the payment of assessments and the distribution of publications, if there are any proposed amendments of the by-laws, he shall provide that each program is accompanied by a copy thereof

He shall transfer fellows from one district to another under the terms of Chapter III, Section 3, and shall report to the Society at its annual meeting the changes in membership during the year

He shall conduct official correspondence and shall notify officers and delegates of their appointments and of their duties

He shall keep a directory of the fellows, and shall publish the same, under the direction of the Committee on Publications, at such intervals as may be determined by the Council. He shall furnish this on request to fellows not in arrears

He shall have jurisdiction over the work of the Executive Secretary and over the work of the Director of Medical Information and Education

He shall perform such other duties as the Society or the Council may require.

## DUTIES OF EXECUTIVE SECRETARY

Section 7 The Executive Secretary, under the jurisdiction of the Secretary, shall assist the officers, the Council and such committees as may request his services. He shall also serve as manager of the general office, and shall help in the arrangement of the annual meeting and of such other meetings as are sponsored in whole or in part by the Society

He shall hold office at the pleasure of the Executive Committee.

## DUTIES OF DIRECTOR OF MEDICAL INFORMATION AND EDUCATION

Section 8 The Director of Medical Information and Education, under the jurisdiction of the Secretary, shall promote, in an ethical manner, the educational usefulness of the Society to the fellows, to all licensed physicians in Massachusetts and to the public. He shall also assist the officers, the Council and such District Societies or committees as may request his services

## EXPENSES OF OFFICERS, EXECUTIVE SECRETARY, DIRECTOR OF MEDICAL INFORMATION AND EDUCATION, AND COMMITTEES

Section 9 The traveling and incidental expenses of the officers, of the Executive Secretary, of the Director of Medical Information and Education, of the committees of the Society elected by districts, and of other committees of the Society, on request, shall be paid by the Treasurer, on presentation of an itemized bill duly approved by the President.

These amendments were favorably acted upon by the Executive Committee of the Council on April 7, 1948

## APPENDIX NO 2

## OFFICERS FOR 1948-1949

President Daniel B Reardon, Quincy, 1186 Hancock St  
President-Elect Arthur W Allen, Boston, 266 Beacon St  
Vice-President Donald Munro, Milton Office, Boston, Boston City Hospital  
Secretary H Quimby Gallupe, Waltham Office, Boston, 8 Fenway  
Treasurer Eliot Hubbard, Jr, Cambridge, 29 Highland St  
Assistant Treasurer Norman A Welch, West Roxbury Office, Boston, 520 Commonwealth Ave  
Orator C Sidney Burwell, Brookline Office, Boston, 25 Shattuck St

## COMMITTEES ELECTED BY THE DISTRICTS

Executive Committee of the Council — Established 1941 (members *ex-officio* and one councilor and alternate elected by the councilors of each district medical society)  
PRESIDENT Daniel B Reardon, Quincy, 1186 Hancock St  
PRESIDENT-ELECT Arthur W Allen, Boston, 266 Beacon St

will find, as their predecessors found, that new problems will arise soon enough and frequently. I have full confidence that we are well set to meet whatever contingencies may arise.

Hippocrates, our father in medicine, composed the following precept (Chapter XII) "If for the sake of a crowded audience, you do wish to hold a lecture, your ambition is no laudable one, and at least avoid all citations from the poets." Accordingly, let me close this report in heartfelt prose. Fellows of the Massachusetts Medical Society, for the honor and privilege of serving you, I am deeply grateful.

Dr. Bagg resumed the chair and asked the Secretary to read the list of those fellows who joined the Society in 1898 and were still active, and requested those present to come forward and receive a gold pin as a memento to remember the occasion.

The Secretary read the following list of names:

Dr. George S. C. Badger, of Boston  
 Dr. Daniel C. Dennett, of Winchester  
 Dr. Clara P. Fitzgerald, of Worcester  
 Dr. Walter W. Fullerton, of Brockton  
 Dr. Joseph A. Hogan, of Lawrence  
 Dr. Myron L. King, of Cambridge  
 Dr. George C. Littlefield, of Webster  
 Dr. Alverne P. Lowell, of Fitchburg  
 Dr. Harry W. Luchsinger, of Great Barrington  
 Dr. George F. MacKay, of Dalton  
 Dr. William V. McDermott, of Salem  
 Dr. William D. McFee, of Haverhill  
 Dr. Harris P. Mosher, of Marblehead  
 Dr. Marion Nute, of Brookline  
 Dr. Joseph H. Pratt, of Boston  
 Dr. Jane D. K. Sabine, of Boston  
 Dr. Frederick W. Stetson, of Boston  
 Dr. Peter H. Thompson, of Boston

The Secretary then offered the following motion:

According to Chapter I, Section 4, of the by-laws, two fellows of the Society, namely, Dr. Bagg and Dr. Gallupe, have nominated Sir Reginald Watson-Jones as an honorary fellow. This has been confirmed by the Committee on Membership and by the Council yesterday.

According to Chapter I, Section 4, this confirmation should have been made at a previous stated meeting of the Council, but it was impossible to do so, owing to lack of time or sufficient foresight.

I move that, according to Article 2 of the Articles of Incorporation, this meeting alter the by-laws temporarily, that the granting of this fellowship may be made possible.

Dr. Bagnall seconded the motion, and it was so voted.

Dr. Gallupe moved that the Massachusetts Medical Society designate Sir Reginald Watson-Jones as honorary fellow. The motion was seconded.

Dr. Bagg spoke as follows:

I won't allow discussion of that. All those in favor, please say Aye. Those opposed, no. It is a vote. I have

delegated Dr. Russell Sullivan as a proxy to bring the recipient to the dais.

Honored Fellow, if your knowledge of Latin is as great as ours, I am prepared to furnish you with a translation of what is inscribed on your diploma. I shall read it.

"Whereas it is usual for a Society devoted to the furtherance of medicine to elect to fellowship men of productive scholarship in this art, the Medical Society of the Commonwealth of Massachusetts, founded A.D. 1848, designates as Honorable Fellow Honorable Sir Reginald Watson-Jones, a man of recognized attainment in advancing the interests of science, and accords him all the privileges of the Society. The Society would express its desire that the recipient of this honor may communicate in the form of papers any original contributions made by him to the art of medicine. In token whereof the Council have ordered this Seal of the Society to be affixed at Boston, Massachusetts, May 25, A.D. 1948, and in the one hundred and seventy-second year of the independence of the United States of America."

I welcome you into fellowship.

Sir Reginald Watson-Jones replied as follows:

I am sorry that this election caused some little disturbance in the matter of the by-laws, but I am very glad that the by-laws situation was resolved so easily and smoothly. I can't tell you how deeply I appreciate the very great honor conferred upon me, the honor of being numbered among the very select few honorary fellows of this oldest medical society in the United States.

Whenever I make any contact with Boston, it seems to me that my friendships with the men of this city, the surgeons of this city and the doctors of this city, increase every time. My first contact was twenty-five years ago. I came here as an extremely unknown, unheard of man as a ship's surgeon on one of the Cunard ships, and I was received in the city as if I were a great leader of surgery. I was even taken out to a clam bake. And every year since then, the number of my friends and the closeness of my friendship with those friends has increased.

This great honor that you have done me is one mark of the warmth of friendship between surgeons on the two sides of the Atlantic. And I have only one hope, sir, and that is that in due course — I believe I can just make it — I may attend here to receive from the hands of the President of 1998, the medal of fifty years' membership in the Society.

The President then called for the delegates from the New England State Medical Societies. Dr. Robert A. Goodell, of Connecticut, responded as follows:

I do not know whether I am the only representative from the New England States, but I wish to have the honor and privilege of bringing you greetings from the Connecticut State Medical Society. Dr. James R. Miller, the retiring president, and Dr. Harvey, the president-elect, both wish me to extend greetings and best wishes, and I am sure that I am doing that also for the entire Society. I wish to congratulate you on your splendid program, and I trust if any of you have the opportunity to visit the meeting of the Connecticut State Medical Society, you will receive as cordial and as gracious a welcome as I have received here.

The President then introduced the incoming officers, after which the one hundred and fortieth annual oration, "The Responsibility of Medicine in the Propagation of Poor Protoplasm," was delivered by Dr. Allen S. Johnson, of Springfield.

Dr. Bagg then declared the one hundred and sixty-seventh annual meeting of the Massachusetts Medical Society adjourned at 12:30 p.m.

H. QUIMBY GALLUPE, Secretary

Bristol South, Henry A Robinson, Norfolk South, Harold F Rowley, Barnstable, Elmer E Thomas, Hampshire

#### Committee on Legislation — Established 1942 (one councillor elected yearly by each district medical society)

BARNSTABLE Julius G Kelley, Pocasset, Barnstable County Sanatorium

BERKSHIRE John Hughes, Pittsfield, 74 North St

BOSTON NORTH William M Stobbs, Attleboro, 63 Bank St

BOSTON SOUTH Curtis C Tripp, New Bedford, 416 County St

BRISTOL NORTH Nicandro F DeCesare, Lawrence, 57 Jackson St

BRISTOL SOUTH Loring Grimes, Swampscott, 84 Humphrey St

FRANKLIN Harold R Mahar, Orange, 1 High St

HAMPDEN Arthur H Riordan, Indian Orchard, 147 Oak St

HAMPSHIRE Justin E Haves, Northampton, 16 Centre St

MIDDLESEX EAST Justin L Anderson, Reading, 55 Woburn St

MIDDLESEX NORTH Joseph D Sweeney, Lowell, 174 Central St

MIDDLESEX SOUTH Kenneth J Tillotson, Waverley, McLean Hospital

NORFOLK Solomon L Skvirsky, Boston, 545 State House

NORFOLK SOUTH David L Belding, Hingham, 215 Main St

PLYMOUTH Alfred L Duncombe, Brockton, 38 Winthrop St

SUFFOLK William E Browne, Boston, 587 Beacon St

WORCESTER John B Butts, Worcester, 24 Franklin St

WORCESTER NORTH C Bertram Gay, Fitchburg, 62 Day St

#### Subcommittee of the Committee on Legislation

##### NATIONAL LEGISLATION — Established 1946

Elmer S Bagnall, Essex North *chairman*, David L Belding, Norfolk South, Vlado A Getting, Middlesex South, Donald Munro, Suffolk, Augustus Thorndike, Suffolk, Charles G Hayden, Norfolk

#### STANDING COMMITTEES FOR 1948-1949

ELECTED BY THE COUNCIL MAY 24, 1948

*Date of Appointment*

#### Publications — Established 1825

Richard M Smith, Suffolk June 6, 1935 (appointed chairman May 21, 1941)  
 Oliver Cope, Middlesex South May 21, 1941  
 John Fallon, Worcester November 14, 1944  
 James P O'Hare, Suffolk June 9, 1936  
 Conrad Wesselhoeft, Suffolk June 2, 1937

#### Arrangements — Established 1849

Harold G Giddings, Middlesex South May 22, 1944 (appointed chairman May 24, 1948)  
 Franklin G Balch, Jr., Suffolk May 19, 1947  
 Gordon A Donaldson, Middlesex South May 19, 1947  
 Albert Ehrenfried, Norfolk May 24, 1948  
 John W Norcross, Middlesex South May 19, 1947

#### Ethics and Discipline — Established 1871

Ralph R Stratton, Middlesex East June 9, 1936 (appointed chairman May 21, 1941)  
 William J Brickley, Suffolk February 3, 1937  
 Archibald R Gardner, Middlesex North May 21, 1941  
 Fred R Jouett, Middlesex South May 21, 1940  
 Allen G Rice, Hampden June 1, 1938

#### Medical Education — Established 1881

Chester S Keefer, Suffolk February 4, 1942 (appointed chairman May 19, 1947)  
 James M Faulkner, Norfolk May 21, 1946  
 George D Henderson, Hampden June 1, 1938  
 Isaac R Jankelson, Norfolk May 25, 1942

#### Membership — Established 1897

Lewis S Pilcher, Middlesex South July 26 1946 (appointed chairman May 24, 1948)  
 William A R Chapin, Hampden May 23, 1945  
 Peirce H Leavitt, Plymouth June 1, 1938  
 Francis P McCarthy, Norfolk May 24, 1948  
 Samuel N Vose, Suffolk March 15, 1944  
 (John E Moran, Franklin, Bancroft C Wheeler, Worcester, Kathlevne S Snow, Norfolk, — representing the Supervising Censors)

#### Public Health — Established 1912

Roy J Ward, Worcester May 22, 1944 (chairman)  
 John J Poutas, Middlesex South May 21, 1946  
 Warren R Sisson, Suffolk May 19, 1947  
 Lawrence J Smith, Hampden May 19, 1947  
 Conrad Wesselhoeft, Suffolk July 27, 1944

#### Subcommittee of the Committee on Public Health

##### MENTAL HEALTH — Established 1947

Walter E Barton, Norfolk February 5 1947 (chairman)  
 William Malamud, Worcester February 5 1947  
 Henry A Tadgell, Hampshire February 5 1947

#### Medical Defense — Established 1927

Horatio Rogers, Suffolk June 7, 1939 (appointed chairman May 19, 1947)  
 Edwin D Gardner, Bristol South June 7, 1929  
 Charles J Kickham, Norfolk May 21, 1946  
 John E Moran, Franklin May 19, 1947  
 William R Morrison, Suffolk June 9, 1936

#### Finance — Established 1938

Robert W Buck, Middlesex South May 21, 1946 (chairman)  
 Francis C Hall, Suffolk July 8, 1943  
 Fabian Packard, Middlesex South May 21, 1946  
 Bancroft C Wheeler, Worcester May 21, 1946  
 Charles F Wilinsky, Suffolk June 2, 1938

#### Society Headquarters — Established 1942

Frank R Ober, Suffolk May 22, 1944 (appointed chairman November 1, 1944)  
 Albert A Hornor, Suffolk November 6, 1944  
 Walter G Phippen, Essex South May 21, 1946  
 George L Steele, Hampden May 19, 1947

#### Industrial Health — Established 1942

Daniel L Lynch, Norfolk May 25, 1942 (appointed chairman May 21, 1946)  
 Joseph C Aub, Suffolk May 25 1942  
 Louis R Daniels, Middlesex South May 22 1944  
 John G Downing, Middlesex South May 22, 1944  
 Harold R Kurth, Essex North May 23, 1945  
 Frederic N Manley, Norfolk South May 19, 1947  
 Henry C Marble, Suffolk May 19, 1947

#### Advisory Committee to Committee on Industrial Health — Established 1942

Philip Drinker  
 Harnet L Hardy  
 Emma S Tousant

VICE-PRESIDENT Donald Munro, Milton Office, Boston, Boston City Hospital  
 SECRETARY H Quimby Gallupe, Waltham Office, Boston, 8 Fenway  
 TREASURER Eliot Hubbard, Jr., Cambridge, 29 Highland St.

*Term Expires 1949*

BARNSTABLE Paul M Butterfield, Harwich (Alternate Paul P Henson, Hyannis, 149 Main St)  
 BRISTOL NORTH Joseph L Murphy, Taunton, 23 Cedar St. (Alternate Curtis B Kingsbury, Taunton, 63 Prospect St.)  
 BRISTOL SOUTH Richard B Butler, Fall River, 278 North Main St. (Alternate Curtis C Tripp, New Bedford, 416 County St.)  
 ESSEX NORTH Rolf C Norris, Methuen, 247 Broadway (Alternate Arnold P George, Haverhill, 32 Summer St.)  
 MIDDLESEX EAST Kenneth L MacLachlan, Melrose, 1 Bellevue Ave (Alternate Justin L Anderson, Reading, 53 Woburn St.)  
 PLYMOUTH George A Moore, Brockton, 167 Newbury St (Alternate John C Angley, Bryantville, School St.)

*Term Expires 1950*

BERKSHIRE John Hughes, Pittsfield, 74 North St. (Alternate Edward Wyman, Great Barrington, 244 Main St.)  
 FRANKLIN Lawrence R Dame, Greenfield, 78 Federal St (Alternate Frank W Dean, East Northfield, 185 Main St.)  
 HAMPDEN Archibald J Douglas, Westfield, 30 Court St (Alternate Frederic Hagler, Springfield, 20 Maple St.)  
 MIDDLESEX NORTH William M Collins, Lowell, 174 Central St. (Alternate Artemas J Stewart, Lowell, 310 Merrimack St.)  
 NORFOLK Charles J E Kickham, Jamaica Plain Office, Brookline, 1101 Beacon St. (Alternate Carl Bearse, Boston, 483 Beacon St.)  
 WORCESTER NORTH John J Curley, Leominster, 89 West St. (Alternate George P Keaveny, Fitchburg, 62 Fox St.)

*Term Expires 1951*

ESSEX SOUTH Albert E Parkhurst, Beverly, 1 Monument Sq (Alternate Edwin D Reynolds, Danvers, 48 High St.)  
 HAMPSHIRE Maurice T Kennedy, Hadley, 11 Middle St (Alternate L Beverley Pond, Easthampton, 115 Main St.)  
 MIDDLESEX SOUTH Joseph C Merriam, Framingham, 198 Union Ave (Alternate John F Casey, Brighton Office, Boston, 475 Commonwealth Ave.)  
 NORFOLK SOUTH Robert L Cook, Quincy, 1245 Hancock St (Alternate William R Helfrich, Quincy, 272 Southern Artery)  
 SUFFOLK Harvey A Kelly, Winthrop, 200 Pleasant St (Alternate William E Browne, Boston, 587 Beacon St.)  
 WORCESTER John Fallon, Worcester, 10 Institute Rd (Alternate Nicholas S Scarcello, Worcester, 1 Sheldon St.)

**Committee on Nominations** — Established 1874 (one councilor and alternate elected yearly by each district medical society)

BARNSTABLE Paul M Butterfield, Harwich (Alternate Harold F Rowley, Harwichport)  
 BERKSHIRE Helen Scoville, Pittsfield, House of Mercy Hospital (Alternate Charles T Leslie, Pittsfield, 18 Bank Row.)  
 BRISTOL NORTH Joseph L Murphy, Taunton, 23 Cedar St (Alternate Curtis B Kingsbury, Taunton, 63 Prospect St.)  
 BRISTOL SOUTH Henry Wardle, Fall River, 173 Purchase St (Alternate Donald R Mills, Edgartown, Box 654)  
 ESSEX NORTH Charles F Warren, Amesbury, 155 Main St (Alternate Percv J Look, Andover, 115 Main St.)  
 ESSEX SOUTH Peer P Johnson, Beverly, 1 Monument Sq (Alternate Olin S Pettingill, Middleton, Essex Sanatorium)  
 FRANKLIN Warren D Thomas, Montague, Central St (Alternate Kenneth H Rice, South Deerfield, 141 Main St.)  
 HAMPDEN George L Schadt, Springfield, 44 Chestnut St (Alternate George L Steele, Springfield, 20 Maple St.)

HAMPSHIRE Joseph R Hobbs, Williamsburg, Main St (Alternate L Beverley Pond, Easthampton, 1b Main St.)  
 MIDDLESEX EAST Edward M Halligan, Reading, 37 Salem St (Alternate John M Wilcox, Woburn, 6 Bennett St.)  
 MIDDLESEX NORTH C Stoyke Baker, Lowell, 8 Memorial St (Alternate William M Collins, Lowell, 174 Central St.)  
 MIDDLESEX SOUTH Harold G Giddings, Newton Centre Office, Boston, 270 Commonwealth Ave. (Alternate Fred R Jouett, Cambridge, 1 Craigie St.)  
 NORFOLK Albert Ehrenfried, Boston, 520 Beacon St. (Alternate Carleton E Allard, Dorchester, 428 Columbia Rd.)  
 NORFOLK SOUTH Henry A Robinson, Hingham, 20b North St (Alternate William R Helfrich, Quincy, 272 Southern Artery.)  
 PLYMOUTH Bradford H Peirce, South Hanson, Plymouth County Hospital (Alternate Alfred L Duncombe, Brockton, 38 Winthrop St.)  
 SUFFOLK Albert A Hornor, Boston, 319 Longwood Ave. (Alternate Conrad Wesselhoeft, Boston, 31b Milbourn St.)  
 WORCESTER Frank B Carr, Worcester, 27 Elm St (Alternate George W Ballantyne, Worcester, 27 Elm St.)  
 WORCESTER NORTH John J Curley, Leominster, 89 West St. (Alternate James V McHugh, Leominster, 20 West St.)

**Committee on Public Relations** — Established 1939 (one councilor elected yearly by each district medical society; the president and president-elect of the Society are chairman and vice-chairman, respectively, and the president and secretary of the Society are members ex-officio)

BARNSTABLE Paul P Henson, Hyannis, 149 Main St  
 BERKSHIRE Patrick J Sullivan, Dalton, 417 Main St  
 BRISTOL NORTH Milton E Johnson, Attleboro, 33 Bank St  
 BRISTOL SOUTH Harold E Perry, New Bedford, 129 Cottage St  
 ESSEX NORTH Harold R Kurth, Lawrence, 57 Jackson St  
 ESSEX SOUTH Bernard Appel, Lynn, 281 Ocean St  
 FRANKLIN John E Moran, Greenfield, 31 Federal St  
 HAMPDEN Frederic Hagler, Springfield, 20 Maple St  
 HAMPSHIRE Joseph R Hobbs, Williamsburg, Main St  
 MIDDLESEX EAST Milton J Quinn, Winchester, 44 Church St  
 MIDDLESEX NORTH Samuel A Dibbins, Lowell, 528 Andover St  
 MIDDLESEX SOUTH Ralph H Wells, Lexington, 140 Massachusetts Ave  
 NORFOLK Dean S Luce, Canton, 553 Washington St  
 NORFOLK SOUTH Henry A Robinson, Hingham, 20b North St  
 PLYMOUTH Charles D McCann, Brockton, 12 Cottage St  
 SUFFOLK Howard F Root, Boston, 81 Bay State Rd  
 WORCESTER Nicholas S Scarcello, Worcester, 1 Sheldon St  
 WORCESTER NORTH James V McHugh, Leominster, 20 West St

**Subcommittees of Committee on Public Relations**

**TAX-SUPPORTED MEDICAL CARE** — Established 1940  
 Thomas Hunter, Worcester, chairman, Frederick S Hopkins, Hampden, Albert A Hornor, Snnfold, Frank W Snow, Essex North

**COMMITTEE TO MEET WITH THE MEDICAL ADVISORY COMMITTEE OF THE INDUSTRIAL ACCIDENT BOARD** — Established 1942  
 Gordon M Morrison, Middlesex South, chairman, Charles H Bradford, Suffolk, Joseph H Burnett, Middlesex South, Somers Fraser, Suffolk, William W Teahan, Hampden

**POSTPAYMENT MEDICAL CARE** — Established 1942  
 Norman A Welch, Norfolk, chairman, Fred A Bartlett, Norfolk South, Michael F Barrett, Plymouth, James H Brewster, Bristol North, James T Brosnan, Worcester, Lucien R Chaput, Essex North, Charles F Fasce, Berkshire, Patrick E Gear, Hampden, Loring Grimes, Essex South, Francis T Jantzen, Suffolk, Egon E Katzwinkel, Middlesex South, Howard M Kemp, Franklin, William B LeBrecht, Worcester North, Wilfred L McKenzie, Middlesex East, Harold E Perry,

representative on the Legislative Committee of the  
Massachusetts Central Health Council

John F Conlin, Suffolk

representative on a Professional Advisory Committee  
Organized by the Division of Vocational Re-  
habilitation of the State Department of  
Education for the Purpose of Establishing  
a Program of Physical Restoration

Joseph H Shortell, Suffolk

representative for Survey by Academy of Pediatrics

Gerald N Hoeffel, Middlesex South

representatives to the Council of the New England  
State Medical Societies

Archibald J Douglas, Hampden, Gerald N Hoeffel,  
Middlesex South, Norman A Welch, Norfolk

twenty-Five Voting Members in Massachusetts  
Hospital Service, Inc

Richard Butler, Bristol South, Laurence D Chapin,  
Hampden, Lucien R Chaput, Essex North, Henry  
W Godfrey, Middlesex South, Roy J Heffernan,  
Norfolk, Albert A Hornor, Suffolk, Harold R  
Kurth, Essex North, John H Lambert, Middle-  
sex North, Alexander A Levi, Middlesex South,  
Joseph C Merriam, Middlesex South, Albert M  
Moloney, Norfolk, Donald Munro, Suffolk, Donald  
A Nickerson, Essex South, James P O'Hare,  
Suffolk, Albert E Parkhurst, Essex South, Bradford  
H Pearce, Plymouth, Lewis S Pilcher, Suffolk,  
Helen S Pittman, Suffolk, Allen G Rice, Hampden,  
Arthur T Roman, Norfolk, Walter L Sargent,  
Norfolk South, Milton J Schlesinger, Norfolk,  
George L Steele, Hampden, Ralph R Stratton,  
Middlesex East, and Sidney C Wiggins, Suffolk

## DELEGATES AND ALTERNATES TO THE HOUSE OF DELEGATES OF THE AMERICAN MEDICAL ASSOCIATION FOR 1948-1949

### Delegates Alternates

June 1, 1947 to June 1, 1949

Charles J Kickham, Norfolk	John Fallon, Worcester
Leland S McKittrick, Suffolk	Harold R Kurth, Essex North

June 1, 1948 to June 1, 1950

Patrick J Sullivan, Berkshire	Nahum R Pillsbury, Norfolk South
John J Curley, Worcester North	Patrick E Gear, Hampden
Walter G Phippen, Essex South	John I B Vail, Barnstable
Frank W Snow, Essex North	Frederick Hinchbliffe, Norfolk South

### COUNCILORS FOR 1948-1949

(ELECTED BY THE DISTRICT MEDICAL SOCIETIES AT THEIR  
ANNUAL MEETINGS, APRIL 15 TO MAY 15, 1948)

#### Barnstable

H P Hopkins, Chatham, V P  
P M Butterfield, Harwich, A E C, M N C  
P P Henson, Hyannis, 149 Main St, E C, P R C  
J G Kelley, Pocasset, Barnstable County Sanatorium,  
Leg C  
H F Rowley, Harwichport, A M N C  
Frederick Sanborn, Osterville, Bates Ave, Sec

#### Berkshire

G S Reynolds, Pittsfield, 100 North St, V P  
D N Beers, Pittsfield, 74 North St, Sec  
Modestino Criscitello, Pittsfield, 28 North St  
Antoine Dumouchel, North Adams, 56 Summer St,  
A E C  
John Hughes, Pittsfield, 74 North St, Leg C

C T Leslie, Pittsfield, 18 Bank Row, A M N C  
Helen M Scoville, Pittsfield, House of Mercy Hospital,  
M N C, E C  
P J Sullivan, Dalton, 471 Main St, P R C  
E R Wyman, Great Barrington, 259 Main St

#### Bristol North

J V Chatigny, Taunton, 43 West Britannia St, V P  
W E Dawson, Taunton, 58 Winthrop St, Sec  
M E Johnson, Attleboro, 33 Bank St, P R C  
C B Kingsbury, Taunton, 63 Prospect St, A E C,  
A M N C  
J L Murphy, Taunton, 23 Cedar St, E C, M N C  
W M Stobbs, Attleboro, 63 Bank St, Leg C

#### Bristol South

A J Pothier, New Bedford, 720 County St, V P  
R B Butler, Fall River, 278 North Main St, E C  
J C Corrigan, Fall River, 422 North Main St  
J E Fell, Fall River, 181 Purchase St, Sec  
J A Fournier, Fall River, 11 Choate St  
D F Gallery, Fall River, 151 Rock St  
E D Gardner, Marion, Box 175  
R H Goodwin, New Bedford, 15 South 6th St  
William Mason, Fall River, 151 Rock St  
D R Mills, Edgartown, Pease Point Way, A M N C  
H E Perry, New Bedford, 159 Cottage St, P R C  
C C Persons, New Bedford, 118 Cottage St  
C C Tripp, New Bedford, 416 County St, A E C,  
Leg C  
Henry Wardle, Fall River, 173 Purchase St, M N C

#### Essex North

R E Blais, Amesbury, 165 Main St, V P  
M F Ames, Newburyport, P O Box 88  
E S Bagnall, Groveland, 281 Main St, Ex-Pres  
R V Baketel, Methuen, 7 Hampshire St  
J A Bradley, Methuen, 103 Lowell St  
N F DeCesare, Lawrence, 57 Jackson St, Leg C  
A P George, Haverhill, 32 Summer St, A E C  
S P Humphreys, Newbury, 155 High Rd  
P J Look, Andover, 115 Main St, A M N C  
H R Kurth, Lawrence, 57 Jackson St, Sec, P R C  
R C Norris, Methuen, 247 Broadway, E C  
F W Snow, Newburyport, 24 Essex St  
L T Stokes, Haverhill, 30 Summer St  
F N Sweetser, Merrimac, 19 Main St  
C F Warren, Amesbury, 1 School St, M N C  
C A Weiss, Lawrence, 160 Jackson St.

#### Essex South

E L Pearson, Salem, 374 Essex St, V P  
Bernard Appel, Lynn, 281 Ocean St, P R C  
W W Babson, Gloucester, 79 Prospect St  
R E Foss, Peabody, 125 Main St  
S N Gardner, Salem, 24 Chestnut St.  
Loring Grimes, Swampscott, 84 Humphrey St, Leg C  
R P Hallett, Gloucester, Beach Rd  
C A Herrick, Manchester, 21 Union St  
P P Johnson, Beverly, 1 Monument Sq, M N C.  
R T Moulton, Salem, 37 Warren St  
A E Parkhurst, Beverly, 1 Monument Sq, E C  
O S Pettingill, Middleton, Essex Sanatorium,  
A M N C  
Walter G Phippen, Salem, 31 Chestnut St, Ex-Pres  
E D Reynolds, Danvers, 48 High St, A E C  
H D Stebbins, Salem, 342 Essex St, Sec  
P E Tivnan, Salem, 70 Washington St  
C F Twomey, East Lynn, 80 Ocean St  
R J Williams, Lynn, 39 Lynn Shore Drive

#### Franklin

L R Dame, Greenfield, 78 Federal St, V P, E C  
F W Dean, East Northfield, 185 Main St, A E C  
H R Mabarr, Orange, 1 High St, Leg C  
J E Moran, Greenfield, 31 Federal St, P R C  
K H Rice, South Deerfield, 141 Main St, A M N C  
M M Sisson, Greenfield, 31 Federal St, Sec  
W D Thomas, Montague, Central St, M N C

## SPECIAL COMMITTEES FOR 1948-1949

ELECTED BY THE COUNCIL, May 24, 1948

## Cancer — Established 1947

Shields Warren, Suffolk, *chairman*, Thomas J Anglem, Suffolk, Ernest M Daland, Suffolk, Allen G Rice, Hampden, Channing C Simmons, Suffolk

## To Meet with the Massachusetts Hospital Association — Established 1940

Albert E Parkhurst, Essex South, *chairman*, Edward A Adams, Worcester North, Edwin D Gardner, Bristol South, Frederic Hagler, Hampden, Justin E Hayes, Hampshire, Nicholas S Scarcello, Worcester, Leland S McKittrick, Suffolk

## Maternal Welfare — Established 1941

Duncan Reid, Middlesex South, *chairman*, James M Baty, Middlesex South, Arthur F G Edgelow, Hampden, Samuel B Kirkwood, Middlesex East, Florence L McKay, Suffolk, Louis E Phaneuf, Suffolk, Raymond S Titus, Norfolk

## Rehabilitation — Established 1941

Joseph H Shortell, Suffolk, *chairman*, Benjamin F Andrews, Worcester, Ralph M Chambers, Bristol North, William M Collins, Middlesex North, James J Regan, Suffolk, Arthur L Watkins, Middlesex South

## Council Rules — Established 1944

Charles E Mongan, Middlesex South, *chairman*, Elmer S Bagnall, Essex North, Frank R Ober, Suffolk, Albert A Hornor, Suffolk

## Postgraduate Medical Education — Established 1944

W Richard Ohler, Norfolk, *chairman*, George A Buckley, Plymouth, Vlado A Getting, Middlesex South, Robert H Goodwin, Bristol South, Lewis M Hurxthal, Suffolk, George P Keaveny, Worcester North, Leo F King, Middlesex North, Charles G Mixer, Suffolk, Joseph W O'Connor, Worcester, Samuel H Proger, Norfolk, George S Reynolds, Berkshire, James L Smead, Hampden, Harry C Solomon, Suffolk, Henry D Stebbins, Essex South, John F Conlin, Suffolk, Claude E Welch, Middlesex South

## Medical Economics — Established 1944

Leland S McKittrick, Suffolk, *chairman*, Elmer S Bagnall, Essex North, Allan M Butler, Suffolk, Vlado A Getting, Middlesex South, Merrill C Sosman, Suffolk

## Physical Medicine — Established 1945

Arthur L Watkins, Middlesex South, *chairman*, Alexander P Aitken, Middlesex East, Ralph M Chambers, Bristol North, Franklin P Lowry, Middlesex South, Henry A Taddell, Hampshire

## To Make Recommendations as to Future Directors of Blue Shield — Established 1945

Leland S McKittrick, Suffolk, *chairman* (term expires 1949), Harold G Giddings, Middlesex South (term expires 1951), Elliott P Joslin, Suffolk (term expires 1952), Peirce H Leavitt, Plymouth (term expires 1950)

## To Meet with General Hawley with View of Formulating Program in Massachusetts for Medical Care of Veterans and Dependents — Established 1945

Humphrey L McCarthy, Norfolk, *chairman*, James K Bragger, Norfolk, Allen S Johnson, Hampden

## To Assist the Council on Medical Education and Hospitals of the American Medical Association in the Provisional Approval of Certain Massachusetts Hospitals — Established 1946

Robert T Monroe, Norfolk, *chairman*, Laurence D Chapin, Hampden, H Quimby Gallupe, Middlesex South, Walter G Phippen, Essex South, Charles F Wilinsky, Suffolk

## Postgraduate Assembly — Established 1946

Leroy E Parkins, Suffolk, *chairman*, Harold G Giddings, Middlesex South, Frederick S Hopkins, Hampden, Charles J Kichham, Norfolk, Joseph Garland, Suffolk, John F Conlin, Suffolk

## To Study Income Level for Blue Shield — Established 1946

Charles F Wilinsky, Suffolk, *chairman*, Norman E Bruce, Middlesex South, Raoul L Draper, Middlesex North, Henry L Kirkendall, Worcester, John W Spellman, Norfolk

## School Health — Established 1947

Ernest Morris, Middlesex South, *chairman*, Elmer S Bagnall, Essex North, Florence L McKay, Suffolk, Joseph Garland, Suffolk, James O Walls, Worcester, Thomas F Reilly, Hampden, Stewart Clifford, Middlesex South, Kenneth L MacLachlan, Middlesex East

## Auditing

Howard B Jackson, Norfolk, *chairman*, Frank T Downey, Middlesex South

## Advisory Council to Women's Auxiliary — Established 1948

John F Conlin, Suffolk, *chairman*, Milton J Quinn, Middlesex East, David L Belding, Norfolk South

## Advisory Committee for Red Cross Blood Bank — Established 1948

John F Conlin, Suffolk, *chairman*, F Harold Allen, Jr., Middlesex South, William B Castle, Suffolk, Stephen Brown, Hampshire, William P Murphy, Suffolk, Joseph F Ross, Suffolk, C Stuart Welch, Norfolk

## Advisory Committee on Malpractice Insurance — Established 1948

Carl Bearse, Norfolk, *chairman*, William J Buckley, Suffolk, Maurice Fremont-Smith, Suffolk, Charles D McCann, Plymouth, Horatio Rogers, Suffolk

## Emergency Medical Service — Established 1948

Reginald Fitz, Suffolk, *chairman*, Donald E Carter, Suffolk, Charles H Bradford, Suffolk, Eugene C Eppinger, Norfolk, J Roswell Gallagher, Essex North, Allen Johnson, Hampden, Thomas Lanier, Suffolk, Edward D Churchill, Middlesex South

## Benevolence — Established 1948

Dwight O'Hara, Middlesex South, *chairman*, Theodore L Badger, Norfolk, Robert W Buck, Middlesex South, Eliot Hubbard, Jr., Middlesex South, Charles C Lund, Suffolk

## Representatives to the Massachusetts Central Health Council

Elmer S Bagnall, Essex North, *chairman*, James W Bunce, Berkshire, Merrill E Champion, Suffolk, Earle M Chapman, Suffolk, Roy J Ward, Worcester, Paul Nathan, Hampden

## Representatives to the Hospital Presidents Association

H Quimby Gallupe, Middlesex South, John W Spellman, Norfolk

B E Barton, West Roxbury, 10 Richwood St., Sec  
 Carl Bearse, Boston, 483 Beacon St., A E C  
 Elizabeth L Broyles, Wellesley, Simpson Infirmary  
 J H Cauley, Dorchester, 8 Carruth St  
 G L Doherty, West Roxbury Office, Boston 15, 466  
 Commonwealth Ave  
 Albert Ehrenfried, Brookline Office, Boston 15, 520  
 Beacon St., M N C  
 J M Faulkner, Brookline Office, Boston, 80 East  
 Concord St  
 P S Foisie, Milton, 65 Hillview Rd  
 Susannah Friedman, Roxbury Office, Boston 15, 485  
 Commonwealth Ave  
 T R Goethals, Brookline, 34 Hawthorn Rd  
 D L Halbersleben, Brookline 46, 42 Goodnough Rd  
 J A Halsted, Dedham Office, Jamaica Plain, Faulkner  
 Hospital  
 H B Harris, Milton Office, Dorchester, 487 Colum-  
 bia Rd  
 C C G Hayden, Brookline Office, Boston, 38 Chaun-  
 cy St  
 R J Heffernan, Jamaica Plain Office, Brookline 46,  
 1101 Beacon St  
 Gilbert Horrax, Brookline Office, Boston, 605 Common-  
 wealth Ave  
 P J Jakmauh, Milton Office, South Boston 27, 509  
 Broadway  
 I R Jankelson, Jamaica Plain Office, Boston 15, 483  
 Beacon St  
 L F Johnson, Brookline, Longwood Towers  
 C J Kichham, Brookline Office, Boston, 508 Common-  
 wealth Ave  
 C J E Kichham, Jamaica Plain Office, Brookline 46,  
 1101 Beacon St., E C  
 D L Lionherger, Dedham, 709 East St  
 D S Luce, Canton, 553 Washington St., P R C  
 C M Lydon, Dorchester, 276 Bowdoin St  
 D L Lynch, Roslindale Office, Boston, 245 State St., C  
 T F P Lyons, Milton Office, Boston 16, 270 Common-  
 wealth Ave  
 F P McCarthy, Milton Office, Boston 15, 371  
 Commonwealth Ave  
 H L McCarthy, Brookline Office, Boston 15, 479  
 Beacon St  
 R L Mason, Wellesley Hills, 17 Allen Rd  
 R T Monroe, Brookline Office, Boston 16, 270 Com-  
 monwealth Ave  
 F J Moran, Dedham, 395 Washington St  
 H R Morrison, Brookline Office, Boston, 370 Marl-  
 boro St  
 Hyman Morrison, Brookline Office, Boston 15, 483  
 Beacon St  
 D J Mullane, Brookline 46, 1101 Beacon St  
 H A Novack, Brookline Office, Boston, 471 Common-  
 wealth Ave  
 J J O'Connell, Dorchester, 1061 Dorchester Ave  
 W R Ohler, Jamaica Plain Office, Boston 15, 319  
 Longwood Ave  
 E E O'Neil, Brookline Office, Boston, 270 Common-  
 wealth Ave  
 R S Palmer, Brookline Office, Boston, 330 Dart-  
 mouth St  
 H C Peterson, West Roxbury Office, Boston 15, 29  
 Bay State Rd  
 S H Proger, Brookline Office, Boston, 30 Bennet St  
 H A Rice, Canton, 742 Washington St  
 S A Robins, Boston 15, 636 Beacon St  
 D D Scannell, Jamaica Plain Office, Boston 15, 475  
 Commonwealth Ave  
 J A Seth, Milton Office, Boston 15, 47 Bay State Rd  
 L A Sieracki, Norwood, 71 Winter St  
 S L Skvirsky, Brighton Office, Boston, 545 State  
 House, Leg C  
 E C Smith, Brookline Office, Boston 15, 520 Common-  
 wealth Ave  
 Kathlyne S Snow, Jamaica Plain Office, Boston 15,  
 466 Commonwealth Ave  
 J W Spellman, Chestnut Hill Office, Brookline, 1101  
 Beacon St  
 A R Stagg, Medfield 25 Pleasant St  
 W J Walton, Dorchester, 106 Bowdoin St

N A Welch, West Roxbury Office, Boston, 520 Com-  
 monwealth Ave., Asst Treas  
 G F Wilkins, Brookline Office, Boston, 245 State St  
 P R Withington, Milton, 350 Randolph Ave  
 Marjorie Woodman, Jamaica Plain Office, Boston, 21  
 Bay State Rd  
 E T Wyman, Brookline Office, Boston 15, 319 Long-  
 wood Ave

#### Norfolk South

Frederick Hinchliffe, Cohasset, 117 South Main St., V P  
 F A Bartlett, Wollaston 70, 308 Beale St  
 D L Belding, Hingham Office, Boston, 80 East Con-  
 cord St., Leg C  
 Harry Braverman, Quincy 69, 43 School St  
 E M Britton, Wollaston, 25 Elm Ave  
 R L Cook, Quincy, 1245 Hancock St E C  
 W R Helfrich, Quincy, 166 Washington St., A M N C,  
 A E C  
 E K Jenkins, South Braintree, Norfolk County Hos-  
 pital, Sec  
 N R Pillsbury, South Braintree, Norfolk County  
 Hospital  
 D B Reardon, Quincy 69, 1186 Hancock St., President  
 H A Robinson, Hingham, 205 North St., P R C,  
 M N C  
 R R Ryan, East Weymouth, 681 Broad St  
 R G Vinal, Norwell, Main St

#### Plymouth

G A Buckley, Brockton, 12 Cottage St., V P  
 J C Angley, Briantville, School St., A E C, A M N C  
 A L Duncombe, Brockton, 38 Winthrop St., Leg C  
 Samuel Gale, Brockton, The Checkerton, Sec  
 H H Hamilton, Plymouth, 70 Court St  
 P H Leavitt, Brockton, 129 West Elm St  
 C D McCann, Brockton, 12 Cottage St., P R C  
 G A Moore, Brockton, 167 Newbury St., E C  
 B H Pearce, South Hanson, Plymouth County Hospital,  
 M N C  
 E L Perry, Middleboro, 39 Oak St

#### Suffolk

A. J A Campbell, Brighton Office, Boston, 520 Com-  
 monwealth Ave., V P  
 H L Alhright, Boston 15, 412 Beacon St  
 A W Allen, Boston 15, 264 Beacon St. President-Elect.  
 T J Anglem, Brookline, 1180 Beacon St  
 M D Altschule, Boston, 330 Brookline Ave  
 J W Bartol, Boston, 1 Chestnut St., Ex-Pres  
 C H Bradford, Boston, 220 Beacon St.  
 W J Brickley, Boston 15, 524 Commonwealth Ave  
 W E Browne, Boston 15, 587 Beacon St., A E C,  
 Leg C  
 A M Butler, Boston 14, Massachusetts General Hospital  
 E M Chapman, Brookline Office, Boston, 266  
 Beacon St  
 M H Clifford, Cambridge Office, Boston, 501 Boyl-  
 ston St  
 A P DerHagopian, Chelsea, 39 Carr Ave  
 H H Faxon, Brookline Office, Boston, 264 Beacon St  
 N W Faxon, Boston 14, Massachusetts General Hospital  
 Reginald Fitz, Boston 15, 319 Longwood Ave., Ex-Pres  
 Maurice Fremont-Smith, Boston 15, 12 Hereford St  
 Channing Frothingham, Boston, 101 Bay State Rd.,  
 Ex-Pres  
 Joseph Garland, Brookline Office, Boston, 8 Fenway  
 G L Gately, East Boston 624 Bennington St  
 A A Hornor, Boston 15, 319 Longwood Ave., M N C  
 H E Kennard, Newton Centre Office, Boston, 372  
 Marlboro St  
 C S Keefer, Boston, 65 East Newton St., C  
 H A Kelt, Winthrop, 200 Pleasant St., E C  
 T H Lanman, Boston 15, 300 Longwood Ave  
 R I Lee, Boston 15, 264 Beacon St., Ex-Pres  
 C C Lund, Boston, 20 Gloucester St  
 C F Maraldi, Boston, 276 Commonwealth Ave  
 L S McKittick, Brookline Office, Boston, 205 Bea-  
 con St  
 W J Mixer, Chestnut Hill Office, Boston 15, 319  
 Longwood Ave

**Hampden**

R D Hildreth, Westfield, 90 Elm St., V P  
 F H Allen, Holyoke, 16 Fairfield St  
 E P Bagg, Holyoke, 207 Elm St. Ex-Pres  
 R L Barrett, Springfield, 21 Maple St  
 J M Birnie, Springfield, 146 Chestnut St., Ex-Pres  
 W A R Chapin, Springfield, 121 Chestnut St  
 J L Chereskin, Springfield, 333 Bridge St  
 G B Corcoran, West Springfield, 84 Park St  
 A J Douglas, Westfield, 30 Court St., E C  
 E C Dubois, Springfield, 174 Buckingham St  
 A F G Edgelow, Springfield, 76 Maple St  
 Adolph Franz, Jr. Holyoke, 1158 Northampton St  
 P E Gear, Holyoke, 188 Chestnut St  
 J M Gilchrist, Springfield, 121 Chestnut St  
 Frederic Hagler, Springfield, 20 Maple St. A E C,  
 P R C  
 F S Hopkins, Springfield, 146 Chestnut St  
 F D Jones, Springfield, 20 Maple St  
 Charles Jurst, Springfield, 70 Chestnut St  
 John Pallo, Westfield, 97 Elm St  
 A G Rice, Springfield, 146 Chestnut St  
 A H Riordan, Indian Orchard, 147 Oak St., Leg C  
 G L Schadt, Springfield, 44 Chestnut St., M N C,  
 Ex-Pres  
 J A Seaman, Springfield, 20 Maple St  
 G L Steele, Springfield, 20 Maple St., A M N C  
 W W Williams, Springfield, 30 Magnolia Terrace, Sec

**Hampshire**

E J Manwell, Northampton, 16 Centre St., V P  
 R S Clapp, Amherst, 110 North Pleasant St  
 J E Hayes, Northampton, 16 Centre St., Leg C  
 J R Hobbs, Williamsburg, Main St., P R C, M N C  
 M T Kennedy, Hadley, 11 Middle St., E C  
 J G Pekala, Northampton, 245 Main St  
 L B Pond, Easthampton, 115 Main St., A E C,  
 A M N C  
 F Mary P Snook, Worthington, Sec

**Middlesex East**

M J Quinn, Winchester, 44 Church St., V P, P R C  
 J L Anderson, Reading, 53 Woburn St., Leg C, A E C  
 J W Burke, Wakefield, 18 Lafayette St  
 T P Devlin, Stoneham, 38 Pleasant St  
 Robert Dutton, Wakefield, 33 Avon St  
 E M Halligan, Reading, 37 Salem St., M N C  
 R W Layton, Melrose, 8 Porter St., Sec  
 K L MacLachlan, Melrose, 1 Bellevue Ave., E C  
 H L Mueller, Winchester, 31 Church St  
 R R Stratton, Melrose, 538 Lynn Fells Parkway, C  
 J M Wilcox, Woburn, 6 Bennet St., A M N C

**Middlesex North**

J Y Rodger, Lowell, 226 Central St., V P  
 C S Baker, Lowell, 8 Merrimack St., M N C  
 R E Cole, Westford  
 W M Collins, Lowell, 174 Central St., A M N C, E C  
 S A Dibbins, Lowell, 528 Andover St., P R C  
 L J Hall, Lowell, 8 Merrimack St  
 L F King, Lowell, 308 Merrimack St  
 B D Leahey, Lowell, 9 Central St., Sec  
 A J Stewart, Lowell, 310 Merrimack St., A E C  
 J D Sweeney, Lowell, 174 Central St., Leg C

**Middlesex South**

J F Casey, Allston Office, Boston 15, 475 Commonwealth Ave., V P, A E C  
 G G Bailey, Belmont Office, Boston 15, 412 Beacon St  
 E W Barron, Malden Office, Boston, 20 Ash St  
 Harris Bass, Everett 49, 351 Broadway  
 J M Baty, Belmont Office, Brookline 46, 1101 Beacon St  
 J D Bennett, West Somerville 44, 72 College Ave  
 W O Blanchard, Newton 58, 465 Centre St  
 H K Bloom, Everett, 834 Broadway  
 G F H Bowers, Newton Highlands 61, 156 Woodward St  
 Alice M Broadhurst, Watertown, 259 Mt Auburn St  
 Madeline R Brown, Cambridge Office, Boston 16, 264 Beacon St  
 R N Brown, Malden, 621 Main St

R W Buck, Waban Office, Boston 15, 5 Bay State Rd., C  
 E J Butler, Cambridge, 25 Garden St  
 C W Clark, Newtonville 60, 363 Walnut St.  
 E A Cooney, Newton Office, Boston 16, 270 Commonwealth Ave  
 Oliver Cope, Cambridge Office, Boston 14, Massachusetts General Hospital  
 W H Crosby, Brighton, 304 Faneuil St  
 J A Daley, Natick, 36 Pond St  
 C L Derick, Newton Highlands Office, Boston 15, 412 Beacon St  
 J G Downing, Newton Office, Boston 15, 520 Commonwealth Ave  
 D J Duggan, Malden 48, 3 Hawthorne St  
 A G Engelbach, Cambridge, 330 Mt Auburn St  
 W C Feeley, Cambridge, 859 Massachusetts Ave.  
 C W Finnerty, West Somerville 44, 440 Broadway  
 J M Flynn, Belmont Office, Boston 15, 412 Beacon St.  
 H Quimby Gallupe, Waltham Office, Boston 15, 8 Fenway, Secretary  
 V A Getting, Belmont. Office, Boston 33, 545 State House  
 H G Giddings, Newton Centre Office, Boston, 270 Commonwealth Ave., M N C, C  
 H W Godfrey, Auburndale 66, 14 Hancock St  
 J L Golden, Medford 55, 86 Forest St  
 A D Guthrie, Medford 55, 408 Salem St  
 Eliot Hubbard, Jr., Cambridge, 29 Highland St., Treasurer  
 A M Jackson, Everett, 512 Broadway  
 F R Jouett, Cambridge, 1 Craigie St., A M N C  
 S B Kelley, West Newton, 34 Exeter St  
 H A Kontoff, Newton Centre. Office, Boston, 479 Beacon St  
 J J Lepore, Marlboro, 96 West Main St  
 A A Levi, Newton Office, Boston 15, 481 Beacon St., Sec  
 H E MacMahon, Cambridge Office, Boston, 416 Huntington Ave  
 A N Makechnie, Cambridge, 14 Upland Rd  
 R A McCarty, Waltham 54, 465 Lexington St  
 J J McSweeney, Somerville, 26 Bow St  
 J C Merriam, Framingham, 198 Union Ave., E C  
 Dudley Merrill, Cambridge, 51 Brattle St  
 C E Mongan, Somerville, 24 Central St., Ex-Pres  
 G M Morrison, Waban Office, Boston 15, 520 Commonwealth Ave., C  
 D G Nutter, Newton Centre, 1094 Centre St  
 Dwight O'Hara, Waltham Office, Boston 15, 416 Huntington Ave., Ex-Pres  
 Fabyan Packard, Belmont, 154 Washington St  
 L G Paul, Newton Centre Office, Boston 16, 270 Commonwealth Ave  
 L S Pilcher, Newton Centre Office, Boston 15, 12 Bay State Rd., C  
 Randolph Piper, Concord, 14 Sudbury Rd  
 T E Reilly, Marlboro, 6 Newton St  
 Max Ritvo, Newton Office, Boston 15, 416 Marlboro St  
 G A Saunders, Arlington, 50 Pleasant St.  
 M J Schlesinger, Newton Office, Boston 15, 330 Brookline Ave  
 E W Small, Belmont, 68 Leonard St  
 H P Stevens, Cambridge, 1 Craigie St  
 K J Tillotson, Waverley, McLean Hospital, Leg C  
 A B Toppan, Watertown, 289 Mt Auburn St  
 J H Townsend, Belmont, 195 Marsh St  
 J E Vance, Natick Office, Boston 15, 29 Bay State Rd  
 C F Walcott, Cambridge, 81 Sparks St  
 A L Watkins, Arlington Office, Boston 14, Massachusetts General Hospital  
 R H Wells, Lexington, 1430 Massachusetts Ave., P R C  
 B M Wein, Newton Office, Boston 15, 471 Commonwealth Ave  
 Alfred Worcester, Waltham 54, 314 Bacon St., Ex-Pres  
 Hovhannes Zovickian, Watertown, 528 Mt Auburn St

**Norfolk**

G W Papan, Brookline Office, Boston 9, 31 Milk St., V P  
 A A Abrams, Brookline 46, 153 Dean Rd  
 C E Allard, Dorchester, 428 Columbia Rd., A M N C

B E Barton, West Roxbury, 10 Richwood St, Sec  
 Carl Bearse, Boston, 485 Beacon St, A E C  
 Elizabeth L Broyles, Wellesley, Simpson Infirmary  
 J H Cauley, Dorchester, 8 Carruth St  
 G L Doherty, West Roxbury Office, Boston 15, 466  
 Commonwealth Ave  
 Albert Ehrenfried, Brookline Office, Boston 15, 520  
 Beacon St, M N C  
 J M Faulkner, Brookline Office, Boston, 80 East  
 Concord St  
 P S Foise, Milton, 65 Hillview Rd  
 Snannah Friedman, Roxbury Office, Boston 15, 485  
 Commonwealth Ave  
 T R Goethals, Brookline, 34 Hawthorn Rd  
 D L Halbersleben, Brookline 46, 42 Goodnough Rd  
 J A Halsted, Dedham Office, Jamaica Plain, Faulkner  
 Hospital  
 H B Harris, Milton Office, Dorchester, 487 Colum-  
 bia Rd  
 C C G Haven, Brookline Office, Boston, 38 Chaun-  
 cy St  
 R J Heffernan, Jamaica Plain Office, Brookline 46,  
 1101 Beacon St  
 Gilbert Horrax, Brookline Office, Boston, 605 Common-  
 wealth Ave  
 P J Jakmauh, Milton Office, South Boston 27, 509  
 Broadway  
 I R Jankelson, Jamaica Plain Office, Boston 15, 483  
 Beacon St  
 L F Johnson, Brookline, Longwood Towers  
 C J Kickham, Brookline Office, Boston, 508 Common-  
 wealth Ave  
 C J E Kickham, Jamaica Plain Office, Brookline 46,  
 1101 Beacon St., E C  
 D L Lionherger, Dedham, 709 East St  
 D S Luce, Canton, 555 Washington St, P R C  
 C M Lydon, Dorchester, 276 Bowdoin St  
 D L Lynch, Roslindale. Office, Boston, 245 State St, C  
 T F P Lyons, Milton Office, Boston 16, 270 Common-  
 wealth Ave  
 F P McCarthy, Milton Office, Boston 15, 371  
 Commonwealth Ave  
 H L McCarthy, Brookline Office, Boston 15, 479  
 Beacon St  
 R L Mason, Wellesley Hills, 17 Allen Rd  
 R T Monroe, Brookline Office, Boston 16, 270 Com-  
 monwealth Ave  
 F J Moran, Dedham, 395 Washington St  
 H R Morrison, Brookline Office, Boston, 370 Marl-  
 boro St  
 Hyman Morrison, Brookline Office, Boston 15, 483  
 Beacon St  
 D J Mullane, Brookline 46, 1101 Beacon St  
 H A Novack, Brookline Office, Boston, 471 Common-  
 wealth Ave  
 J J O'Connell, Dorchester, 1061 Dorchester Ave  
 W R Ohler, Jamaica Plain Office, Boston 15, 319  
 Longwood Ave  
 E E O'Neil, Brookline Office, Boston, 270 Common-  
 wealth Ave  
 R S Palmer, Brookline Office, Boston, 350 Dart-  
 mouth St  
 H C Peterson, West Roxbury Office, Boston 15, 29  
 Bay State Rd  
 S H Proger, Brookline Office, Boston, 30 Bennet St  
 H A Rice, Canton, 742 Washington St  
 S A Rohins, Boston 15, 636 Beacon St  
 D D Scannell, Jamaica Plain Office, Boston 15, 475  
 Commonwealth Ave  
 J A Seth, Milton Office, Boston 15, 47 Bay State Rd  
 L A Sieracki, Norwood, 71 Winter St  
 S L Skvirsky, Brighton Office, Boston, 545 State  
 House, Leg C  
 E C Smith, Brookline Office, Boston 15, 520 Common-  
 wealth Ave  
 Kathlyne S Snow, Jamaica Plain Office, Boston 15,  
 466 Commonwealth Ave  
 J W Spellman, Chestnut Hill Office, Brookline, 1101  
 Beacon St  
 A R Stagg, Medfield, 25 Pleasant St  
 W J Walton, Dorchester, 106 Bowdoin St

N A Welch, West Roxbury Office, Boston, 520 Com-  
 monwealth Ave, Asst Treas  
 G F Wilkins, Brookline Office, Boston, 245 State St  
 P R Withington, Milton, 350 Randolph Ave  
 Marjorie Woodman, Jamaica Plain Office, Boston, 21  
 Bay State Rd  
 E T Wyman, Brookline Office, Boston 15, 319 Long-  
 wood Ave

# Norfolk South

Frederick Hinchliffe, Cohasset, 117 South Main St, V P  
 F A Bartlett, Wollaston 70, 308 Beale St  
 D L Belding, Hingham Office Boston, 80 East Con-  
 cord St, Leg C  
 Harry Braverman, Quincy 69, 43 School St  
 E M Britton, Wollaston, 25 Elm Ave  
 R L Cook, Quincy, 1245 Hancock St E C  
 W R Helfrich, Quincy, 166 Washington St., A M N C,  
 A E C  
 E K Jenkins, South Braintree, Norfolk County Hos-  
 pital, Sec  
 N R Pillsbury, South Braintree, Norfolk County  
 Hospital  
 D B Reardon, Quincy 69, 1186 Hancock St, President  
 H A Robinson, Hingham, 205 North St, P R C,  
 M N C  
 R R Ryan, East Weymouth, 681 Broad St  
 R G Vinal, Norwell, Main St

# Plymouth

G A Bucklev, Brockton, 12 Cottage St, V P  
 J C Angley, Bryantville, School St, A E C, A M N C.  
 A L Duncombe, Brockton, 38 Winthrop St, Leg C  
 Samuel Gale, Brockton, The Checkerton, Sec.  
 H H Hamilton, Plymouth, 70 Court St  
 P H Leavitt, Brockton, 129 West Elm St  
 C D McCann, Brockton, 12 Cottage St, P R C  
 G A Moore, Brockton, 167 Newbury St E C  
 B H Peirce, South Hanson, Plymouth County Hospital,  
 M N C  
 E L Perry, Middleboro, 39 Oak St

# Suffolk

A J A Campbell, Brighton Office, Boston, 520 Com-  
 monwealth Ave, V P  
 H L Albright, Boston 15, 412 Beacon St  
 A W Allen, Boston 15, 264 Beacon St. President-Elect  
 T J Anglem, Brookline, 1180 Beacon St  
 M D Altschule, Boston, 330 Brookline Ave  
 J W Bartol, Boston, 1 Chestnut St, Ex-Pres  
 C H Bradford, Boston, 220 Beacon St.  
 W J Brickley, Boston 15, 524 Commonwealth Ave  
 W E Browne, Boston 15, 587 Beacon St, A E C,  
 Leg C  
 A M Butler, Boston 14, Massachusetts General Hospital  
 E M Chapman, Brookline Office, Boston, 266  
 Beacon St  
 M H Clifford, Cambridge Office, Boston, 501 Boyl-  
 ston St  
 A P DerHagopian, Chelsea, 39 Cary Ave.  
 H H Faxon, Brookline Office, Boston, 264 Beacon St.  
 N W Faxon, Boston 14, Massachusetts General Hospital  
 Reginald Fitz, Boston 15, 319 Longwood Ave., Ex-Pres  
 Maurice Fremont-Smith, Boston 15, 12 Hereford St.  
 Channing Frothingham, Boston, 101 Bay State Rd,  
 Ex-Pres  
 Joseph Garland, Brookline Office, Boston, 8 Fenway  
 G L Gately, East Boston, 624 Bennington St  
 A A Horner, Boston 15, 319 Longwood Ave, M N C  
 H E Kennard, Newton Centre Office, Boston, 372  
 Marlboro St  
 C S Keefer, Boston, 65 East Newton St, C  
 H A Kelly, Winthrop, 200 Pleasant St, E C  
 T H Lanman, Boston 15, 300 Longwood Ave  
 R I Lee, Boston 15, 264 Beacon St, Ex-Pres  
 C C Lund, Boston, 20 Gloucester St  
 C F Maraldi, Boston, 276 Commonwealth Ave  
 L S McKittrick, Brookline Office, Boston, 205 Bea-  
 con St  
 W J Mixer, Chestnut Hill Office, Boston 15, 319  
 Longwood Ave

Donald Munro, Boston 18, 818 Harrison Ave., Vice-President  
 H L Musgrave, Revere, 620 Beach St  
 F R Ober, Boston, 234 Marlboro St., Ex-Pres  
 F W O'Brien, Boston 15, 475 Beacon St  
 J P O'Hare, Chestnut Hill Office, Boston, 520 Commonwealth Ave  
 L E Parkins, Brookline Office, Boston 15, 12 Bay State Rd., C  
 L E Phaneuf, Boston 16, 270 Commonwealth Ave  
 Helen S Pittman, Boston 16, 264 Beacon St  
 J H Pratt, Boston 11, 30 Bennet St  
 J J Regan, South Boston Office, Boston, 520 Commonwealth Ave  
 W H Robey, Boston, 202 Commonwealth Ave., Ex-Pres  
 Horatio Rogers, Boston, 264 Beacon St., C  
 H F Root, Boston, 81 Bay State Rd., P R C  
 C G Shedd, Boston, 422 Beacon St., Sec  
 R M Smith, Boston, 330 Dartmouth St., C  
 C M Stearns, Chelsea, 116 Hawthorn St  
 Augustus Thorndike, Boston 15, 319 Longwood Ave  
 Conrad Wesselhoeft, Boston, 315 Marlboro St  
 A M N C  
 C F Wilinsky, Boston, 330 Brookline Ave

### Worcester

J J Dumphy, Worcester, 390 Main St., V P  
 A W Atwood, Worcester, 390 Main St  
 G W Ballantyne, Worcester, 27 Elm St., A M N C  
 F P Bousquet, Worcester, 390 Main St  
 J B Butts, Worcester, 24 Franklin St., Leg C  
 J T B Carmody, Worcester, 340 Main St  
 F B Carr, Worcester, 27 Elm St., M N C  
 E J Crane, Holden, Armington Lane  
 Paul Dufault, Rutland, Rutland State Sanatorium  
 G R Dunlop, Worcester, 53 Massachusetts Ave  
 John Fallon, Worcester, 10 Institute Rd., E C  
 Donald Hight, Worcester, 27 Elm St., Sec  
 Thomas Hunter, Shrewsbury, 545 Main St., C  
 H L Kirkendall, Worcester, 27 Elm St  
 D G Ljungberg, Worcester, 36 Pleasant St  
 J A Lundy, Oxford, 26 Main St  
 J C McCann, Worcester, 390 Main St  
 D K McClusky, Worcester, 7 Hawthorne St  
 J W McKoan, Worcester, 36 Pleasant St  
 J M Olson, Westboro, 54 West Main St  
 F A O'Toole, Clinton, 181 Chestnut St  
 E L Richmond, Worcester, 390 Main St  
 N S Scarcello, Worcester, 1 Sheldon St., P R C,  
 A E C  
 R J Ward, Worcester, 9 Bellevue St., C  
 B C Wheeler, Worcester, 27 Elm St

### Worcester North

D B Cheetham, Athol, 164 Exchange St., V P  
 J J Curley, Leominster, 89 West St., E C, M N C  
 C B Gay, Fitchburg, 62 Day St., Leg C  
 G P Keaveny, Fitchburg, 62 Fox St., A E C  
 J V McHugh, Leominster, 55 West St., P R C,  
 A M N C  
 C N McPeak, Fitchburg, 18 Hartwell St  
 J G Simmons, Fitchburg, 30 Myrtle Ave., Sec

The initials E C following the name of a Councilor indicate that he is a member of the Executive Committee and A E C that he is an alternate member of the Executive Committee. M N C that he is a member of the Committee on Nominations and A M N C that he is an alternate member of the Committee on Nominations. Leg C that he is a member of the Committee on Legislation. P R C that he is a member of the Committee on Public Relations. V P that a member is a councilor by virtue of his office as president of a district society and to vice president of the general society. C by virtue of his office as chairman of a standing committee. Sec by virtue of his office as secretary of a district society and Ex-Pres by virtue of being a past president.

## CENSORS FOR 1948-1949

### Barnstable

P P Henson, Hyannis, *supervisor*  
 D H Hiebert, Provincetown  
 D E Higgins, Barnstable  
 Joseph Kelley, Orleans  
 O S Simpson, Barnstable

### Berkshire

C T Leslie, Pittsfield, *supervisor*  
 A C England, Pittsfield  
 W T Frawley, Pittsfield  
 A M Gangemi, North Adams  
 G S Wickham, Lee.

### Bristol North

J L Murphy, Taunton, *supervisor*  
 J H Brewster, Attleboro  
 C B Kingsbury, Taunton  
 A J Leddy, Taunton  
 H G Vaughan, Attleboro

### Bristol South

Henry Wardle, Fall River, *supervisor*  
 F M Howes, New Bedford  
 W F MacKnight, Fall River  
 E A. McCarthy, Fall River  
 C C Persons, New Bedford

### Essex North

L C Peirce, Newburyport, *supervisor*  
 H M Allen, Lawrence  
 A. B. George, Haverhill  
 Julius Kay, North Andover  
 H. G. Nichols, Haverhill

### Essex South

S N Gardner, Salem, *supervisor*  
 L F Box, Beverly  
 W R. Irving, Gloucester  
 J R Shaughnessy, Salem  
 C F Twomey, Lynn

### Franklin

F J Barnard, Greenfield, *supervisor*  
 John Collieran, South Deerfield  
 Wendell Matthews, Shelburne Falls  
 John E Moran, Greenfield  
 H A Rys, Turners Falls

### Hampden

John Fallo, Westfield, *supervisor*  
 Eugene Beauchamp, Springfield  
 Alphonso Palermo, Springfield  
 Lawrence Putnam, Holyoke.  
 J L Smead, Springfield

### Hampshire

L B Pond, Easthampton, *supervisor*  
 Stephen Brown, Northampton  
 M E Cooney, Northampton  
 T F Corriden, Northampton  
 J E Hayes, Northampton

### Middlesex East

T P Devlin, Stoneham, *supervisor*  
 C R Baisley, Reading  
 H A Bouvé, Wakefield  
 S H Moses, Winchester  
 M H Rovner, Melrose

### Middlesex North

L F King, Lowell, *supervisor*  
 Philip Berman, Lowell  
 Harry Black, Lowell  
 E H Latham, Lowell  
 Charles Roughan, Lowell.

### Middlesex South

J M Baty, Belmont, *supervisor*  
 W O Blanchard, Newton  
 Oliver Cope, Cambridge  
 H J Crumb, Lexington  
 E A. Gaston, Framingham

### Norfolk

K. S. Snow, Jamaica Plain, *supervisor*  
 I R Jankelson, Jamaica Plain  
 W C Moloney, Forest Hills  
 H A Novack, Brookline  
 E E O'Neil, Chestnut Hill

## Norfolk South

F A Bartlett, Wollaston, *supervisor*  
 Arthur Rapoport, Quincy  
 H S Reid, Cohasset  
 R E Ross, South Braintree  
 W L Sargent, Quincy

## Plymouth

E L Perry, Middleboro, *supervisor*  
 L A Allen, Lakeville  
 Jacob Brenner, North Easton  
 E B Gilmore, Brockton  
 R E Swenson, Plymouth

## Suffolk

J H Pratt, Boston, *supervisor*  
 J F Collins, Revere  
 R L Goodale, Boston  
 L M Hurxthal, Boston  
 J J Todd, Boston

## Worcester

B C Wheeler, Worcester, *supervisor*  
 J B Butts, Worcester  
 Thomas Hunter, Shrewsbury  
 H L Kirkendall, Worcester  
 J W McKeon, Worcester

## Worcester North

C B Gav, Fitchburg, *supervisor*  
 E J Jolma, Gardner  
 J W Mason, Ashburnham  
 E R Pickwick, Fitchburg  
 C A Wheeler, Leominster

Plymouth — W M Carr, Whitman

Suffolk — Augustus Thorndike, Chestnut Hill

Worcester — A W Atwood, Worcester

Worcester North — W E Currier, Leominster

## OFFICERS OF THE SECTIONS FOR 1948-1949

## Medicine

*Chairman*, Laurence C Ellis, Cambridge, *vice-chairman*,  
 Allen S Johnson, Longmeadow, *secretary*, James A.  
 Halsted, Dedham

## Surgery

*Chairman*, Robert E Gross, Boston, *secretary*, Franklin  
 G Balch, Jr, Boston Executive Committee —  
 J Hartwell Harrison, Brookline

## Pediatrics

*Chairman*, W Bradford Adams, Springfield, *secretary*,  
 Gerald N Hoeffel, Boston

## Obstetrics and Gynecology

*Chairman*, James F Conway, Brookline, *vice-chairman*,  
 Daniel McSweeney, Boston, *secretary*, Dnnan E.  
 Reid, Boston

## Radiology

*Chairman*, Albert B Maloney, Boston, *secretary*,  
 Lawrence Robbins, Boston

## Physiotherapy

*Chairman*, David C Ditmore, Boston, *secretary*, Arthur  
 L Watkins, Boston

## Dermatology and Syphilology

*Chairman*, Francis P McCarthy, Boston, *secretary*,  
 Alfred Hollander, Springfield

## Anesthesiology

*Chairman*, Morris J Nicholson, Boston, *secretary*,  
 Jacob Fine, Beverly

VICE-PRESIDENTS OF THE MASSACHUSETTS MEDICAL  
SOCIETY (*Ex-Officio*) FOR 1948-1949

## PRESIDENTS OF DISTRICT MEDICAL SOCIETIES

(Arranged according to seniority of fellowship in  
 the Massachusetts Medical Society)

Norfolk South — Frederick Hinchliffe, Cohasset  
 Middlesex South — John F Casey, Boston  
 Plymouth — George A Buckley, Brockton  
 Middlesex North — James Y Rodger, Lowell  
 Norfolk — George W Papen, Brookline  
 Bristol North — Joseph V Chagny, Taunton  
 Worcester — John J Dumphy, Worcester  
 Bristol South — Aubrey J Pothier, New Bedford  
 Worcester North — Donald B Cheetham, Athol  
 Middlesex East — Milton J Quinn, Winchester  
 Berkshire — George S Reynolds, Pittsfield  
 Suffolk — Alexander J A Campbell, Brighton  
 Essex North — Robert E Blais, Amesbury  
 Essex South — Edward L Pearson, Salem  
 Franklin — Lawrence R Dame, Greenfield  
 Hampden — Robert D Hildreth, Westfield  
 Barnstable — Henry P Hopkins, Chatham  
 Hampshire — Edward J Manwell, Northampton

## COMMISSIONERS OF TRIAL FOR 1948-1949

Barnstable — F O Cass, Provincetown  
 Berkshire — J W Bunce, North Adams  
 Bristol North — J W Cook, Mansfield  
 Bristol South — A C Lewis, Fall River  
 Essex North — R V Baketel, Methuen  
 Essex South — L H Limauro, Lynn  
 Franklin — Kenneth Jacobus, Turners Falls  
 Hampden — G D Hendersson, Holyoke  
 Hampshire — R C Byrne, Hatfield  
 Middlesex East — G R Murphy, Melrose  
 Middlesex North — C M Roughan, Lowell  
 Middlesex South — H P Stevens, Cambridge  
 Norfolk — W J Walton, Dorchester  
 Norfolk South — W L Sargent, Quincy

OFFICERS OF THE DISTRICT MEDICAL SOCIETIES  
FOR 1948-1949

Barnstable — *President*, Henry P Hopkins, Chatham,  
*vice-president*, Arthur J D'Elia, Harwichport, *secretary*,  
 Frederick Sanborn, Osterville, *treasurer*, Frank Travers,  
 Barnstable, *librarian*, Carroll H Keene, Chatham, *executive*  
*and public relations counselor*, Paul P Henson, Hyannis,  
*legislative counselor*, Julius G Kelley, Pocasset.

Berkshire — *President*, George S Reynolds, Pittsfield,  
*vice-president*, N B McWilliams, Williamstown, *secretary*,  
 Daniel N Beers, Pittsfield, *treasurer*, Theodore W Jones,  
 Pittsfield, *executive counselor*, Helen M Scoville, Pittsfield,  
*public relations counselor*, Patrick J Sullivan, Dalton, *legis-*  
*lative counselor*, John Hughes, Pittsfield

Bristol North — *President*, Joseph V Chagny, Taunton,  
*vice-president*, James H Brewster, Attleboro, *secretary*,  
 William E Dawson, Taunton, *treasurer*, Charles E  
 Hove, Taunton, *executive counselor*, Joseph L Murphy,  
 Taunton, *public relations counselor*, Milton E Johnson,  
 Attleboro, *legislative counselor*, William M Stobbs, Attle-  
 boro

Bristol South — *President*, Aubrey J Pothier, New  
 Bedford, *vice-president*, John S Fielden, Fall River, *secretary*  
*and treasurer*, James E Fell, Fall River, *executive*  
*counselor*, Richard B Butler, Fall River, *public relations*  
*counselor*, Harold E Perry, New Bedford, *legislative coun-*  
*cilor*, Curtis C Tripp, New Bedford

Essex North — *President*, Robert E Blais, Amesbury,  
*vice-president*, Z William Colson, Lawrence, *secretary*,  
 Harold R Kurth, Lawrence, *treasurer*, J Leroy Wood,  
 Lawrence, *librarian*, Frank W Stockwell, Newburyport,  
*executive counselor*, Rolf C Norris, Methuen, *public rela-*  
*tions counselor*, Harold R Kurth, Lawrence, *legislative*  
*counselor*, Nicandro F DeCesare, Lawrence.

**Essex South** — *President*, Edward L. Peirson, Salem, *vice-president*, Burleigh B. Mansfield, Ipswich, *secretary*, Henry D. Stebbins, Salem, *treasurer*, Andrew Nichols, III, Danvers, *executive councilor*, Albert E. Parkhurst, Beverly, *public relations councilor*, Bernard Appel, Lynn, *legislative councilor*, Loring Grimes, Swampscott

**Franklin** — *President*, Lawrence R. Dame, Greenfield, *vice-president*, Perrin N. Freeman, Greenfield, *secretary and treasurer*, Milton M. Sisson, Greenfield, *executive councilor*, Lawrence R. Dame, Greenfield, *public relations councilor*, John E. Moran, Greenfield, *legislative councilor*, Harold R. Mahar, Orange

**Hampden** — *President*, Robert Hildreth, Westfield, *vice-president*, Arthur Riordan, Springfield, *secretary and treasurer*, Walter Williams, Springfield, *executive councilor*, Archibald Douglas, Westfield, *public relations councilor*, Frederic Hagler, Springfield, *legislative councilor*, Arthur Riordan, Springfield

**Hampshire** — *President*, Edward J. Manwell, Northampton, *vice-president*, Henry Taddell, Belchertown, *secretary and treasurer*, F. Mary P. Snook, Worthington, *librarian*, Abbie O'Keefe, Northampton, *executive councilor*, Maurice Kennedy, Hadley, *public relations councilor*, Joseph R. Hobbs, Williamsburg, *legislative councilor*, Justin E. Hayes, Northampton

**Middlesex East** — *President*, Milton J. Quinn, Winchester, *vice-president*, Ira W. Richardson, Wakefield, *secretary*, Roy W. Layton, Melrose, *treasurer*, Charles W. DeWolf, Wakefield, *librarian*, Angelo L. Maetta, Winchester, *executive councilor*, Kenneth L. MacLachlan, Melrose, *public relations councilor*, Milton J. Quinn, Winchester, *legislative councilor*, Justin L. Anderson, Reading

**Middlesex North** — *President*, James Y. Rodger, Lowell, *vice-president*, Harry Coburn, Lowell, *secretary*, Brendan D. Leachev, Lowell, *treasurer*, Alason D. Bryant, Lowell, *executive councilor*, William M. Collins, Lowell, *public relations councilor*, Samuel A. Dibbins, Lowell, *legislative councilor*, Joseph Sweeney, Lowell

**Middlesex South** — *President*, John F. Casey, Allston, *vice-president*, James M. Baty, Belmont, *secretary*, Alexander A. Levi, Newton, *treasurer*, Fabian Packard, Belmont, *orator*, Alfred O. Ludwig, Belmont, *executive councilor*,

Joseph C. Merriam, Framingham, *public relations councilor*, Ralph H. Wells, Lexington, *legislative councilor*, Kenneth J. Tillotson, Belmont

**Norfolk** — *President*, George W. Papen, Brookline, *vice-president*, W. Richard Ohler, Jamaica Plain, *secretary*, Basil E. Barton, West Roxbury, *treasurer*, Albert Ehrenfried, Brookline, *executive councilor*, Charles J. E. Kichham, Jamaica Plain, *public relations councilor*, Dean S. Luce, Canton, *legislative councilor*, Solomon L. Skvirsky, Brighton

**Norfolk South** — *President*, Frederick Hinchliffe, Cohasset, *vice-president*, Edmund B. Fitzgerald, Wollaston, *secretary and librarian*, Ebenezer K. Jenkins, South Braintree, *treasurer*, Raymond G. Vinal, Norwell, *executive councilor*, Robert L. Cook, Quincy, *public relations councilor*, Henry A. Robinson, Hingham, *legislative councilor*, David L. Belding, Hingham

**Plymouth** — *President*, George A. Buckley, Brockton, *vice-president*, Mildred L. Ryan, Brockton, *secretary*, Samuel Gale, Brockton, *treasurer*, Henry Rabnowitz, Brockton, *librarian*, J. H. Weller, Bridgewater, *executive councilor*, George A. Moore, Brockton, *public relations councilor*, Charles D. McCann, Brockton, *legislative councilor*, Alfred L. Duncombe, Brockton

**Suffolk** — *President*, Alexander J. A. Campbell, Brighton, *vice-president*, Lawrence J. McCarthy, Chelsea, *secretary*, Charles G. Shedd, Wellesley, *treasurer*, Sidney C. Wiggins, Waban, *executive councilor*, Harvey A. Kelly, Winthrop, *public relations councilor*, Howard F. Root, Boston, *legislative councilor*, William E. Browne, Boston

**Worcester** — *President*, John J. Dumphy, Worcester, *vice-president*, Bancroft C. Wheeler, Worcester, *secretary*, Donald Hight, Worcester, *treasurer*, Arthur D. Ward, Worcester, *librarian*, Philip H. Cook, Worcester, *executive councilor*, John Fallon, Worcester, *public relations councilor*, Nicholas S. Scarcello, Worcester, *legislative councilor*, John B. Butts, Worcester

**Worcester North** — *President*, Donald B. Cheetham, Athol, *vice-president*, C. Bertram Gay, Fitchburg, *secretary*, James G. Simmons, Fitchburg, *treasurer*, Frederick H. Thompson, Jr., Fitchburg, *executive councilor*, John V. Curley, Leominster, *public relations councilor*, James V. McHugh, Leominster, *legislative councilor*, C. Bertram Gay, Fitchburg

### ADMISSIONS RECORDED FROM MAY 22, 1947, TO MAY 22, 1948

YEAR OF ADMISSION	NAME AND RESIDENCE	MEDICAL SCHOOL
1947	Abbott, Richard N., Natick	Yale
1947	Abdu, Louis, Brockton	Tufts
1947	Abrams, Arthur L., Brookline	Harvard
1948	Alexander, Daniel David, E. Gardner	Middlesex
1948	Altenhaus, George, Rutland	University of Vienna
1948	Anderson, Ernest G., Belmont	Friedrich Wilhelm University, Berlin
1947	Appel, Charles F., Cambridge	Jefferson Medical College
1947	Armstrong, Beverly, Brighton	Syracuse University
1948	Armstrong, Catherine, Wellesley	University of Vermont
1948	Arnot, Robert E., Brookline	Harvard
1947	Avola, Francis A., Medford	Tufts
1948	Bacastow, Merle S., Worcester	University of Pennsylvania
1947	Ballantine, Henry T., Jr., Brookline	Johns Hopkins University
1947	Barger, A. Clifford, Brighton	Harvard
1948	Barkan, Donald B., Lynn	Boston University
1947	Barnes, John D., New Bedford	University of Maryland
1948	Barnes, William E., Taunton	Tufts
1948	Barnes, William L., Lowell	Middlesex
1947	Barone, Henry, Newton	Middlesex
1947	Barry, John J., Chelmsford	Middlesex
1947	Beer, Ernest G., Lowell	University of Heidelberg
1947	Belinkoff, Stanton, New Bedford	Middlesex
1948	Bell, William R., Marblehead	Yale
1948	Belock, John E., Beverly	University of Vermont
1947	Bergan, Carl A., Lenox	Middlesex
1948	Berman, Samuel S., Roxbury	Middlesex
1947	Bernstein, Joseph I., Springfield	Middlesex
1948	Bill, Alexander H., Jr., Boston	Harvard
1948	Bilski, Theodore D., Westfield	University of Halle, Germany
1948	Blacklow, Daniel J., Cambridge	Tufts

1948	Blanev, Lamson, Springfield	Cornell University
1947	Bloom, Bernard, Springfield	New York University
1948	Blotner, Carl, Lawrence	St. Louis University
1948	Blotnick, William, Medford	Middlesex
1947	Blumenthal, Frederick F, Bridgewater	University of Berlin
1947	Blumenthal, Irving J, Bedford	University of Freiburg
1948	Bonzey, Charles Merrill, Jr, Natick	Boston University
1948	Bradford, Martin L, Sharon	Boston University
1948	Bragg, Ernest A, Jr, Wellesley Hills	Boston University
1948	Brazelton, Thomas B, Boston	Columbia University
1947	Brean, Henry P, Boston	Harvard
1947	Breitwieser, Edna Ruth, Wellesley	University of Pennsylvania
1948	Briggs, Edward F, Truro	Baltimore Medical College
1947	Britton, Lee, Stoughton	Boston University
1948	Broderick, Thomas F, Jr, Boston	Tufts
1948	Bronson, Benjamin, Westfield	Middlesex
1948	Brooks, Oscar D, Dorchester	Middlesex
1948	Brown, Charles B, Rockport	University of Toronto
1947	Brown, Wesley C, Petersham	College of Physicians and Surgeons, Boston
1947	Brunner-Orne, Martha, Westwood	University of Vienna
1947	Burbank, Charles B, Brookline	Harvard
1947	Burke, John A, Holyoke	Tufts
1948	Burkhardt, Henry, So Hadley	Wayne University
1948	Callahan, Charles L, Indian Orchard	Georgetown University
1947	Cannon, Raymond G, So Boston	Middlesex
1948	Carey, Wm A, Quincy	Yale
1947	Carp, J Stanley, Saugus	Middlesex
1948	Carter, Max G, Boston	Harvard
1947	Cavanaugh, James E, Northampton	Columbia University
1947	Chapman, Carleton B, Boston	Harvard
1947	Clancy, Daniel H, Jr, Weymouth	Tufts
1947	Clark, John Q, Haverhill	Middlesex
1948	Clifford, William P J, Worcester	Boston University
1947	Cohen, Milton, Brookline	Tufts
1947	Colby, Raymond G, Pittsfield	New York Medical College
1947	Coleman, Nathan W, Milton	Middlesex
1948	Collings, Robert Z, Jr, Fitchburg	University of Chicago
1948	Commons, Robert R, Framingham	Harvard
1947	Condon, Robert V, Roslindale	Tufts
1947	Conway, Raymond F, Holvake	Boston University
1948	Cooper, Maurice Z, Wollaston	Long Island College of Medicine
1948	Coren, Simon, Attleboro	Middlesex
1948	Corwin, Harry J, East Longmeadow	Middlesex
1948	Costin, Maurice E, Framingham	Harvard
1948	Costrino, John J, Fall River	Tufts
1947	Crismond, Louis A, Quincy	George Washington University
1947	Crocker, Oscar, Pepperell	Middlesex
1948	Cronin, Thomas P, Jr, Somerville	Columbia University
1948	Crowell, David P, Wayland	Boston University
1947	Curtis, Exer, Gloucester	Tulane University
1948	Crudin, Myrtle B, Baldwinville	Marquette University
1947	Dahl, Lewis K, Boston	University of Pennsylvania
1948	Davis, Sulman G, Jr, Salem	University of Vermont
1947	Del Campo, Dante A, Lynn	Boston University
1948	DelColliano, Michael R, So Boston	Middlesex
1947	Dennen, William I, Wellesley	University of Rochester
1948	DeWeese, Byron, Pittsfield	Kansas City University
1947	Dexter, Chester J, Brighton	Harvard
1947	Diamond, Israel, Boston	School of Medicine of Royal College of Edinburgh
1948	Dickson, William A, Jamaica Plain	Cornell University
1947	Dietel, Robert C, So Hadley Falls	Jefferson Medical College
1948	Dixon, Stanley R, Springfield	University of Missouri
1947	Dodd, Wilson F, Mount Hermon	Cornell University
1947	Domenici, Trento J, Medford	Marquette University
1947	Donev, Frank C, Pittsfield	Middlesex
1947	Donnelly, James F, Rockland	Middlesex
1947	Donovan, Robert E, Arlington	Middlesex
1948	Dorfman, William A, Springfield	Middlesex
1947	Dowd, George C, Worcester	Middlesex
1947	Downing, William M, Boston	Boston University
1947	Drake, Emerson H, Dedham	Columbia University
1947	Drake, William L, Jr, Brookline	Marquette University
1947	Dubin, Max, Beverly	University of Vermont
1947	Dudis, Roger G, Athol	Albany Medical College
1947	Dunn, Paul P, Fall River	Tufts
1948	Dykens, James W, Worcester	University of Vermont
1947	Egan, Donald F, Springfield	Tufts
1947	Elgossin, Emid D, Millers Falls	McGill University
1947	Emerson, Charles P, Jr, Wellesley Hills	Harvard
1947	Ettenberg, Max	Middlesex
1947	Failla, John A, Greenfield	Boston University
1947	Fletcher, Mary E, Worcester	Syracuse University

**Essex South** — *President*, Edward L. Pearson, Salem, *vice-president*, Burleigh B. Mansfield, Ipswich, *secretary*, Henry D. Stebbins, Salem, *treasurer*, Andrew Nichols, III, Danvers, *executive councilor*, Albert E. Parkhurst, Beverly, *public relations councilor*, Bernard Appel, Lynn, *legislative councilor*, Loring Grimes, Swampscott

**Franklin** — *President*, Lawrence R. Dame, Greenfield, *vice-president*, Percin N. Freeman, Greenfield, *secretary and treasurer*, Milton M. Sisson, Greenfield, *executive councilor*, Lawrence R. Dame, Greenfield, *public relations councilor*, John E. Moran, Greenfield, *legislative councilor*, Harold R. Mahar, Orange

**Hampden** — *President*, Robert Hildreth, Westfield, *vice-president*, Arthur Riordan, Springfield, *secretary and treasurer*, Walter Williams, Springfield, *executive councilor*, Archibald Douglas, Westfield, *public relations councilor*, Frederic Hagler, Springfield, *legislative councilor*, Arthur Riordan, Springfield

**Hampshire** — *President*, Edward J. Manwell, Northampton, *vice-president*, Henry Taggell, Belchertown, *secretary and treasurer*, F. Mary P. Snook, Worthington, *librarian*, Abbie O'Keefe, Northampton, *executive councilor*, Maurice Kennedy, Hadley, *public relations councilor*, Joseph R. Hobbs, Williamsburg, *legislative councilor*, Justin E. Hayes, Northampton

**Middlesex East** — *President*, Milton J. Quinn, Winchester, *vice-president*, Ira W. Richardson, Wakefield, *secretary*, Roy W. Layton, Melrose, *treasurer*, Charles W. DeWolf, Wakefield, *librarian*, Angelo L. Maietta, Winchester, *executive councilor*, Kenneth L. MacLachlan, Melrose, *public relations councilor*, Milton J. Quinn, Winchester, *legislative councilor*, Justin L. Anderson, Reading

**Middlesex North** — *President*, James Y. Rodger, Lowell, *vice-president*, Harry Coburn, Lowell, *secretary*, Brendan D. Leahey, Lowell, *treasurer*, Mason D. Bryant, Lowell, *executive councilor*, William M. Collins, Lowell, *public relations councilor*, Samuel A. Dibbins, Lowell, *legislative councilor*, Joseph Sweeney, Lowell

**Middlesex South** — *President*, John F. Casey, Allston, *vice-president*, James M. Baty, Belmont, *secretary*, Alexander A. Levi, Newton, *treasurer*, Fabyan Packard, Belmont, *orator*, Alfred O. Ludwig, Belmont, *executive councilor*,

Joseph C. Merriam, Framingham, *public relations councilor*, Ralph H. Wells, Lexington, *legislative councilor*, Kenneth J. Tillotson, Belmont

**Norfolk** — *President*, George W. Papez, Brookline, *vice-president*, W. Richard Ohler, Jamaica Plain, *secretary*, Basil E. Barton, West Roxbury, *treasurer*, Albert Ehrenfried, Brookline, *executive councilor*, Charles J. E. Kichham, Jamaica Plain, *public relations councilor*, Dean S. Luce, Canton, *legislative councilor*, Solomon L. Skvirsky, Brighton

**Norfolk South** — *President*, Frederick Hinchliffe, Cohasset, *vice-president*, Edmund B. FitzGerald, Wollaston, *secretary and librarian*, Ebenezer K. Jenkins, South Braintree, *treasurer*, Raymond G. Vinal, Norwell, *executive councilor*, Robert L. Cook, Quincy, *public relations councilor*, Henry A. Robinson, Hingham, *legislative councilor*, David L. Belding, Hingham

**Plymouth** — *President*, George A. Buckley, Brockton, *vice-president*, Mildred L. Ryan, Brockton, *secretary*, Samuel Gale, Brockton, *treasurer*, Henry Rabnowitz, Brockton, *librarian*, J. H. Weller, Bridgewater, *executive councilor*, George A. Moore, Brockton, *public relations councilor*, Charles D. McCann, Brockton, *legislative councilor*, Alfred L. Duncombe, Brockton

**Suffolk** — *President*, Alexander J. A. Campbell, Brighton, *vice-president*, Lawrence J. McCarthy, Chelsea, *secretary*, Charles G. Shedd, Wellesley, *treasurer*, Sidney C. Wiggin, Waban, *executive councilor*, Harvey A. Kelly, Winthrop, *public relations councilor*, Howard F. Root, Boston, *legislative councilor*, William E. Browne, Boston

**Worcester** — *President*, John J. Dumphy, Worcester, *vice-president*, Bancroft C. Wheeler, Worcester, *secretary*, Donald Hight, Worcester, *treasurer*, Arthur D. Ward, Worcester, *librarian*, Philip H. Cook, Worcester, *executive councilor*, John Fallon, Worcester, *public relations councilor*, Nicholas S. Scarcello, Worcester, *legislative councilor*, John B. Butts, Worcester

**Worcester North** — *President*, Donald B. Cheetham, Athol, *vice-president*, C. Bertram Gay, Fitchburg, *secretary*, James G. Simmons, Fitchburg, *treasurer*, Frederick H. Thompson, Jr., Fitchburg, *executive councilor*, John J. Curley, Leominster, *public relations councilor*, James V. McHugh, Leominster, *legislative councilor*, C. Bertram Gay, Fitchburg

### ADMISSIONS RECORDED FROM MAY 22, 1947, TO MAY 22, 1948

YEAR OF ADMISSION	NAME AND RESIDENCE	MEDICAL SCHOOL
1947	Abbott, Richard N., Natick	Yale
1947	Abdu, Louis, Brockton	Tufts
1947	Abrams, Arthur L., Brookline	Harvard
1948	Alexander, Daniel David, E. Gardner	Middlesex
1948	Altenhaus, George, Rutland	University of Vienna
1948	Anderson, Ernest G., Belmont	Friedrich Wilhelm University, Berlin
1947	Appel, Charles F., Cambridge	Jefferson Medical College
1947	Armstrong, Beverly, Brighton	Syracuse University
1948	Armstrong, Catherine, Wellesley	University of Vermont
1948	Arnot, Robert E., Brookline	Harvard
1947	Avola, Francis A., Medford	Tufts
1948	Bacastow, Merle S., Worcester	University of Pennsylvania
1947	Ballantine, Henry T., Jr., Brookline	Johns Hopkins University
1947	Barger, A. Clifford, Brighton	Harvard
1948	Barlan, Donald B., Lynn	Boston University
1947	Barnes, John D., New Bedford	University of Maryland
1948	Barnes, William E., Taunton	Tufts
1948	Barnes, William L., Lowell	Middlesex
1947	Barone, Henry, Newton	Middlesex
1947	Barry, John J., Chelmsford	Middlesex
1947	Beer, Ernest G., Lowell	University of Heidelberg
1947	Belinkoff, Stanton, New Bedford	Middlesex
1948	Bell, William R., Marblehead	Yale
1948	Belock, John E., Beverly	University of Vermont
1947	Bergan, Carl A., Lenox	Middlesex
1948	Berman, Samuel S., Roxbury	Middlesex
1947	Bernstein, Joseph I., Springfield	Middlesex
1948	Bill, Alexander H., Jr., Boston	Harvard
1948	Bilski, Theodore D., Westfield	University of Halle, Germany
1948	Blacklow, Daniel J., Cambridge	Tufts

1948	Leard, Samuel E , Boston	Boston University
1948	Leary, Gerald C , Westwood	Tufts
1947	Leavell, Hugh R , Cambridge	Harvard
1948	Lec, Charles F , Andover	Middlesex
1947	Levine, Sidney A , Melrose	George Washington University
1947	Lewis, Emery C , New Bedford	University of Vermont
1947	Licht, Sidney, Cambridge	New York University
1948	Lichty, Joseph S , Brookline	Harvard
1947	Lief, Philip A , Roxbury	New York University
1947	Lingos, John W , Brockton	Middlesex
1948	Lockshin, Abraham D , Medford	Middlesex
1948	Loeb, Elsie K , No Attleboro	University of Munich
1947	Lucacer, Michael, Cambridge	Royal University, Palermo, Italy
1947	Lynch, J P , Jr, Marlboro	Boston University
1947	MacKenzie, Michael V , Medford	Tufts
1947	Madoff, Irving, Clinton	New York University
1948	Maffeo, Peter A R , E Boston	Tufts
1947	Maison, George L , Needham	Northwestern University
1948	Malone, Edward H , Waban	Boston University
1947	Manning, John J , Worcester	University of Pennsylvania
1948	Martens, Theodore G , Fall River	University of Rochester
1948	Martin, Francis, Boston	Queens University, Canada
1947	Massik, Paul, Dorchester	Tufts
1948	Maynard, Guv B , Jr, New Bedford	Cornell University
1947	Mayo, Frederic B , Swampscott	Cornell University
1948	Mayo, Walter V , Kingston	Middlesex
1948	McCarter, Robert H , Boston	Jefferson Medical College
1947	McCarthy, Francis D , Melrose	Tufts
1948	McDermott, John R , Boston	Yale
1947	McEneaney, Joseph P , Lawrence	Boston University
1947	McEnroe, Donald F , Whitman	Middlesex
1947	McGinty, John F , Jr, Lawrence	Jefferson Medical College
1947	McKernan, Bernard F , Upton	Middlesex
1947	McLean, Donald E , Winchester	Harvard
1947	McMahon, Francis J , Holbrook	Boston University
1948	McManama, John C , Waltham	Tufts
1948	McVay, John F , Dedham	Tufts
1947	Meilman, Edward, Boston	Harvard
1947	Meilin, Jacob, Bedford	University of Lausanne
1947	Meline, David I , West Roxbury	Middlesex
1948	Merlis, Jerome K , Framingham	University of Louisville
1947	Meshorer, Edward, Quincy	Kansas City University of Physicians and Surgeons
1948	Michaelson, Abraham I , Lynn	Middlesex
1948	Michaud, Raymond R. A , Salem	Tufts
1947	Mickiewicz, Matthew S , Northampton	New York University
1947	Milden, Forrest, Haverhill	Middlesex
1947	Millen, Hyman, Dorchester	Middlesex
1948	Miller, Nathaniel B , Haverhill	Middlesex
1948	Mills, Waldo O , Brookline	University of Oregon
1948	Moll, Frederic C , Boston	University of Rochester
1948	Moll, Gretchen H , Boston	Yale
1947	Monahan, John L , Dorchester	Tufts
1948	Moore, Frederick T , West Springfield	Tufts
1947	Moore, Robert L , Jr, Worcester	Boston University
1947	Morris, John M , Boston	Harvard
1948	Morrison, Jonathan I , Brookline	Dalhousie University
1947	Mulligan, William J , Brookline	University of Vermont
1947	Murphy, Rosemary A , Boston	Boston University
1948	Murray, Edward S , Boston	University of Iowa
1947	Nalband, Edward H , Wollaston	Tufts
1947	Nelson, Robert E , Arlington	University of Oregon
1948	Nelson, Rosemary, Boston	University of Chicago
1948	Neves, Edmund F , Fall River	Jefferson Medical College
1947	Newcombe, Richard V	University of Vermont
1947	Newerla, Gerbard J , Waltham	Middlesex
1948	Newman, Walter, Springfield	University of Graz (Austria)
1947	O'Hare, James M , Chestnut Hill	Harvard
1947	Orbach, Rudi J , Quincy	University of Berlin
1948	Orr, Robert B , Boston	University of Virginia
1947	Orns, Israel, Lynn	Wayne University
1947	Pagel, Max M , Newton Centre	University of Breslau
1948	Pagliauca, Gerald F , Medford	College of Physicians and Surgeons, Boston
1947	Paster, Harold I , Brockton	Middlesex
1947	Paul, Oglesby, Boston	Harvard
1947	Peloquin, Laval U , Lowell	Georgetown University
1947	Pendola, Joseph J , Longmeadow	Habnemann Medical College
1948	Pereira, Manuel C , Fall River	Lycum of Ponta Delgada, Azores
1947	Perkins, Herbert A , Lynn	Tufts
1947	Perry, Helen N , Boston	Tufts
1948	Peters, James M , Newton Centre	Tufts
1947	Petrell, N R , Plymouth	Middlesex
1947	Picaniello, Americo, Somerville	Middlesex

1947	Flynn, John G., Swampscott	Boston University
1947	Foley, Joseph M., Dorchester	Harvard
1948	Fowler, Richard L., Spencer	University of Maryland
1947	Gates, Philip H., Cambridge	University of Minnesota
1948	Gephart, Francis T., Boston	Harvard
1948	Gewin, Edwin E., Gloucester	University of Tennessee
1948	Gilligan, Thomas J., Jr., Pittsfield	Columbia University
1947	Gleason, Charles S., Wareham	Tufts
1948	Glodt, Herbert R., Pittsfield	Tufts
1947	Goldstein, Robert, Brookline	Harvard
1947	Golub, Leon M., Dorchester	Boston University
1948	Goodwin, Arthur H., Wilbraham	Tufts
1947	Gorfine, Morris, Cambridge	Middlesex
1948	Gottler, Jacob, Dorchester	Boston University
1947	Grainger, Henry B., Tewksbury	Tufts
1948	Gray, Basil, Wellesley Hills	Syracuse University
1947	Gray, William, Brookline	University of Nebraska
1948	Green, Ross W., Worcester	Tufts
1947	Greenfield, Theodore B., Greenfield	Boston University
1948	Greer, William E. R., Jamaica Plain	Boston University
1947	Gregory, Irving F., Brighton	Tufts
1947	Grimes, Arthur J., Jr., Ipswich	Georgetown University
1948	Grogan, Richard H., Watertown	Harvard
1947	Guenther, Richard A., Medford	Tufts
1947	Haddad, Albert, Worcester	Albany Medical College
1948	Haentzschel, Lester E., Longmeadow	Washington (St. Louis University)
1948	Halpern, William, Brookline	University of Pennsylvania
1947	Halton, Edward J., Holyoke	Jefferson Medical College
1948	Halton, Gerald J., Holyoke	Cornell University
1948	Hamblin, William N., Westfield	Syracuse University
1947	Harrigan, Francis J., Salem	Middlesex
1948	Harris, Sidney, Worcester	New York University
1947	Hayek, Augusta, Brookline	University of Vienna
1947	Healy, Thomas, Worcester	Harvard
1947	Hebert, Roger D., Chicopee	Laval University, Quebec
1947	Hechler, Robert, Rutland Heights	Columbia University
1947	Helsel, Milton J., Lynn	Kansas City Medical College
1948	Hertzmark, Frederic, Dorchester	University of Buffalo
1947	Hester, James W., Cambridge	Tufts
1947	Hirschman, Kurt L., Pittsfield	University of Vienna
1948	Hochstadt, Otto, Brookline	University of Vienna
1948	Hoffman, Sumner H., Boston	Tufts
1948	Holden, Robert B., Boston	Harvard
1947	Homans, John, Jr., Brookline	Harvard
1947	Honig, Jerome L., Pittsfield	Duke University
1947	Horgan, John D., Cummington	New York Medical College
1948	Hubbell, John P., Jr., Brookline	Harvard
1948	Hunter, Henry J., So. Weymouth	Temple University
1947	Huntress, William W., Boston	Tufts
1948	Hurley, Francis E., Springfield	Tufts
1948	Hurley, Joseph P., Worcester	Tufts
1948	Hurley, Paul D., Jamaica Plain	Tufts
1948	Ingersoll, Robert E., Belmont	University of Rochester
1947	Inserra, Frank, Medford	Tufts
1948	Jacobs, Leon G., Quincy	Middlesex
1948	Jenney, William L., New Bedford	Yale
1948	Jennison, David B., Northampton	Harvard
1947	Johnson, Kingsland E., New Bedford	Middlesex
1947	Joseph, Alfred T., Cambridge	Tufts
1947	Jordan, Frank J., Jr., Springfield	Tufts
1948	Kahika, Karl, Lowell	Midwest Medical College
1948	Kaplan, Louis S., Salisbury	Middlesex
1948	Karlin, Harold, Brookline	Boston University
1947	Karras, Joseph D., Brookline	Middlesex
1947	Kaufman, Irving, Taunton	George Washington University
1947	Kaufman, Irving C., Auburndale	Long Island Medical College
1947	Kaye, Abraham, Worcester	Boston University
1947	Kefferstan, Frank J., Andover	Columbia University
1947	Keitlen, Philip B., Springfield	Eclectic Medical College, Cincinnati
1948	Kelly, John F., Hyde Park	Boston University
1947	Kent, Charles, Allston	University of Prague
1947	Kiarsis, Victor, New Bedford	Dartmouth
1948	Kiehl, Anna K., Boston	University of Kansas
1947	Koenig, Arthur T., Roslindale	New York Medical College
1947	Kroger, Louis E., Brighton	University of Cincinnati
1947	Krush, Thaddeus P., Newton	Western Reserve University
1947	Kubin, Ludwig, Waltham	University of Vienna
1947	Kurland, Leonard T., Brighton	University of Maryland
1947	Lane, Helen E., Boston	Boston University
1947	Larkin, John J., W. Roxbury	Harvard
1947	Lawrence, Bradford W., Attleboro	Tufts
1947	Lazansky, Joseph P., Belmont	University of Prague

1947	Thompson, William J, Canton	Middlesex
1947	Timberlake, William H, Cambridge	Tufts
1947	Tolpin, Isidor, Lynn	Middlesex
1947	Trakas, John C, Milton	Harvard
1947	Trott, Arthur W, Wollaston	Harvard
1947	Trouhalos, Stephen, Brighton	Marquette University
1947	Tye, Mauray J, Haverhill	Tufts
1948	Valenstein, Arthur F, Boston	Cornell University
1948	VanKeuren, Howard C, Weymouth	Albany Medical College
1947	Vaughan, Robert H, Dedham	Harvard
1948	Velon, Bruce P, Taunton	Middlesex
1947	Visconti, James J, West Springfield	Midwest Medical College
1947	Waldinger, Clara, Jamaica Plain	University of Vienna
1948	Wallace, Robert W, Westwood	University of Pittsburgh
1948	Waring, George W, Jr, Brookline	Johns Hopkins University
1947	Warner, Frank A, Boston	Harvard
1947	Webster, Earle H, Hyannis	Harvard
1947	Weinreb, Joseph, Newton Centre	Vanderbilt University
1947	Weinstein, Max I, Lawrence	Middlesex
1948	Weiss, Daniel, Dorchester	Boston University
1947	Weiss, Samuel, Brockton	Tufts
1948	Weller, Thomas H, Boston	Harvard
1947	West, George V, Reading	Tufts
1947	Whiting, George L, Abington	Tufts
1947	Whitney, Byron V, Bangor, Maine	Tufts
1948	Wholey, John J, Lawrence	Middlesex
1947	Whorton, Carl M, Squantum	Vanderbilt University
1948	Wilder, Francis D, Brockton	University of Lausanne
1948	Wilker, Sydney R, Roxbury	Boston University
1947	Wilson, Norman J, Boston	University of Maryland
1947	Wilson, Norman L, Quincy	University of Virginia
1947	Winsten, Sol Stephen, Northampton	University of Berne
1948	Witmer, Donald S, Fall River	College of Physicians and Surgeons, Boston
1947	Wixted, Francis J, East Milton	New York Medical College
1948	Woodman, Ernest L, Jr, Lawrence	Tufts
1948	Woodruff, Charlotte S, Pittsfield	Long Island College of Medicine
1947	Wool, Jack, Boston	University of Vermont
1947	Yaukopolus, Konstantine G, New Bedford	Boston University
1947	Yatsuhashi, Masao, Brookline	Harvard
1947	Yosko, Norman, E Longmeadow	Chicago Medical School
1947	Yudell, Milton H, Worcester	Rush Medical College
1947	Zamcheck, Norman, Boston	Harvard
1947	Zanconato, Guerrino J, West Stockbridge	Tufts
1947	Zarecki, Peter S, Jr, Lynn	Tufts
1948	Zawislak, Joseph J, Lawrence	Middlesex
1947	Zielinski, Joseph F, Holyoke	Jefferson Medical College

## DEATHS REPORTED FROM MAY 22, 1947 TO MAY 22, 1948

ADMITTED	NAME	PLACE OF DEATH	DATE OF DEATH	AGE
1954	Louis Alpert	Middleboro	August 17, 1947	44
1906	Louis Arkin	Sharon	October 1, 1947	70
1917	Avedis D Avedisyan	Brighton	November 16, 1947	75
1894	Silas H Ayer	Boston	September, 1947	86
1906	John B Bain	Boston	October 13, 1947	68
1900	†John A Barton	Fitchburg	1948	74
1912	Ewald G Baum	Canaan, New Hampshire	October 22, 1947	63
1925	G R Baxter	Boston	July 24, 1947	52
1912	Charles F K Bean	West Medford	September, 1947	60
1904	Orrin C Blair	Lynn	August 3, 1947	68
1879	Walter P Bowers	Chnton	July 22, 1947	92
1950	Melville G Boyd	Ontario	September, 1947	46
1907	James C Bright	Fall River	November 12, 1947	74
1893	Martin M Brown	North Adams	September 19, 1947	84
1942	William G Cole	Bermuda	April 16, 1948	46
1910	George J Connor	Haverhill	April 1948	62
1909	Charles L Curtis	Salem	December 11, 1947	62
1916	Elliott C Cutler	Brookline	August 16, 1947	59
1895	†Charles B Darling	Waban	April 19, 1948	79
1905	Hilbert F Day	Cambridge	May 17, 1947	68
1885	Samuel Delano	New Britain, Connecticut	November 18, 1947	89
1896	Isaac S F Dodd	Pittsfield	January, 1948	80
1908	Arthur H Ellis	Greenfield	March 14, 1948	66
1880	†Frederick W Ellis	Newton Centre	April 30, 1948	90
1905	†Frederick L Everett	Watertown, New York	March 6, 1948	76
1897	John E. Fish	Canton	March 30, 1948	75
1902	†Elisha Flagg	New York	June 8, 1947	82
1914	Edwin R Fleming	Medford	March 4, 1948	69

1947	Pick, Walter, Boston	Harvard
1947	Pious, Lawrence K., Lexington	Middlesex
1947	Polatin, Sydney, Roslindale	Middlesex
1947	Potsubay, Samuel F., Holyoke	Harvard
1948	Powers, Harry T., Fall River	Cornell University
1948	Putnam, Hazel E., Plymouth	McGill University
1947	Quinn, Edmund P., Medford	Tufts
1947	Racioppi, Francesca M., Wellesley	Boston University
1948	Ramsay, Beatty H., Brookline	University of Manitoba
1947	Rand, Harry, Dorchester	Middlesex
1947	Raphael, Sumner I., Brighton	Tufts
1948	Rappaport, David, Oak Bluffs	Middlesex
1947	Reagan, Daniel J., Worcester	Harvard
1947	Reid, David H., Melrose	Tufts
1948	Reppucci, Anthony, Lowell	Middlesex
1947	Richmond, Paul, Jr., Worcester	Georgetown University
1948	Riemer, Karl, Boston	Tufts
1947	Riemer, Robert W., Norwood	Tufts
1947	Riggs, Benjamin C., Topsfield	Columbia University
1947	Riley, Leo H., Jr., Newton	Boston University
1948	Risley, Thomas S., Boston	Harvard
1948	Robertson, Charles W., Boston	Syracuse University
1948	Rockwood, Lawrence, Medford	Tufts
1947	Rogers, Joseph, Boston	Harvard
1947	Roopenian, Aram, South Boston	Tufts
1947	Rosen, Daniel, Roxbury	University of Vienna
1947	Rosenbaum, Jack D., Framingham	Yale
1947	Rosenberg, Isadore N., Boston	Harvard
1948	Rosengard, David E., South Boston	Tufts
1948	Ross, Helen M., Boston	Tufts
1948	Rowbotham, John L., Canton	Harvard
1947	Rowell, Russell J., Beverly	Tufts
1947	Roy, James E., Worcester	Harvard
1947	Sands, Herman C., Salem	Middlesex
1947	Sapareto, Rocco L., Haverhill	University of Maryland
1947	Sapienza, Peter L., Everett	Boston University
1947	Scannell, John G., Belmont	Harvard
1948	Schlessinger, Paul J., Cambridge	Harvard
1947	Schultz, John D., Jr., Boston	Johns Hopkins University
1948	Scoville, Peter G., Hyde Park	College of Physicians and Surgeons, Boston
1948	Sears, Robert A., Brookline	Yale
1948	Seeler, Albert O., Boston	Harvard
1946	Selverstone, Bertram, Belmont	Harvard
1947	Senesac, Archibald E., New Bedford	Tufts
1947	Sennott, Francis W., Cambridge	Tufts
1947	Shauffer, Irving A., Brookline	Tufts
1947	Shaw, John E., Newburyport	Georgetown University
1948	Shea, Daniel J., Jr., Beverly	Boston University
1948	Shuman, Samuel B., Dorchester	Middlesex
1948	Siegel, Henry W., Dorchester	Middlesex
1947	Silver, Joseph M., Fitchburg	Middlesex
1948	Simon, Aaron I., Fitchburg	Ohio State University
1948	Skornik, Nathan, W. Newton	Middlesex
1947	Snyder, Franklin F., Newton Centre	Johns Hopkins University
1948	Sotirion, George A., Springfield	Duke University
1947	Soule, Robert M., Melrose	Harvard
1947	Soulotis, Paul T., Cambridge	Hahnemann Medical College
1947	Sparling, Harold J., Whalom	Boston University
1947	Sparling, Seda A., Whalom	Boston University
1947	Spelfogel, Benjamin, Mattapan	Middlesex
1947	Spelman, Philip J., Plymouth	Columbia University
1947	Spindler, James F., Boston	University of Georgia
1947	Spitzer, Maurice G., North Adams	Middlesex
1948	Stewart, Goodwill M., Brockton	Tufts
1947	Stoddard, Eben, Salem	Rush Medical College
1948	Stone, Bartlett H., Brookline	University of Vermont
1947	Stone, Timothy P., Southboro	Tufts
1947	Straccia, Frank A., Hawthorne	Tufts
1947	Streeter, C. Clarke, Harvard	Tufts
1948	Sullivan, Thomas H., Fall River	Middlesex
1947	Sweet, William H., Brookline	Harvard
1947	Szydlowski, Sigmund J., Wakefield	Middlesex
1948	Taft, Edgar B., Cambridge	Yale
1948	Taggart, William G., Westfield	Jefferson Medical College
1948	Talbot, Timothy R., Jr., Boston	University of Pennsylvania
1948	Tannenbaum, Harold S., Jamaica Plain	Middlesex
1947	Tatlock, Hugh, Northampton	Harvard
1948	Tauber, Joseph, Springfield	University of Vienna
1947	Tedeschi, Cesare G., Framingham	University of Bologna
1948	Terranova, Anthony J., Attleboro	Middlesex
1948	Thatcher, Lyndon H., Dennis	Columbia University
1947	Thompson, John R., Dalton	McGill University

Thomas G Brown  
J H Humphrey  
Ernest A Johnson  
Harold B Leland  
Arthur W Allen, M D  
Elmer S Bagnall, M D  
Roswell F Phelps  
Norman A. Welch, M D  
Hugh Nawn  
Joseph K. Miliken  
Eugene Walker, M D

W A R. Chapin, M D  
C Bertram Gay, M D  
Harold G Giddings, M D  
Eliot Hubbard, Jr, M D  
Charles J Kickham, M D  
Kenneth L. MacLachlan, M D  
Roger W Hardy, acting executive director,  
38 Chauncy St., Boston  
C G Hayden, M D, medical director,  
38 Chauncy St., Boston  
Dwight O'Hara, M D  
Walter G Phippen, M D  
Daniel B Reardon, M D  
William F Ryan, M D  
Henry A Taddell, M D  
Bancroft C Wheeler, M D

## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

TRACY B MALLORY, M D, *Editor*

BENJAMIN CASTLEMAN, M D, *Associate Editor*

EDITH E PARRIS, *Assistant Editor*

### CASE 34311

#### PRESENTATION OF CASE

A seventy-five-year-old Negro was admitted to the hospital complaining of pain in the right flank.

About six years before admission the patient began having superficial pain in the right lower thigh. No other accompanying signs or symptoms were noted. Four months before admission there was sudden weakness of the right leg, and standing caused severe pain. Since then he had been unable to walk. There was no joint pain, chills or fever. About two months before admission there was occasional mild right-flank pain, which did not bother the patient unduly. Defecation and urination were normal at that time, and there were no gastrointestinal symptoms. The pain later became severe and persistent and occasionally radiated to the right groin. The patient's wife stated that he had had black stools. She also stated that he had been under treatment for "high blood pressure" for four years and that eight weeks before admission he had an episode of very labored breathing. He had had an easily reducible right scrotal hernia for fifty years.

Physical examination revealed a poorly nourished, confused, dyspneic and acutely ill man. The veins of the scalp and neck were engorged but not pulsating. The lungs were emphysematous. Medium moist rales were heard throughout both bases. The right leaf of the diaphragm was much elevated and showed limited excursion. The heart was enlarged to the left. A Grade II systolic murmur was heard over the whole precordium. There was moderate distention of the abdomen, and peristalsis was normally active. Voluntary resistance was

encountered over the right flank, which was filled by a tender, poorly defined mass. Little, if any, costo-vertebral angle tenderness was elicited. Rectal examination revealed tenderness on the right. The prostate was slightly enlarged and nodular. A large, right scrotal mass was present, in which gurgles were heard. There was superficial and deep tenderness on the anterior aspect of the right thigh. Knee jerks were normal. No edema was present.

The temperature was 97.5°F, the pulse 90, and the respirations 22. The blood pressure was 100 systolic, 68 diastolic.

Examination of the blood revealed a white-cell count of 23,000, with 88 per cent neutrophils, and a red-cell count of 4,000,000. The hemoglobin was 12 gm. The urine had a specific gravity of 1.019 and contained + albumin. No casts were seen, but the sediment was "loaded" with leukocytes. The stool was brown and had a ++ guaiac reaction. The nonprotein nitrogen was 42 mg, the serum calcium 7.7 mg and the phosphorus 3.0 mg per 100 cc. The alkaline phosphatase was 4.8 and the acid phosphatase 1.4 units per 100 cc. The total serum protein was 5.7 gm per 100 cc. The chloride was 94 and the carbon dioxide 21.2 milliequiv per liter.

X-ray examination of the chest showed an elevated diaphragm, linear streaks of atelectasis at the right base, enlargement of the heart, and elongation and tortuosity of the thoracic aorta. No free air was seen beneath the diaphragm. There was extensive Paget's disease involving the pelvis and lumbar spine. A diffuse increased density was seen in the right side of the abdomen. Neither kidney contour was visualized, and the right psoas shadow was not present. There was a single large calcification, about 1 cm in diameter, and several smaller calcifications superimposed on the right kidney shadow. Calcification was seen in the abdominal aorta. An excretory urogram revealed an essentially normal left upper urinary system. No dye was excreted from the right kidney. A barium enema was negative except for the scrotal hernia, which contained cecum and small bowel. A retrograde pyelogram was attempted but the catheter would not pass up the ureter more than 0.5 cm. No efflux was seen from either orifice.

On the fourth hospital day an operation was performed.

1920	Edward H. Ganley	Methuen	January 23, 1948
1919	Walter T. Garfield	Belmont	May 31, 1947
1947	Maurice A. Gilbert	Chelsea	January 18, 1948
1909	Florence Gilman	New Hampshire	August 1, 1947
1925	Edwin B. Goodall	Boston	August 6, 1947
1905 } 1910 }	George H. Gorham	Jamaica Plain	March 12, 1948
1932	Henry M. Grady	Dedham	July 30, 1947
1905	Arthur M. Greenwood	Marlboro	December 14, 1947
1908	Henry Hawkins	Sullivan, Maine	September 4, 1947
1899	Thomas R. Healy	Newburyport	February 25, 1948
1911	Francis F. Henderson	Milton	November 20, 1947
1912	Thomas F. Hennessey	Swampscott	July 21, 1947
1914	George V. Higgins	Randolph	September 9, 1947
1913	Samuel Hoberman	Malden	February 18, 1948
1906	†Walter A. Hoslev	Topsfield	March 25, 1948
1885	†Oliver H. Howe	Cohasset	March 11, 1948
1917	Winfred L. Howe	Everett	August 18, 1947
1903	Ernest L. Hunt	Worcester	January 17, 1948
1926	†Reid Hunt	Boston	March 10, 1948
1921	Vincent J. Irwin	Springfield	February 26, 1948
1894	Mary W. L. Johnson	Brighton	September 13, 1947
1903	Raymond C. Jones	Ashby	December 2, 1947
1914	Ernest H. Judd	Springfield	October 17, 1947
1880	Patrick H. Keefe	Providence, Rhode Island	October, 1947
1931	Connie H. King	Duxbury	January 22, 1948
1902	Frederick A. King	Marshfield	September 14, 1947
1910	George C. King	Fall River	December 21, 1947
1901	Frederick D. Lambert	Tyngsboro	April 20, 1948
1919	Leslie P. Leland	Worcester	March 16, 1948
1947	William J. Lord	Great Barrington	December 14, 1947
1927	Henry Lubinski	Fall River	May 25, 1948
1897	†James A. Mansfield	Dorchester	June 29, 1947
1916	†James V. May	Watertown	December 24, 1947
1907 } 1942 }	†Leo T. McCready	Jamaica Plain	May 5, 1948
1882	†Herbert McIntire	Cambridge	April 21, 1948
1923	Archibald McMillan	Athol	January 16, 1948
1883	†William H. McOwen	New York	March 9, 1948
1920	Leon J. Menard	Fall River	August 23, 1947
1928	†Grace Milliken	Brookline	January 19, 1948
1930	Herman A. Morrill	Gardner	May 28, 1947
1917	Harold A. Murphy	Jamaica Plain	September 23, 1947
1900	James Nightingale	Worcester	July, 1947
1921	Robert N. Nye	Chestnut Hill	September 10, 1947
1912	E. J. O'Brien, Jr.	Boston	February 16, 1948
1917	†John C. O'Brien	Turners Falls	March 18, 1948
1932	Carver H. Osborne	Brookline	January 3, 1948
1920	William J. Pelletier	Turners Falls	November 16, 1947
1940	Anthony S. Pendola	Holyoke	January 10, 1948
1897	†Ernest D. Pillsbury	Stoughton	January 6, 1948
1932	Mendel Poliak	Springfield	September 15, 1947
1910	John A. Reese	Attleboro	December 10, 1947
1922	Frederick Reis	Jamaica Plain	February 4, 1948
1943	John D. Rice	West Boylston	October 4, 1947
1918	Carroll H. Ricker	Worcester	September 6, 1947
1945	Albert I. Robbins	New Haven, Connecticut	April 14, 1948
1936	Leon J. Robinson	Springfield	February, 1948
1915	Moses V. Safford	Jamaica Plain	June 20, 1947
1891	James A. Shatswell	Beverly	August 26, 1947
1908	Benjamin E. Sibley	Brookline	November 19, 1947
1900	Albert E. Small	Boston	June 9, 1947
1894	Frederick G. Smith	Somerville	January 9, 1948
1912	Elizabeth C. Underhill	New York	September 21, 1947
1922	John M. Wise	Watertown	August 7, 1947

†Retired fellow

Total number of deaths of active fellows	76
Total number of deaths of retired fellows	15
Grand total	91

## MASSACHUSETTS MEDICAL SERVICE

## Officers and Directors

James C. McCann, M.D., president  
 Philip M. Morgan, vice-president  
 Edmund L. Twomey, treasurer  
 Daniel J. Boyle

## Members of the Corporation

Edward P. Bagg, M.D.  
 Richard B. Butler, M.D.  
 Paul M. Butterfield, M.D.  
 A. J. A. Campbell, M.D.  
 George A. Moore, M.D.  
 John E. Moran, M.D.  
 Joseph L. Murphy, M.D.  
 Rolf C. Norris, M.D.

DR WYMAN I do not believe that it is safe for us to say that the kidney on the right is displaced laterally. There is a faint hint from the available films that it is farther lateral than usual. The position of the stone is more lateral than one would see with pelvic stone.

DR YOUNG Is there a chance that this mass of which you speak and which I have disregarded could be an aneurysm?

DR WYMAN I was thinking of that, but I cannot outline calcium in it with any degree of certainty. There is a fair amount of calcium lying up here. I do not know what it is.

DR YOUNG The description does not suggest that the mass pulsated.

DR WYMAN I wondered about an aneurysm of the renal artery or some such thing pushing the kidney up.

DR YOUNG It did not pulsate.

#### CLINICAL DIAGNOSIS

Calculus pyonephrosis

#### DR YOUNG'S DIAGNOSIS

Calculus pyonephrosis

Tumor of kidney?

Tuberculosis of kidney?

#### ANATOMICAL DIAGNOSES

*Retroperitoneal fibrosarcoma, with pressure on right kidney, extension into inferior vena cava, duodenum, and ascending colon, and with metastases to lung*

Perinephritis, acute, chronic

Peritonitis, acute

Operation nephrostomy, right

#### PATHOLOGICAL DISCUSSION

DR BENJAMIN CASTLEMAN The kidney was explored through a right transverse incision and chronically inflamed perirenal tissue was encountered as the lumbodorsal fascia was opened. At that time aspiration of the tissue yielded thick, greenish pus. An incision was made through the kidney cortex into the pelvis and the stone, seen by x-ray, was removed. A nephrostomy tube was placed in the pelvis. At the time of operation a biopsy of some of this inflamed tissue around the kidney was taken on which a diagnosis of fibrosarcoma was made. The patient did not do well postoperatively and died a few days later.

At autopsy we found that the kidney was displaced a great deal, in fact, it lay almost horizontally. This horizontal position of the kidney was due to a large retroperitoneal mass in the right side of the abdomen which pushed the kidney up. Anterior to the mass was the ascending colon and medially and superiorly was the duodenum. They were both intimately connected by the mass, which had eroded through into their lumens. This ade-

quately explains the tarry stools noticed by the patient's wife and the positive guaiac test in the hospital. The mass was tremendous in size and proved to be a fibrosarcoma arising in the retroperitoneal space. A very interesting finding was an extension of the tumor into the inferior vena cava in a polypoid fashion. Microscopic sections of the surface of this polyp showed endothelium of the vena cava, so that the tumor was really pushing the vena cava ahead. The tumor did not arise within the kidney substance at all, the fibrous capsule of the kidney being clearly visible between renal parenchyma and tumor. The tumor had metastasized to the lung.

DR YOUNG You did not check the bone?

DR CASTLEMAN One section of bone showed no evidence of metastases. The pus that the operator had found at operation was due to the perforation of the ascending colon with spillage of fecal material.

DR YOUNG Between the tumor and the ascending colon?

DR CASTLEMAN Yes. At the time of autopsy that had extended up along the right gutter into the peritoneal cavity and had produced peritonitis on the right side.

DR YOUNG Did they get through to the kidney?

DR CASTLEMAN No, there was no stone in the kidney.

DR YOUNG But they got into the pelvis?

DR CASTLEMAN Yes, the nephrostomy tube was in the kidney pelvis, but the tumor had completely obstructed the ureter on that side.

DR YOUNG Did the tumor involve the nerve to cause the leg symptoms?

DR CASTLEMAN I cannot answer that. It might well have.

#### CASE 34312

#### PRESENTATION OF CASE

A seventy-one-year-old man entered the hospital because of an abdominal mass.

The abdomen had always been of rather extensive proportions, but three months before admission he noted a hard swelling on the right side which did not change appreciably in size following discovery. His appetite was always good although for three years he was bothered by increasing belching following meals. There was never any food intolerance, abdominal pain or vomiting. His diet had always been good. Gradually increasing constipation also bothered him during the three years before admission, although there was no change in the character of the stools and never any diarrhea. There were never any symptoms of liver disease and no weight loss.

The patient was born in Greece, where he was brought up on a farm. He came to the United States at the age of thirty-one and went to work in a shoe

## DIFFERENTIAL DIAGNOSIS

DR EDWARD L. YOUNG A medical man must have made the statement about the mass in the right flank. If it had been made by a trained urologist, he would have said whether or not it gave the impression of going through to the flank on ballottement, if it is kidney, there is generally the sensation that the mass goes through or close to the costovertebral angle.

The blood picture is surprisingly good for a man as sick as this.

Let us discuss the x-ray films at this point.

DR STANLEY M. WYMAN The heart is considerably enlarged, it looks to be chiefly left ventricular enlargement. The aorta is quite tortuous, especially in the descending portion, and there is some calcification in the wall. The ascending portion of the aorta appears dilated and may be dilated as far as the descending portion, although one cannot be sure of the latter. There is some atelectasis in the lower portion of the right lung field. I cannot localize it because there is no lateral view. The humerus shows some changes quite consistent with Paget's disease. The films of the abdomen show the area of calcification described, overlying the right kidney, in the lateral view it is seen to lie far posteriorly, again coincident with the kidney. I cannot outline the kidney itself on either side with any degree of certainty. The intravenous dye is excreted by the left kidney in fair concentration, and the major and minor calyces are grossly normal so far as can be determined. The kidney appears approximately normal in size. There are several films that show a faint linear shadow in the region of the right kidney, which makes me wonder if it could be the medial margin of the kidney. If so, the kidney is displaced laterally. However, this is not certain enough to make any definite statement. There is a well defined arc of calcification just to the left of the lumbar spine, which in the lateral view is seen to be a considerably dilated abdominal aorta. The bones of the lumbar spine and pelvis are normal.

DR YOUNG Are you sure that what you see in the bones is Paget's disease and not metastases?

DR WYMAN I think it is Paget's disease.

DR YOUNG Are you always able to differentiate?

DR WYMAN No. The differential point is the increased size of the bone and the involvement chiefly of the cortex. These are fairly definite in this particular person. The thickening in the ilium lies along the margin and inner aspect of the pelvis. Paget's disease is more likely than osteoblastic metastases.

DR YOUNG Will you comment on the reason why you think there is stone in the kidney?

DR WYMAN The character of the calcification is rather discrete. It is not homogeneous but mottled. It lies far posteriorly, at the expected

location of the kidney itself. All these add up to make it more likely to be a kidney stone than a calcified lymph node or a gallstone. I think the shadow in the right flank, which is described in the protocol, may represent the colon filled with fluid because on the barium enema there is a large loop of colon overlying the ilium, and one can see a big hernial sac containing cecum and ileum.

DR YOUNG The whole picture seems to me to be somewhat confusing. We have an old man who is sick. The pain in his leg may have been due to hypertrophic changes, which are usually seen in the spine in a man of seventy-five, or to Paget's disease. The black stools are difficult for me to put into the picture. That statement was made by his wife but apparently no attempt was made to find out whether medication had been given that might have caused them. We are not sure that they were due to blood. He was treated for high blood pressure four years ago—and yet he comes in with a blood pressure far below what is expected. We can attribute that to his poor general condition. He has a leukocytosis, a mass in the right flank, a shadow that suggests kidney stone, and pus in the urine. The right ureter could not be catheterized. That does not necessarily mean that it was completely blocked. It often is difficult to catheterize the ureter because of stiffness—when actually there is a passageway through it. The white count suggests that there was infection going on even though he had no temperature. The other kidney was working. The specific gravity was 1.019. The nonprotein nitrogen did not show much elevation, in fact, 42 mg would be within high normal limits.

The first thought here would be a calculus pyonephrosis, but one must remember that although tuberculosis of the urinary tract almost always shows itself in bladder irritation, it occasionally occurs without it. It is not impossible that there is a background here of tuberculosis and mixed infection, although that is not usual. We must not forget that tumor of the kidney can have a stone present. There was a negative barium enema, and I cannot seem to connect the blood in the stool with this unless we have a condition of congestion due to cardiac decompensation. So I think that this constitutes a calculus pyonephrosis, with or without one of the other two things being present. He is an extraordinarily poor risk because of what we know about his general condition, yet today with the ability we have to increase the body chemistry of the patient to a level more closely normal we can get away with what ten or fifteen years ago would have been murder. If this is calculus pyonephrosis, a two-stage operation may give him a chance. There may be something entirely different, but I will put calculus pyonephrosis as my first choice, with or without the other.

asymptomatic with a fairly large mass in his abdomen

Could we be wrong about the diagnosis? Unfortunately, yes. However, the mass is lobulated and apparently cystic — and I know of no other cystic mass that could grow to this size in the right upper quadrant without producing symptoms. Any solid mass of this size would undoubtedly produce symptoms. The mass was certainly cystic. Those who took care of him thought so because they describe it as fluctuant and went so far as to try to transilluminate it. If it did not involve the under surface of the right diaphragm one would have to consider such things as large multilocular pancreatic cysts — they grow to huge proportions. If it were on the left, a splenic cyst would have to be thought of, or an omental cyst. But under the circumstances there is nothing to indicate any other diagnosis but an echinococcus cyst.

How do you feel about it, Dr. Adams?

DR F DENNETTE ADAMS. I agree that it would be a job to get it out and the chances for spilling are great.

DR KRANES. The risk of spilling seems greater than the risk of leaving it alone. He apparently did well.

#### CLINICAL DIAGNOSIS

Echinococcus cyst

#### DR KRANES'S DIAGNOSIS

Echinococcus cyst

#### ANATOMICAL DIAGNOSIS

Echinococcus cyst

#### PATHOLOGICAL DISCUSSION

DR RONALD C SNIFFEN. The patient was operated on with a preoperative diagnosis of echinococcus cyst, and it was found that the cyst ran

from the pelvis up to the liver and occupied almost the entire right lobe of that organ. It was surrounded by peritoneal adhesions, and daughter cysts were noticed in the remaining liver. A partial excision of the cyst was performed and a drain was inserted into the remaining cavity. Microscopically the wall of the cyst showed the characteristic laminated chitinous membrane and germinative epithelium of an echinococcus cyst. It is now about two and a half months since operation. The patient is back at work and feels well, but a small amount of material is draining through the sinus in the right upper quadrant.

DR GRANTLEY W TAYLOR. The medical service wanted to have us carry out laparotomy in this case for confirmation of the diagnosis. Peritoneoscopy had been considered as an alternative method of investigation but it was felt that this would yield less positive findings. The operative findings have been described. Many of the cysts were thick walled and necrotic and contained opaque thick purulent-like material. Others were thin walled and contained clear fluid. Two or three basinfuls of these cysts were collected and cleansed to be used for antigen. My impression was that there had been previous minor ruptures of these cysts to account for the numerous adhesions and the dispersion which was present.

I cannot agree entirely with Dr. Kranes that there is no indication for operation because sometimes large cysts of this type are ruptured by relatively minor trauma and then constitute a real abdominal emergency. In addition I think that the record perhaps fails to emphasize that the pressure symptoms were reaching the point where they caused the patient considerable trouble, not only with the function of the gastrointestinal tract but in respiration as well.

factory. He continued in this business until admission to the hospital and was exposed to numerous types of chemicals. This exposure occasioned visits to the skin clinic of the hospital twice several years previously at which time diagnoses of contact dermatitis were made.

Physical examination showed a well developed but poorly nourished man. Examination of the chest was not remarkable except for a high relatively fixed diaphragm. The abdomen was large and asymmetrical. There was a fluctuant, non-tender, apparently lobulated mass, which moved with respiration and extended from the fourth intercostal space on the right to two inches below the umbilicus and could be felt in both flanks, being more prominent on the right. It could not be transilluminated. There were bilateral reducible inguinal hernias and bilateral varicoceles.

The temperature, pulse and respirations were within normal limits. The blood pressure was 148 systolic, 90 diastolic.

The blood, urine and stool tests were negative except for slight anemia, a hemoglobin of 11.5 gm, and a 10 per cent eosinophilia. The nonprotein nitrogen, fasting blood sugar, amylase, cephalin flocculation, van den Bergh, and bromsulfalein test, phosphorus, alkaline phosphatase, and prothrombin time were all within normal limits. The total protein was 8 gm per 100 cc, with an albumin-globulin ratio of 0.85. An x-ray film of the chest showed nodularity of the right diaphragm. A gastrointestinal series showed a negative esophagus, a stomach displaced to the left and posteriorly, and no intrinsic involvement of the gastrointestinal tract. It was thought that the mass was related to the liver. There were a number of calcifications in the upper portion of the liver. An echinococcus skin test was positive.

On the sixth hospital day an operation was performed.

#### DIFFERENTIAL DIAGNOSIS

DR ALFRED KRANES: There are two statements in the record to which I should like to take exception. One is the description of the mass, which is said to extend from the fourth intercostal space on the right to two inches below the umbilicus. I do not see how one can feel a mass of this size in the fourth intercostal space. What is meant is that the area of liver dullness extended up to the fourth intercostal space. I find it hard to believe that the mass could be felt that high, although that is the

impression one gets from the description. One can only say that the mass extended so far below the costal margin. The other statement that I question is the description by x-ray of nodularity of the diaphragm. I think what is meant is irregularity. One cannot say that the diaphragm is nodular, can one?

DR STANLEY M. WYMAN: No.

DR KRANES: That implies a third dimension which, of course, we do not have.

DR WYMAN: The radiologist's statement in the record was, "There is irregularity of the right leaf of the diaphragm resulting from nodularity or masses projecting from the superior aspect of the liver."

DR KRANES: That makes the diagnosis easier.

DR WYMAN: The right leaf of the diaphragm is definitely elevated and as you see comes to the fourth interspace. The lung fields otherwise appear intrinsically clear. The heart shadow is prominent toward the left, probably in the region of the left ventricle. The barium-filled stomach is faintly seen in this film displaced toward the left, and the duodenal cap is displaced downward and to the left. The entire right side of the abdomen is dense and there is a suggestion of several small areas of calcification. There is a very definite mass, nodular and lobulated, on the right.

DR KRANES: As I see this problem there is no differential diagnosis. What else can this be but an echinococcus cyst? If that diagnosis is correct, and I can see no other one to make, I must say that I would not have him operated on. You must remember that he is seventy-one years old. The disease started before the age of thirty-one and although he gave a history of having felt the mass only three months before entry, you will all agree, I am sure, that an echinococcus cyst of this size must have been growing for many, many years. Furthermore, despite its size, and it does seem to be huge, it has produced absolutely no symptoms. The record states that the man was feeling quite well except for a few mild symptoms of belching and constipation. Nor has it interfered with the function of any organ although it has displaced the stomach. While it may involve a fairly large part of the liver, it has not interfered with the liver's function or produced any alteration in the laboratory tests. They were all normal. Consequently, I probably would not have advised this patient to be operated on since I see nothing to be gained by operation at seventy-one on an asymptomatic echinococcus cyst. The chances are that he might have gone another five or ten years still.

asymptomatic with a fairly large mass in his abdomen

Could we be wrong about the diagnosis? Unfortunately, yes. However, the mass is lobulated and apparently cystic — and I know of no other cystic mass that could grow to this size in the right upper quadrant without producing symptoms. Any solid mass of this size would undoubtedly produce symptoms. The mass was certainly cystic. Those who took care of him thought so because they describe it as fluctuant and went so far as to try to transilluminate it. If it did not involve the under surface of the right diaphragm one would have to consider such things as large multilocular pancreatic cysts — they grow to huge proportions. If it were on the left, a splenic cyst would have to be thought of, or an omental cyst. But under the circumstances there is nothing to indicate any other diagnosis but an echinococcus cyst.

How do you feel about it, Dr. Adams?

DR. F. DENNETTE ADAMS: I agree that it would be a job to get it out and the chances for spilling are great.

DR. KRANES: The risk of spilling seems greater than the risk of leaving it alone. He apparently did well.

CLINICAL DIAGNOSIS

Echinococcus cyst

DR. KRANES'S DIAGNOSIS

Echinococcus cyst

ANATOMICAL DIAGNOSIS

Echinococcus cyst

PATHOLOGICAL DISCUSSION

DR. RONALD C. SNIFFEN: The patient was operated on with a preoperative diagnosis of echinococcus cyst, and it was found that the cyst ran

from the pelvis up to the liver and occupied almost the entire right lobe of that organ. It was surrounded by peritoneal adhesions, and daughter cysts were noticed in the remaining liver. A partial excision of the cyst was performed and a drain was inserted into the remaining cavity. Microscopically the wall of the cyst showed the characteristic laminated chitinous membrane and germinative epithelium of an echinococcus cyst. It is now about two and a half months since operation. The patient is back at work and feels well, but a small amount of material is draining through the sinus in the right upper quadrant.

DR. GRANTLEY W. TAYLOR: The medical service wanted to have us carry out laparotomy in this case for confirmation of the diagnosis. Peritoneoscopy had been considered as an alternative method of investigation but it was felt that this would yield less positive findings. The operative findings have been described. Many of the cysts were thick walled and necrotic and contained opaque thick purulent-like material. Others were thin walled and contained clear fluid. Two or three basinfuls of these cysts were collected and cleansed to be used for antigen. My impression was that there had been previous minor ruptures of these cysts to account for the numerous adhesions and the dispersion which was present.

I cannot agree entirely with Dr. Kranes that there is no indication for operation because sometimes large cysts of this type are ruptured by relatively minor trauma and then constitute a real abdominal emergency. In addition I think that the record perhaps fails to emphasize that the pressure symptoms were reaching the point where they caused the patient considerable trouble, not only with the function of the gastrointestinal tract but in respiration as well.

factory. He continued in this business until admission to the hospital and was exposed to numerous types of chemicals. This exposure occasioned visits to the skin clinic of the hospital twice several years previously at which time diagnoses of contact dermatitis were made.

Physical examination showed a well developed but poorly nourished man. Examination of the chest was not remarkable except for a high relatively fixed diaphragm. The abdomen was large and asymmetrical. There was a fluctuant, non-tender, apparently lobulated mass, which moved with respiration and extended from the fourth intercostal space on the right to two inches below the umbilicus and could be felt in both flanks, being more prominent on the right. It could not be transilluminated. There were bilateral reducible inguinal hernias and bilateral varicoceles.

The temperature, pulse and respirations were within normal limits. The blood pressure was 148 systolic, 90 diastolic.

The blood, urine and stool tests were negative except for slight anemia, a hemoglobin of 11.5 gm, and a 10 per cent eosinophilia. The nonprotein nitrogen, fasting blood sugar, amylase, cephalin flocculation, van den Bergh, and bromsulfalein test, phosphorus, alkaline phosphatase, and prothrombin time were all within normal limits. The total protein was 8 gm per 100 cc, with an albumin-globulin ratio of 0.85. An x-ray film of the chest showed nodularity of the right diaphragm. A gastrointestinal series showed a negative esophagus, a stomach displaced to the left and posteriorly, and no intrinsic involvement of the gastrointestinal tract. It was thought that the mass was related to the liver. There were a number of calcifications in the upper portion of the liver. An echinococcus skin test was positive.

On the sixth hospital day an operation was performed.

#### DIFFERENTIAL DIAGNOSIS

DR ALFRED KRANES: There are two statements in the record to which I should like to take exception. One is the description of the mass, which is said to extend from the fourth intercostal space on the right to two inches below the umbilicus. I do not see how one can feel a mass of this size in the fourth intercostal space. What is meant is that the area of liver dullness extended up to the fourth intercostal space. I find it hard to believe that the mass could be felt that high, although that is the

impression one gets from the description. One can only say that the mass extended so far below the costal margin. The other statement that I question is the description by x-ray of nodularity of the diaphragm. I think what is meant is irregularity. One cannot say that the diaphragm is nodular, can one?

DR STANLEY M. WYMAN: No.

DR KRANES: That implies a third dimension which, of course, we do not have.

DR WYMAN: The radiologist's statement in the record was, "There is irregularity of the right leaf of the diaphragm resulting from nodularity or masses projecting from the superior aspect of the liver."

DR KRANES: That makes the diagnosis easier.

DR WYMAN: The right leaf of the diaphragm is definitely elevated and as you see comes to the fourth interspace. The lung fields otherwise appear intrinsically clear. The heart shadow is prominent toward the left, probably in the region of the left ventricle. The barium-filled stomach is faintly seen in this film displaced toward the left, and the duodenal cap is displaced downward and to the left. The entire right side of the abdomen is dense and there is a suggestion of several small areas of calcification. There is a very definite mass, nodular and lobulated, on the right.

DR KRANES: As I see this problem there is no differential diagnosis. What else can this be but an echinococcus cyst? If that diagnosis is correct, and I can see no other one to make, I must say that I would not have him operated on. You must remember that he is seventy-one years old. The disease started before the age of thirty-one and although he gave a history of having felt the mass only three months before entry, you will all agree, I am sure, that an echinococcus cyst of this size must have been growing for many, many years. Furthermore, despite its size, and it does seem to be huge, it has produced absolutely no symptoms. The record states that the man was feeling quite well except for a few mild symptoms of belching and constipation. Nor has it interfered with the function of any organ although it has displaced the stomach. While it may involve a fairly large part of the liver, it has not interfered with the liver's function or produced any alteration in the laboratory tests. They were all normal. Consequently, I probably would not have advised this patient to be operated on since I see nothing to be gained by operation at seventy-one on an asymptomatic echinococcus cyst. The chances are that he might have gone another five or ten years still.

are to blame because the problem has been aggravated by their professional jealousy, indifference, over-specialization, sensitive pocketbooks and profound aversion to co-operative action." A strong indictment, indeed, but one suggesting so strong a bias as to weaken the rest of the witness's evidence.

The doctors of every town and every district society should be so organized that emergency calls, real or imaginary, are handled with reasonable dispatch. The need has been sounded by the American Medical Association and has been emphasized in these pages. Physicians cannot, however, keep themselves constantly on tap like hot and cold running water as so many of the unthinking public expect of them. Certainly, organization to meet legitimate expectations should and will be put into operation wherever possible.

So go the indictments. The doctors are accused of dodging unwelcome calls (in other words, of being human), of failing in cordiality toward those elements of the population that they know intend to cheat them, of overspecializing — specialization, according to the *Bulletin*, being both the triumph and the bane of American medicine, of indifference to chronic disease and the care of the aged, in spite of the growing interest in geriatrics and the tremendous effort being exerted for the study of cancer and heart disease, of overstressing the pocketbook, of missing its chance to improve rural care and of failing to provide adequate care to millions because of rising costs.

There is no need here of offering detailed explanations or of finding excuses. Patients who have organized their own medical affairs to the point of having reliable family doctors "whom they occasionally consult are much less likely to find themselves in urgent difficulties than those who use the profession only in an emergency, real or supposed, and then send their panic calls to the telephone operator or the police. Unfortunate incidents will occur, accidents will happen, and coronary vessels will occlude when no physician is immediately available. They are the chances that are taken in life.

In the practice of medicine as in other human activities, technic has outrun the present capacity of society to place scientific progress at the service of mankind. At this point while the spirit may be considered as willing, the social and economic flesh presents its weaknesses. A few workers of proved merit are responsible for the development of science,

human relations are dependent on the ability of entire populations to co-operate.

It is encouraging to note the interest that the *Evening Bulletin* has shown even if it is difficult to turn all its criticisms into constructive effort.

## OPERATION MUSK OX

AN analysis of the many surveys and trials of rations that were conducted on the United States and Canadian troops during the war years 1941-1946\* reveals that soldiers remained fit and healthy in temperate, desert, jungle, mountain or Arctic areas if they received plenty of beef, vegetables, white bread and butter, milk and coffee with sugar, fruit juice, pie and ice cream, candy and preserves, "provided they were able to avoid injury and disease".<sup>1</sup> It was also demonstrated that dry biscuits are not a good substitute for bread, that canned stewed meat and vegetables are not so good as roast beef and that the human being is unable to accustom himself to an insufficient supply of water.

The problem that the Army had to face was the reconciliation of these facts (the truth of which must have been suspected even before the surveys were conducted) with the obvious difficulty of providing the great American diet three times a day in every area in which bodies of troops had to be maintained if the main purposes of the war were to be accomplished. Here is indeed a poser toward the solution of which the nutritional scientists have little to offer. They are better able to describe what happens if the normal demands for food of the healthy young American adult are not met.

For example, men collapsed and were totally unfit for duty after three days during which their sole diet consisted of pemmican, tea and cigarets (a ration proposed by V. Stefansson because of its "lightness, compactness and easy preservability" — virtues that are also inherent in sawdust or baled hay). Jerked beef may have sustained Davy Crockett and Dr. Kane, but it won't do for Jack Armstrong.

On the other hand, participants in Operation Musk Ox, a Canadian army mobile exercise conducted in the Northwest Territories, from February

\*Johnson, R. E. and Kark, R. M. *Feeding Problems in War as Related to Environment: An analysis of United States and Canadian Army ration trials and surveys 1941-1946*. 94 pp. Quartermaster Food and Container Institute for the Armed Forces and United States Army Medical Nutrition Laboratory. Chicago, Illinois, 1947.

# The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established 1828

Official Organ of

THE MASSACHUSETTS MEDICAL SOCIETY  
and

THE NEW HAMPSHIRE MEDICAL SOCIETY

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND

PUBLISHED WEEKLY UNDER THE JURISDICTION

OF THE COMMITTEE ON PUBLICATIONS

James P. O'Hare, M.D. Richard M. Smith, M.D. Chairman  
Oliver Cope, M.D. Conrad Wesselhoeft, M.D.  
John Fallon, M.D.

Joseph Garland, M.D., Editor

Associate Editors

Thomas H. Lanman, M.D. Donald Munro, M.D.  
Henry Jackson, Jr., M.D.

Clara D. Davies, Executive Editor

Robert O'Leary, Assistant Editor

EDITORIAL BOARD

C. Guy Lane, M.D.	Maxwell Finland, M.D.
Henry R. Viets, M.D.	James M. Faulkner, M.D.
Robert M. Green, M.D.	Carroll B. Larson, M.D.
Dwight O'Hare, M.D.	Francis D. Moore, M.D.
Fletcher H. Colby, M.D.	C. Stuart Welch, M.D.
Robert L. Goodale, M.D.	Vernon P. Williams, M.D.
Chester M. Jones, M.D.	Benjamin Castleman, M.D.
Harvey R. Morrison, M.D.	Hugh R. Leavell, M.D.

SUBSCRIPTION TERMS: \$7.00 per year in advance, postage paid for the United States (medical students \$4.00 per year), Canada \$8.00 per year (Boston funds) \$9.50 per year for all foreign countries belonging to the Postal Union.

MATERIAL should be received not later than noon on Thursday three weeks before date of publication.

THE JOURNAL does not hold itself responsible for statements made by any contributor.

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts. Telephone KE 6-2094.

NEW ENGLAND ADVERTISING REPRESENTATIVE: Edwin B. Tyler, 89 State Street, Boston, Massachusetts. Telephone LA 3-5516.

## THE PROVIDENCE EVENING BULLETIN LOOKS AT MEDICINE

THIRTEEN articles that appeared serially last May in the *Providence Evening Bulletin* under the ambitious title "American Medicine — Diagnosis and Prescription" have furnished a minor *cause célèbre*. This earnest effort to point out the need for reforms in medical practice cannot be dismissed lightly, for it brings to the surface certain indisputable facts. It indicates that medical service is far from perfect. It indicates the definite discontent of a considerable part of the public with the service it is receiving, and it indicates a lack of any clear understanding of the type of service

that may reasonably be expected, and how it may be obtained.

The staff reporter of the *Evening Bulletin* does not alone share with the public either its discontent or its failure to see clearly the ideal relations between physicians and their patients, and how to attain them. The very many physicians of the country — the vast majority, it may be hoped — who adhere to the ancient ideals of their profession as a calling of service share also in this discontent and in the confusion that prevails regarding the best way of improving that service.

The representative of the *Evening Bulletin* as he went his way about the country, interviewing leaders in practice, in education and in public health, in an effort to present "a synthesis of some of the best thinking that is being done on how to bring adequate medical care to the people of the United States," found more questions than could be satisfactorily answered. Many of these questions have various answers with no present indications of which are the right ones. No single group or combinations of groups of persons or even that amorphous, somewhat suspect professional conglomerate known as "organized medicine" can guarantee that its own plan is the only true one regardless of its numbers or of its expertness in vociferation.

The intention of the *Evening Bulletin* was to secure thoughtful answers to such questions as these: Is there a shortage of doctors? Is "socialized medicine" the solution for our medical problems? Is there too much specialization? Why is it hard to get a doctor in an emergency? How can the cost of medical care be reduced? What are the major trends in American Medicine? Obviously the *Bulletin* is asking questions and posing problems — by no means new ones — the answers to which the Sibylline Oracles would also like to know.

Unfortunately for the interests of a fair appraisal and the securing of thoughtful answers to these vexing problems, the *Evening Bulletin's* investigator, despite the effort that he has made to reach to the heart of the matter, shows in the presentation of his theses a regrettable failure to see both sides of the issue. In discussing the difficulty that was encountered in a number of instances in finding a doctor to answer emergency calls, no true analysis of the situations was presented, twenty doctors, on a certain Sunday afternoon were unavailable or were not immediately available, and consequently "they

The whole word method of teaching reading in the primary grades has now been in use for many school generations. It may work well for the majority,—as physicians we are not competent to judge,—but we know from experience with our own patients as well as by the increasing complaints from the secondary schools and colleges that it fails lamentably in a large minority and is apparently responsible for much of the disability in the upper grades.

The best treatment is prevention, as outlined by Koehler,<sup>2</sup> which seems to succeed with most. Failing this, we have to fall back on “remedial reading,” either individually or in small groups. Such tutoring is necessarily expensive and takes time. The wealthy can easily afford it, the middle class only at a sacrifice, and the majority not at all. Furthermore, there are not enough properly trained persons in the country to handle all the cases.

The only solution is to adapt the teaching of reading in the early grades to these children’s capabilities. As physicians and citizens we should urge this on our local school boards and teachers.

REFERENCES

1. Eustis, R. S. Specific reading disability: information for parents and teachers. *Independent School Bull.* 4, April, 1948.  
2. Koehler, W. Specific reading disability: classroom view. *Independent School Bull.* 5, May 1948.

THE COSTS OF MEDICAL CARE

As has been suspected in various professional circles, the cost of living has risen more rapidly than the fees charged by physicians for medical services. This observation is noted particularly in a study, “Comparative Increases in the Costs of Medical Care and the Costs of Living” recently published by Frank G. Dickinson, Ph.D., director of the Bureau of Medical Economic Research of the American Medical Association.

The quantity of medical care has apparently increased much more rapidly than has the number of physicians practicing, the average physician, if he is keeping up with the cost of living, is doing so by increasing the load he carries rather than the rates he charges. The public that he serves is not entirely aware of this probability. It continues to grumble at all the costs of living in an extremely complicated social and economic setup.

The quantity of physicians’ services delivered in 1946 was approximately one half greater than in 1935-1939, but the number of physicians was only one seventh greater. The American people spent \$5,600,000,000 for medical care in the same year, or 3.9 per cent of its total personal-consumer expenditures. This may be compared with a 4.3 per cent expenditure in 1940.

MASSACHUSETTS MEDICAL SOCIETY

DEATH

STRATTON — Harold L. Stratton, M.D., of Worcester, died on January 31. He was in his fifty-eighth year. Dr. Stratton received his degree from Tufts College Medical School in 1939. His widow and a sister survive.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR JUNE, 1948

RÉSUMÉ			
DISEASES	JUNE 1948	JUNE 1947	SEVEN-YEAR MEDIAN
Chancroid	0	1	1*
Chicken pox	1674	1823	1282
Diphtheria	53	37	14
Dog bite	1563	1432	1318
Dysentery bacillary	27	11	2
German measles	192	90	53
Gonorrhea	310	316	353
Granuloma inguinale	0	0	0*
Lymphogranuloma venereum	1	0	2*
Malaria	0	6	12
Measles	6569	1292	5652
Meningitis, meningococcal	4	1	16
Meningitis Pfeiffer-bacillus	6	3	2
Meningitis pneumococcal	0	4	4†
Meningitis staphylococcal	0	0	0†
Meningitis streptococcal	0	0	0†
Meningitis other forms	3	0	1†
Meningitis mumps	1	0	0†
Meningitis undetermined	0	1	5†
Mumps	204	888	966
Pneumonia, lobar	60	99	154
Polio myelitis	3	2	1
Salmonellosis	9	7	8
Scarlet fever	915	282	791
Syphilis	203	243	391
Tuberculosis pulmonary	259	240	264
Tuberculosis other forms	17	25	22
Typhoid fever	5	0	3
Undulant fever	5	16	6
Whooping cough	103	508	521

\*Four year median  
†Six year median

COMMENT

Those diseases with incidence above the seven-year median are chicken pox, diphtheria, bacillary dysentery, measles, mumps, poliomyelitis, scarlet fever and typhoid fever. Those diseases with incidence below the seven-year median are German measles, lobar pneumonia and whooping cough. Diphtheria has had a higher incidence for June only once in the last twelve years, and measles only once since 1915. Bacillary dysentery is at the highest prevalence for June for the last nine years, mumps at the highest since 1915, and typhoid fever at the highest since 1945.

GEOGRAPHIC DISTRIBUTION OF CERTAIN DISEASES

Diphtheria was reported from Boston, 4, Cambridge, 2, Chelsea, 2, Chicopee, 2, Foxboro, 8, Lowell, 1, Malden, 2, Medford, 1, Melrose, 1, Needham, 1, Revere, 2, Saugus, 1, Taunton, 1, Waltham, 4, Westport, 1, total, 33.

to May, 1946, who were protected by vehicles, modern clothing and equipment against ill effects from the environment and were supplied by air at all times, with a wide variety of fresh food and packaged rations, experienced none of the classic diseases and hazards of Arctic travel such as exposure, frostbite, snow blindness, psychosis, exhaustion, starvation, scurvy, edema and cold nephritis, although many of them were troubled by symptoms of carbon monoxide poisoning as a result of inhaling exhaust gases blown back into their vehicles by a strong following wind near Baker Lake, and one obese (225-pound) person lost 29 pounds between Churchill and Fort Nelson, where when seen he was in excellent health.

In desert areas, an example of misguided planning was the lining of canvas Lyster bags with a plastic to prevent evaporation. This resulted in warm water with a queer taste. By contrast, the traditional evaporating canvas desert bag produced cool, palatable water, and little was wasted. It was also learned that teaching soldiers to salt their food heavily in hot climates is preferable to giving them uncoated salt tablets, which may nauseate them.

United States troops, it is reported, will never force themselves to eat for long periods items that they dislike, even though they go hungry. This is illustrated by the tendency of the American soldier to throw away the dog biscuits in his C ration. The fact that these packages were usually at least twelve months old before they reached the consumer probably explains his reaction.

Napoleon is credited with the statement that an army marches on its stomach, and Grant with the remark that beans killed more of his soldiers than bullets. The results of these contemporary studies indicate that one must still take to heart the observations of such veteran campaigners.

## TEACHER AND DOCTOR AGREE

Nor infrequently articles of great interest to physicians turn up in the publications of other professions, where they usually escape the doctors' notice. A recent example is the appearance of two articles on specific reading disability in the current April and May issues of the *Independent School Bulletin*. One is by a member of the staff of the Language Clinic of the Massachusetts General Hospital,<sup>1</sup> and the other by a teacher at Milton

Academy.<sup>2</sup> They are prefaced by a brief editorial note giving them the enthusiastic commendation of the principals of five well known secondary schools. The information contained in them deserves wider publicity.

The two papers are written in nontechnical language suitable for intelligent parents as well as for teachers and physicians. The first summarizes what physicians have learned about specific reading disability, and the second what an alert school can do to prevent the disastrous consequences that frequently result from failure to recognize or improper handling of children with the disability.

The authors agree that specific disability in the use of language, particularly reading, afflicts between 10 and 15 per cent of intelligent children and that, unless recognized early and handled properly, it results in scholastic failure, in a variety of behavior problems and eventually, in some cases in misplaced and maladjusted adults. In all but the smallest communities one tenth of the pupils means a good many children, and the number for the country as a whole must run close to two and a half million.

The subject is one with which all physicians dealing with children should be familiar. Unrecognized cases are taken to ophthalmologists because teachers and parents believe that there must be something wrong with the children's eyes, to general practitioners and to pediatricians because there must be something wrong with their general health or their "glands," and to neurologists and psychiatrists because the children seem stupid or inattentive or simply mischievous at school, whereas the real trouble is in the way the victims' brains are organized. Their intelligence is normal or often superior, but their visual memory for language is so slow and faulty that they are unable to learn to read by the currently popular whole-word method. That their failure is not due to lack of attention on their part or to emotional blocking is shown by the fact that they can and do learn when they are taught phonetically with auditory and kinesthetic re-enforcement.

Koehler<sup>2</sup> brings out in his article that there are only ninety-four letters and letter combinations for the child taught in this way to memorize, which is a much lighter load on the visual language memory than the many hundreds of individual words that the average third grade pupil is supposed to be able to recognize by sight.

NOTICES (Concluded from page 212)

## SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, AUGUST 5

FRIDAY AUGUST 6

\*10:00 a.m. - 12:00 m Medical Staff Rounds. Peter Bent Brigham Hospital

TUESDAY AUGUST 10

\*12:15-1:15 p.m. Clinicoroentgenological Conference Peter Bent Brigham Hospital.

\*1:30-2:30 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.

WEDNESDAY AUGUST 11

\*12:00 m.-1:00 p.m. Clinical Conference (Children's Hospital) Amphitheater Peter Bent Brigham Hospital.

\*Open to the medical profession

AUGUST 11-21 International Congress on Mental Health. Page 344, issue of March 4.

AUGUST 23-26. International Society of Hematology Page 419 issue of March 18

AUGUST 26-28 American Association of Blood Banks Page 420 issue of March 18.

SEPTEMBER 7-11 American Congress of Physical Medicine. Page 582 issue of April 15

SEPTEMBER 7-11 American Occupational Therapy Association Page 419 issue of July 8

SEPTEMBER 9 Some of the Advances in Surgery Dr. Frank H. Lahey Pentucket Association of Physicians. 8:30 p.m. Haverhill

SEPTEMBER 13-15 American Academy of Pediatrics. Olympic Hotel Seattle, Washington

SEPTEMBER 16-18 Vermont State Medical Society Annual Meeting Burlington.

SEPTEMBER 20-23 American Hospital Association Page 310 issue of February 26.

SEPTEMBER 29 Mississippi Valley Medical Editors' Association. Page 170 issue of January 29

OCTOBER 6-9 American Board of Ophthalmology Page 170 issue of January 29

OCTOBER 18-22. American College of Surgeons. Page 34, issue of July 1

OCTOBER 27 New England Obstetrical and Gynecological Society Annual Meeting Hotel Somerset, Boston

NOVEMBER 1-3 American Clinical and Climatological Association. Page 582, issue of April 15

NOVEMBER 8-12. American Public Health Association Page 420, issue of March 18.

NOVEMBER 10-13 Association of Military Surgeons of the United States. Page 722, issue of May 13

NOVEMBER 20-23 American Academy of Pediatrics. Annual Meeting. Chalfonte-Haddon Hall Hotel Atlantic City, New Jersey

DECEMBER 7-9 Southern Surgical Association Annual Meeting Page 543 issue of April 8

DECEMBER 9 and 10 New York State Society of Anesthesiologists. Page 34 issue of July 1

MARCH 28-APRIL 1 1949 American College of Physicians. Page 158 issue of July 22.

NOVEMBER 11 17 1949 Third Inter-American Congress of Radiology Page 158 issue of July 22

## TWO-WAY PROTECTION

### Tablets FERROSATE (Kenmore)

(Ferrous Sulfate gr. iv)

are coated twice to provide a doubly protected Ferrous Sulfate offering these therapeutic advantages

- 1 Inner coating prevents premature oxidation in vivo
- 2 Outer coating increases palatability and aids in preventing tooth discoloration

Write Dept. N7 Kenmore Pharmacy, Inc.  
for professional sample. 500 Commonwealth Ave.  
Boston Mass U.S.A.

Advertisement



From where I sit  
by Joe Marsh

## It's Leap Year, Girls!

*First girl in our town to "get her man" on Leap Year was the Smiths' daughter, Tiny, who wed Bill Webster's boy last Saturday*

When I asked Bill Jr. if it was true that Tiny really did the proposing, Bill said No, but she made it mighty plain that she'd make an ideal wife. Instead of looking for diversion or excitement every evening, she was content to chat beside the fire

*"I could plainly see," says Bill, "that we'd really have a happy home life—which is just exactly what I want from marriage"*

I know it's customary for older folks to shake their heads over the younger generation (It's gone on now for hundreds of years)

*But from where I sit, young people of marrying age today are every bit as commendable as their elders were—in their temperance (a glass of beer for instance), tolerance, and common sense. So to Tiny and Bill—the best of luck!*

Joe Marsh

Dysentery, bacillary, was reported from Worcester, 27, total, 27

Encephalitis, infectious, was reported from Lowell, 1, Lynn, 1, Millbury, 1, Quincy, 1, Saugus, 1, total, 5

Lymphocytic choriomeningitis was reported from Waltham, 1, total, 1

Meningitis, meningococcal, was reported from Boston, 1, Cambridge, 1, Fall River, 2, total, 4

Meningitis, Pfeiffer-bacillus, was reported from Cambridge, 1, Hatfield, 1, Holyoke, 1, Lynn, 2, Winchester, 1, total, 6

Meningitis, other forms, was reported from Middleboro, 1, Somerville, 1, Worcester, 1, total, 3

Meningitis, mumps, was reported from Walpole, 1, total, 1

Meningitis, undetermined, was reported from Cambridge, 3, North Adams, 1, Randolph, 1, Springfield, 1, Waltham, 2, Westwood, 1, total, 9

Polymyelitis was reported from Dover, 1, Gloucester, 1, Melrose, 1, total, 3

Salmonellosis was reported from Brockton, 1, Chelsea, 1, Gloucester, 1, Hatfield, 1, Malden, 1, Somerville, 1, Winthrop, 2, Worcester, 1, total, 9

Septic sore throat was reported from Boston, 2, Cambridge, 1, Easthampton, 1, Medford, 1, Methuen, 1, North Adams, 1, total, 7

Tetanus was reported from Somerville, 1, Worcester, 1, total, 2

Trachoma was reported from Fall River, 1, total, 1

Trichinosis was reported from Gloucester, 1, Salem, 1, total, 2

Typhoid fever was reported from Boston, 3, Springfield, 2, total, 5

Undulant fever was reported from Lunenburg, 1, Maynard, 1, Newton, 1, Pepperell, 1, Webster, 1, total, 5

Awarded the Nobel Prize in Medicine and Physiology in 1934 with Dr William P Murphy, of Boston, and Dr George H Whipple, of Rochester, New York, for discoveries in the treatment of anemias, Dr Minot has devoted over thirty years to medical research teaching and has made important contributions to the subjects of anemia, abnormal bleeding and the treatment of leukemia by x-ray

Dr Castle has received honorary degrees from Yale University and from the University of Utrecht, Holland. He is also the recipient of the John Phillips Memorial Award of the American College of Physicians, the William Procter, Jr., International Award for Distinguished Service in Promoting Health, and the Walter Reed Medal of the American Society of Tropical Medicine

## ODONTOLOGIC CHARACTERISTICS OF LONG-TAILED PRIMATES

New World monkeys, according to Sir Frank Colyer, (*Brit M J* 1 1202, 1948) differ from Old World monkeys in various anatomic particulars, especially various odontologic characteristics. The green monkeys of St. Kitts, however, exhibit the greatest capacity for dental variations. The incidence of supernumerary teeth, abnormal positions, rotations and inward displacements is three or four times as great in this species as in comparable groups of African monkeys

## STUDENTS OF ADMINISTRATION PLACED

At the completion of the first year of Yale University's course in hospital administration, 8 students found immediate placement. Of these, 1 remained at the Grace-New Haven Community Hospital, 5 found positions in Boston, 1 accepted an administrative internship in Rochester, N Y, and 1 will fill a similar position in Valhalla, N Y

## MISCELLANY

### ASSOCIATION OF SCHOOLS OF PUBLIC HEALTH

Brigadier General James S Simmons (Retired), dean of Harvard School of Public Health, was recently elected president of the Association of Schools of Public Health at the annual meeting of the Association

### JAMES D BRUCE MEMORIAL LECTURE AND MEDAL

The James D Bruce Memorial Lecture in Preventive Medicine was recently delivered by Brigadier General James S Simmons (Retired), dean of Harvard School of Public Health, at the annual convocation of the American College of Physicians in San Francisco. His subject was "The Challenge of Preventive Medicine"

General Simmons was awarded the James D Bruce Memorial Medal for achievement in preventive medicine

### CAT-OF-NINE-TAILS DEBARRED

England's House of Lords, according to the *British Medical Journal* (June 12, 1948), debated two days and deleted the clause inserted in the Criminal Justice Bill by the House of Commons for the suspension of the death penalty for murder. Flogging was retained as a penalty, but the use of the cat-of-nine-tails was debarred

### DIRECTOR OF THORNDIKE MEMORIAL LABORATORY

Dr William B Castle, professor of medicine at the Harvard Medical School, has been named to succeed Dr George R. Minot as director of the Thorndike Memorial Laboratory of the Boston City Hospital, where he has been associate director since 1932

With Dr Castle's appointment, Dr Minot, Nobel Prize winner in 1934, retires from his joint positions as professor of medicine at the Harvard Medical School and director of the Thorndike Memorial Laboratory

## CORRESPONDENCE

### IN CORPORE SANO

To the Editor: Congratulations to Professor Koon on his article in the *Boston Traveler* on June 11, 1948. The last paragraph says, "Bark beetles which carry the fungus of the Dutch elm disease will not breed in healthy living tree tissue. Keep your elms healthy by feeding them."

The organic gardeners have proved for years that healthy plants are practically free from diseases and bugs. Many people, including some doctors, are of the belief that a good part of the increase of cancer is due to poor food. Much of this poor food is due to an excessive use of commercial fertilizers. The organic method, with no commercial fertilizers, dusts or sprays and plenty of humus in the soil, produces vegetables that make healthier people and less sickness. The organic gardeners are called zealots or fad dists by some. It is the opinion of many that those opposed to organic gardening are either jealous or are connected in some way with the all-powerful chemical companies. We would not go back to the old chemical method if the chemical companies offered us a life pension!

GEORGE H CROSSIE  
An organic gardener

North Scituate  
Massachusetts

## NOTICES

### ANNOUNCEMENTS

Dr Albert Aranson announces the opening of his office at 73 Deering Street, Portland, Maine, for the practice of internal medicine and chest diseases

Dr William H Horwitz announces the removal of his office to 1093 Beacon Street, Brookline, for the practice of pediatrics and pediatric allergy

(Notices concluded on page ix)

NOTICES (Concluded from page 212)

## SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING  
THURSDAY, AUGUST 5

FRIDAY AUGUST 6

\*10:00 a.m.-12:00 m Medical Staff Rounds Peter Bent Brigham  
Hospital

SATURDAY AUGUST 10

\*12:15-1:15 p.m. Clinico-roentgenological Conference. Peter Bent  
Brigham Hospital\*1:30-2:30 p.m. Pediatric Rounds. Burnham Memorial Hospital for  
Children Massachusetts General Hospital.

WEDNESDAY AUGUST 11

\*12:00 m.-1:00 p.m. Clinical Conference (Children's Hospital)  
Amphitheater, Peter Bent Brigham Hospital.

\*Open to the medical profession

August 11-21 International Congress on Mental Health. Page 344  
issue of March 4.August 23-26. International Society of Hematology Page 419 issue  
of March 18August 26-28 American Association of Blood Banks Page 420 issue  
of March 18.SEPTEMBER 7-11 American Congress of Physical Medicine. Page 582  
issue of April 15SEPTEMBER 7-11 American Occupational Therapy Association Page  
419 issue of July 8SEPTEMBER 9 Some of the Advances in Surgery Dr Frank H. Lahey  
Pentucket Association of Physicians. 8:30 p.m. Haverhill.SEPTEMBER 13-15 American Academy of Pediatrics Olympic Hotel,  
Seattle, Washington.SEPTEMBER 16-18. Vermont State Medical Society Annual Meeting  
Bringington.SEPTEMBER 20-23 American Hospital Association Page 310 issue of  
February 26.SEPTEMBER 29 Mississippi Valley Medical Editors' Association.  
Page 170 issue of January 29OCTOBER 6-9 American Board of Ophthalmology Page 170 issue of  
January 29OCTOBER 18-22. American College of Surgeons. Page 34 issue of  
July 1.OCTOBER 27 New England Obstetrical and Gynecological Society  
Annual Meeting Hotel Somerset, BostonNOVEMBER 1-3 American Clinical and Climatological Association.  
Page 382 issue of April 15NOVEMBER 8-12. American Public Health Association. Page 420 issue  
of March 18.NOVEMBER 10-13 Association of Military Surgeons of the United  
States Page 722, issue of May 13NOVEMBER 20-23 American Academy of Pediatrics. Annual Meeting  
Chalfonte Haddon Hall Hotel Atlantic City New JerseyDECEMBER 7-9 Southern Surgical Association Annual Meeting  
Page 543 issue of April 8DECEMBER 9 and 10 New York State Society of Anesthesiologists.  
Page 34 issue of July 1.MARCH 28-APRIL 1 1949 American College of Physicians Page 158  
issue of July 22NOVEMBER 11-17 1949 Third Inter-American Congress of Radiology  
Page 158 issue of July 22.

## TWO-WAY PROTECTION

## Tablets FERROSATE (Kenmore)

(Ferrous Sulfate, gr. iv)

are coated twice to provide a doubly  
protected Ferrous Sulfate offering  
these therapeutic advantages

- 1 Inner coating prevents premature oxidation  
in vivo
- 2 Outer coating increases palatability and aids  
in preventing tooth discoloration.

Write Dept. N7  
for professional  
sample.

Kenmore Pharmacy, Inc.

500 Commonwealth Ave.  
Boston, Mass U.S.A.

Advertisement



From where I sit  
by Joe Marsh

## It's Leap Year, Girls!

*First girl in our town to "get her man" on Leap Year was the Smiths' daughter, Tiny, who wed Bill Webster's boy last Saturday.*


When I asked Bill Jr if it was true that Tiny really did the proposing, Bill said No, but she made it mighty plain that she'd make an ideal wife. Instead of looking for diversion or excitement every evening, she was content to chat beside the fire

*"I could plainly see," says Bill, "that we'd really have a happy home life—which is just exactly what I want from marriage"*

I know it's customary for older folks to shake their heads over the younger generation (It's gone on now for hundreds of years)

*But from where I sit, young people of marrying age today are every bit as commendable as their elders were—in their temperance (a glass of beer for instance), tolerance, and common sense. So to Tiny and Bill—the best of luck!*

Joe Marsh



This baby's mother learned  
about Mead's Oleum Percomor-  
phum from her physician, not from  
public advertising or displays

*"Servamus Fidem"*

## HOW much sun does the infant really get?

*Not very much* (1) When the baby is bunched to protect against weather or (2) when shaded to protect against glare or (3) when the sun does not shine for days at a time Mead's Oleum Percomorphum is a prophylactic against rickets available 365½ days in the year, in measurable potency and in controllable dosage *Use the sun, too*

Mead Johnson & Co., Evansville, Ind., U S A

# The New England Journal of Medicine

Copyright, 1948 by the Massachusetts Medical Society

Volume 239

AUGUST 5, 1948

Number 6

## TRAUMATIC NECROSIS OF PRETIBIAL MUSCLES\*

CARL PEARSON, M.D.,† RAYMOND D. ADAMS, M.D.,‡ AND D. DENNY-BROWN, M.D.§

BOSTON

**A**N UNUSUAL case in which the pretibial muscles of both legs became acutely swollen, painful and paralyzed after a period of vigorous activity was recently observed on one of the medical wards of the Boston City Hospital. The clinical features were puzzling, and it was only after a biopsy had disclosed hemorrhage and necrosis that a clue to the nature of this disorder was obtained. Since we were unfamiliar with this condition and are unable to find verification of exactly similar cases in the medical literature, the following case is reported.

### CASE REPORT

**S T**, a 24-year-old man, who had emigrated from Greece less than a year before, could not express himself well in English, and the history was therefore obtained through an interpreter.

It was learned that his general health had always been good. His only important illness in the past had been malaria 2 years before entry, which had been treated by intramuscular injections of an unknown medicine. The only other item of possible interest was an easy fatigability of the legs, which had been present for the past year. The patient denied the ingestion of pork. Ten days before admission to the hospital he had had a sore throat and hoarseness from which he had recovered within 24 to 48 hours without interruption of his work as a bus boy.

At about 2 p.m. on May 19, 1947, he had competed with two companions in broad jumping on a cement pavement. Later during the same evening he began to experience sharp pains in both legs, and there was tenderness of the muscles from knees to ankles. He felt feverish, had general malaise and, after a restless night, was admitted to the hospital.

Physical examination disclosed a patient whose face was flushed and who was suffering considerable pain. He was alert and co-operative. Oral hygiene was poor, and one tonsil was enlarged and red. There was a Grade I apical systolic murmur. The heart and lungs were not remarkable. The liver and spleen could not be palpated. The patient lay with his legs flexed at hips and knees. The skin over the anterior surface of both legs from knees to ankles was pink and distinctly warmer than elsewhere. We examined the patient at this time and noted that all the muscles in

the anterior tibial compartment were very firm and exceedingly tender. There was foot drop bilaterally and complete paralysis of the anterior tibial, extensor digitorum longus and extensor hallucis longus muscles. Passive flexion or extension of the feet at the ankles was painful. The peroneal, gastrocnemius and other muscles in the legs and thighs contracted normally and were not tender. The joints were neither swollen nor tender, and no thrombosed veins could be felt. There was slight hyperalgesia over the erythematous skin surface. The knee and ankle jerks were present, and the plantar reflexes were flexor bilaterally. Vibratory and



FIGURE 1 Right Anterior Tibial Muscle Seventeen Days after Injury ( $\times 50$ )

*Regenerating muscle fibers and remnants of necrotic muscle are widely separated by proliferating fibrous connective tissue, in which lymphocytes, plasma cells and macrophages are seen.*

position senses in the feet were normal. Pulsations were felt in the dorsalis pedis and posterior tibial arteries.

The temperature was 100.8°F, the pulse 84, and the respirations 22. The blood pressure was 128/88.

At the time of entry the urine was normal, but on the 3rd and 5th hospital days it gave +++ and ++ tests for albumin respectively. The white-cell count was initially 10,800, with 85 per cent neutrophils, 14 per cent lymphocytes and 4 per cent monocytes. Subsequently it was 8050, with a normal differential, except on the 6th hospital day, when there was an eosinophil count of 4 per cent. The hemoglobin was 14 gm per 100 cc. The nonprotein nitrogen and fasting blood sugar were within normal limits. The stool was negative for blood and parasites. The blood Wassermann, Hinton and gonococcus complement-fixation tests were all negative. The skin test with trichina antigen gave no reaction. The concentrations of creatine and creatinine in the blood and urine were normal. The cerebrospinal fluid was examined twice, each time being entirely within normal

\*From the Mallory Institute of Pathology and the Neurological Unit, Boston City Hospital, and the Department of Neurology, Harvard Medical School.

†Intern, Mallory Institute of Pathology, Boston City Hospital.

‡Assistant professor of neurology, Harvard Medical School, visiting neurologist and assistant pathologist, Boston City Hospital, neurologist, Joseph H. Pratt Diagnostic Hospital.

§Jackson Putnam Professor of Neurology, Harvard Medical School, Director, Neurological Unit, Boston City Hospital.

limits. X-ray films of the chest and legs disclosed no abnormalities. Watson's test for porphyrins in the urine was negative. An electrocardiogram was normal.

On the 3rd hospital day the temperature rose to 102.4°F, and the patient appeared quite uncomfortable. Penicillin

Some of the pieces contained apparently normal muscle fibers, whereas in others the normal skeletal muscle architecture was severely disrupted and there was a marked fibrous tissue replacement (Fig 1 and 2). In these areas, muscle fibers were observed in all stages of degeneration. Some were swollen, intensely acidophilic and devoid of nuclei and striations, others were granular and vacuolated,



FIGURE 2 Cross-Section from the Area Demonstrated in the Upper Part of Figure 1, showing the Rounded Contours, Occasional Vacuolization and Hyperplasia of Muscle Nuclei in the Remaining Fibers ( $\times 200$ )

was then given intramuscularly in doses of 25,000 units every 3 hours. The temperature gradually subsided over a period of 4 days. The leg muscles remained hard and indurated but were less tender, and the pretibial erythema gradually faded. By the 14th hospital day the patient was feeling quite well though foot drop and paralysis of the extensor muscles of the feet and toes continued. Tests of the electrical excitability of these muscles showed no reaction to either faradic or galvanic stimulus. On the 17th hospital day a biopsy of the upper part of the anterior tibial muscle of the right leg was performed. From this a diagnosis of traumatic myopathy was made. Improvement in the patient's general condition continued, but when he was dis-



FIGURE 4 Longitudinal Section of a Part of the Muscle that is Undergoing Regeneration ( $\times 200$ )

There are rows of muscle nuclei in the fibers. The fiber in the right upper corner has acquired transverse and longitudinal striations. The fibroblasts and interstitial cellular reaction consisting of macrophages, lymphocytes and plasma cells are demonstrated.

and their nuclei were shrunken and pyknotic. In two places the general architecture of a fasciculus could be distinguished. In these the central portion of each fasciculus was necrotic, consisting of swollen eosinophilic fibers with frequent transverse fissures and shrunken pyknotic nuclear remnants.

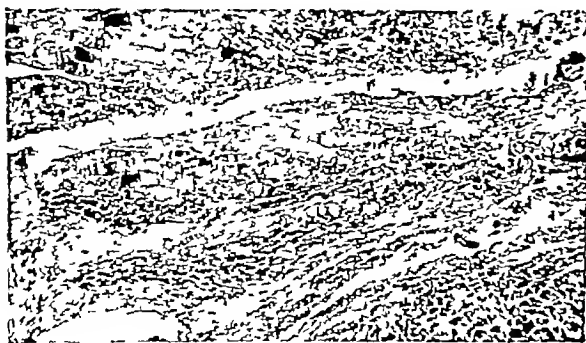


FIGURE 3 Longitudinal Section of Muscle ( $\times 50$ )

The fibers in the center of the field, which are necrotic, are stained a bright red, are homogeneous and lacking in either transverse or longitudinal striations and are cracked transversely. In the lower margin active phagocytosis of the degenerated muscle fibers is demonstrated.

charged after 27 days in the hospital, the anterior tibial muscles were still paralyzed.

Several small pieces of the right anterior tibial muscle were excised, fixed in Zenker's solution and stained with phloxine and methylene blue, and phosphotungstic acid hematoxylin.

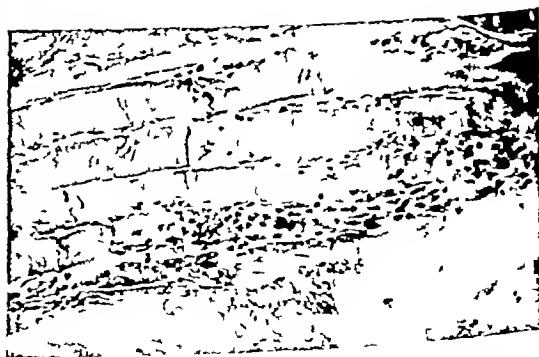


FIGURE 5 Higher Magnification of the Lower Part of the Field Demonstrated in Figure 3, Showing the Necrotic Muscle Fibers and Their Removal by Macrophages ( $\times 200$ )

(Fig 3) The connective tissue appeared to be inactive. At the borders of each fasciculus extensive regenerative activity was evident (Fig 4). The muscle fibers in this region were small, and contained large numbers of well stained muscle nuclei. Longitudinal splitting was commonly observed, and the sarcoplasm had a well developed longitudinal striation. In one fasciculus hemorrhage had separated both necrotic and regenerating fibers. Some fibers were invaded and surrounded by macrophages and hemorrhage. (Fig 5) All that remained of many muscle fibers were the sarcolemmal sheaths. Many of these were partially collapsed and contained granular clumps of acidophilic material, some of which was present in macrophages (Fig 6).

The interstitial fibrous connective tissue was increased in amount and was present in the form of broad bands and slender strands, which separated the remaining muscle fibers. The connective tissue was cellular, fibroblast nuclei were increased in number and size. In addition, there were many macrophages, somewhat fewer lymphocytes, a few plasma cells and an occasional neutrophil. Large numbers of well preserved red cells were widely dispersed throughout the damaged parts of the muscle, and many macrophages contained yellow-brown granules of pigment, presumably hemosiderin (Fig 7). The walls of the small arteries were thickened, and their endothelial cells were unusually large and numerous.

No less striking were the evidences of changes usually interpreted as regeneration of muscle fibers (Fig 4). In many fibers there was a marked proliferation of the muscle nuclei. Closely packed clusters or rows of nuclei were seen, either just beneath the sarcolemma or in the center of the fiber. As many as fifty could be counted in a short segment of a fiber. Narrow, elongated buds of muscle protoplasm extended out from the muscle fibers exhibiting this nuclear hyperplasia. Some of the thin regenerating fibers were arranged parallel to one another, and others were not oriented in any particular plane. There were well developed transverse and longitudinal striations in some of these fibers.

When the patient was last examined, 5 months after the onset of the illness, bilateral foot drop was still present, and

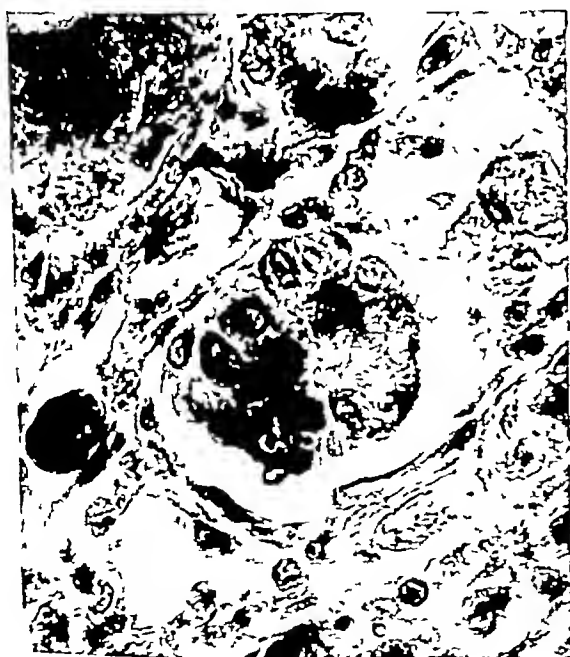


FIGURE 6 Cross-Section of a Necrotic Muscle Fiber the Remnants of Which are Surrounded by Phagocytic Cells (x 800)

there was moderate atrophy but no tenderness of the anterior tibial muscles. An electromyogram was done by one of us (D D-B) at that time. No evidence of electrical activity could be obtained from any part of the tibialis anticus muscle on either side. The natural rhythms of motor activity were present in the peroneal group of muscles on both sides. The tibialis anticus muscle felt unusually firm but was no longer swollen or tender. Passive plantar flexion of the ankle was limited owing to fibrous resistance in the tibialis anticus muscle. Plantar flexion of the great toe on both sides was limited slightly by a similar contracture.

DISCUSSION

The pain, tenderness, firm swelling and paralysis of the pretibial muscles that constituted the chief symptoms were indicative of a primary disorder of muscles. The absence of reflex changes and sensory loss and the lack of electrical excitability

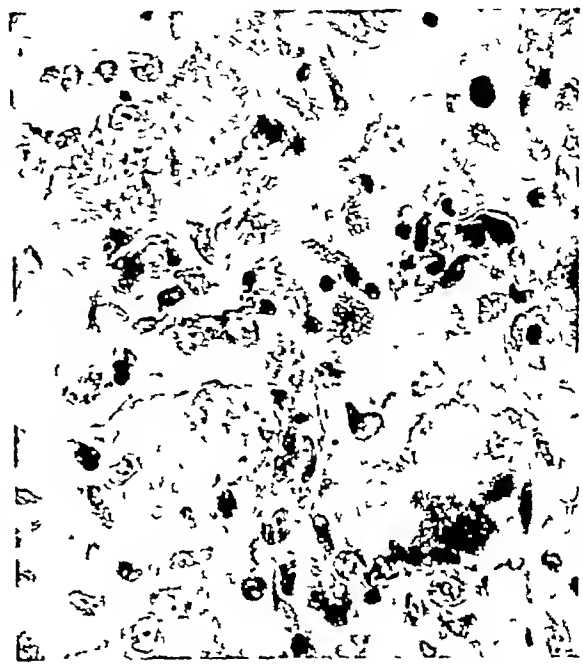


FIGURE 7 Hemosiderin in Macrophages Appearing as Refractile Granules and Lymphocytes, with the Plasma Cells and Macrophages between Multinucleated Muscle Fibers (x 800)

of the involved muscles tended to exclude the possibility of disease of the peripheral nerves. The erythema and warmth of the skin were believed to signify an acute inflammatory reaction in the underlying muscles,—an acute myositis,—and the fever, malaise and albuminuria were regarded as systemic manifestations.

There was at first much uncertainty about the type of muscular disease with which we were dealing. Polymyositis, dermatomyositis, trichinosis and acute suppurative myositis were all considered but seemed unlikely because of the acute onset after strenuous exertion, the lack of definite skin lesions and the restriction of the process to the pretibial muscles. Other diseases considered in the differential diagnosis were erythema nodosum, diffuse vascular diseases, such as disseminated lupus erythematosus and periarteritis nodosa, and pretibial fever. Erythema nodosum was ruled out by the absence of definite skin nodules and by the occurrence of pronounced muscle swelling and paralysis, to which we could find no reference in

medical writings. Diffuse vascular diseases could not be established since most of the cardinal criteria of these diseases were lacking. Pretibial fever, in which the leading clinical manifestations have recently been described by Daniels and Grennan,<sup>1</sup> was suggested by the location of the pain, the fever and the systemic symptoms. However, the case reported above deviated widely from published accounts of this disease, in which fever, splenomegaly and skin eruption were prominent features and muscle paralysis did not occur.

The muscle biopsy, though giving only a fragmentary picture of the pathology, was of considerable help in ascertaining the possible causes of this clinical condition. The extensive necrosis of muscle fibers, the hemorrhage, the proliferation of fibrous connective tissue and the muscle regeneration indicated an acute destructive process that was subsiding. The lymphocytes, the occasional neutrophils and eosinophils and the plasma cells were believed to be a reaction of tissue necrosis. These findings corresponded approximately to the microscopical changes described in human beings by Lorenz<sup>2</sup> and others and by Clark<sup>3</sup> in animals several days after experimental crushing of muscle tissue. The histopathology in this case differed from that reported in bacterial and parasitic infections of muscle and from the less well defined dermatomyositis or polymyositis.

The origin of the muscle necrosis could not be established with certainty. Since strenuous exertion—namely, broad jumping on a cement pavement—had initiated the illness, trauma was considered an important factor. Indeed the occurrence of muscle necrosis due to trauma is not without precedent in the medical literature. There is in fact an extensive literature on this subject, which is well summarized by Lorenz<sup>2</sup> and by von Myenburg et al.<sup>4</sup>

However, we have been able to find only 2 cases similar to the one reported above. One was included among a series of cases discussed by Sirbu, Murphy and White.<sup>5</sup> Their patient was a thirty-eight-year-old Filipino soldier who developed severe pain over the anterior aspect of both lower legs after a prolonged march. The anterior tibial muscles of both legs were swollen and tender and at operation bulged through the incised fascia as gray-white masses. Upon release of pressure by removal of a portion of the crural fascia the right leg recovered fairly well, but the muscles of the left were almost completely gangrenous and had to be excised. The subsequent course of this illness is not given. The authors suspected a vascular lesion because of the extent of the necrosis.

The other case was recently presented by Phalen,<sup>6</sup> who reported 4 cases of ischemic necrosis of the anterior crural muscles incident to trauma. Three of his cases were quite different from ours in that a fracture of the tibia and fibula had been at-

tended by necrosis of the pretibial muscles. But in the other case painful swelling and paralysis of the pretibial muscles of one leg had occurred in a young man who had walked a half mile. At operation the muscle tissue was found to be soft, friable and reddish gray. Injury or functional occlusion of the anterior tibial artery was offered as an explanation for the muscle paralysis.

The possible relation of this condition to the mild and relatively common affliction of muscles known as "shin splints" and to traumatic myalgia is interesting. Every athletic coach is well acquainted with the tenderness and pain in the pretibial muscles that occurs when runners, broad jumpers and hikers begin to train. The affected muscles become firm and swollen, and any attempt at active or passive flexion and extension at the ankle is painful. The cause is assumed to be recurrent trauma of the unconditioned muscles, nothing is known of the pathology. Rest and warm applications may be required in severe cases, but most athletes "walk off" their ailment. We have been unable to find any record of paralysis and subsequent atrophy of muscles, and Dr. Christoff\* here knew of none. Trauma, which produces acute and chronic myalgia, is also quite common, but again no adequate pathological studies are available and it seems unlikely that it would be attended by complete paralysis.

Rupture of muscles after violent exertion is also well known, occurring not infrequently as an occupational disease. This subject is reviewed in detail by Lorenz.<sup>2</sup> Gilcreest,<sup>7</sup> who has discussed the subject at length, has observed rupture of the neck muscles in loaders and packers, of the biceps and triceps in baseball pitchers and weight lifters, of the adductors of the thigh in horseback riders and of the rectus abdominis in an Indian broad jumper. The usual sequence of events is a violent contraction of a muscle group when the antagonists are suddenly brought into action, a snap, severe pain, swelling and local bulge in the muscle. The rupture, which may become complete only after twenty-four hours, is usually in the belly of the muscle and although the muscle is weakened, paralysis does not occur unless all the tendinous attachments are torn. It is unlikely that muscle rupture can be held responsible for the firm swelling, paralysis, erythema of the skin and fever that occurred in the case reported above.

The only satisfactory explanation of the pathogenesis of this syndrome that we are able to suggest is that violent contraction led to rupture of muscle fibers and possibly to hemorrhage. The affected pretibial muscles, contained as they are in a fairly rigid compartment formed by the tibia, fibula, interosseous membrane and crural fascia were further damaged by the ischemia incident

\*Director, Department of Student Health, Boston University (personal communication).

to edema and hemorrhage. We were unable to obtain evidence, either clinical or pathological, of injury to the anterior tibial artery as proposed by Sirbu and his co-workers<sup>5</sup> and Phalen.<sup>6</sup> However, more complete pathological studies are necessary to settle this point. The possibility that influenza or respiratory infection had predisposed the muscles to trauma can neither be affirmed nor denied though the lack of distinct symptoms preceding the trauma makes this unlikely.

SUMMARY

A case of a young man who developed severe pain, swelling and erythema of the anterior aspects of both legs after broad jumping on a cement pavement is presented. This was followed by paralysis of the pretibial muscles, which subsequently underwent atrophy. A muscle biopsy, performed seventeen days later, revealed extensive destruction of

muscle tissue and hemorrhage and slight regenerative activity of some muscle fibers. Trauma was believed to be the main etiologic factor.

REFERENCES

1 Daniels W B., and Grennan H. A. Pretibial fever obscure disease. *J A M A* 122 361-365 1945  
2 Lorenz, H. *Die Muskelerkrankungen.* 304 pp. Wien Alfred Hölder 1898 Pp 15 39  
3 Clark, W E. L. Experimental study of regeneration of mammalian striped muscle. *J Anat* 80 24-36 1946  
4 von Myenburg H. Die quergestreifte Muskulatur. In *Handbuch der speziellen pathologischen Anatomie und Histologie*. Edited by F Henke and O Lubarsch. Vol. 9. Berlin Julius Springer 1929 Pp 355 359  
5 Sirbu A. B. Murphy M. J. and White A. S. Soft tissue complications of fractures of leg. *California & West Med.* 60 53 56, 1944  
6 Phalen G S. Ischemic necrosis of anterior crural muscles. *Ann. Surg.* 127 112-120 1948  
7 Gilcreast, E. L. Rupture of muscles and tendons, particularly simultaneous rupture of biceps flexor cubiti. *J A M A* 84 1819-1822 1925

ADDITIONAL REFERENCE

Forbes W D. Pathologic changes in voluntary muscle. I. Degeneration and regeneration of rectus abdominis in pneumonia. *Arch Path.* 23:18-359 1926

NODULAR GOITER AND THYROID CANCER

THOMAS J ANGLEM, M D,\* AND MARTIN L BRADFORD, M D†

BROOKLINE, MASSACHUSETTS

IN THE therapeutic attack on malignant tumors in general, the accumulated experience of generations has established as virtually axiomatic certain well defined principles.

The first is the folly of attempting to arrive at a diagnosis by observation of the continued growth of a tumor or area of nodularity until its malignant nature is clear and unmistakable. As stated by Taylor,<sup>1</sup> one must answer the question, "What is the disease?" It must be answered early, by biopsy or by removal of the lesion in question.

A second is the great utility of the principle of prophylactic removal of lesions that, though apparently benign, are known to be at times actually malignant or to be capable of malignant degeneration. This principle is almost universally accepted in the therapy of such conditions as leukoplakia of the oral cavity, keratosis of the skin, papillomas of the bladder, polyps of the rectum and colon and kraurosis vulvae.

On the basis of this fundamental attitude, supported by an impressive array of statistical evidence indicating a high incidence of cancer in the nontoxic nodular goiter, most surgeons who have concerned themselves with the subject have favored removal of such growths. The incidence of cancer in nontoxic nodular goiter, as reported from representative surgical clinics in different parts of the country,

varies from 4.8 to 11.0 per cent (Table 1). All reporting clinics have shown a higher incidence in single adenoma than in the multinodular nontoxic

TABLE 1 Incidence of Cancer in Nontoxic Adenomatous Goiters

AUTHOR	CASES OF GOITER	CASES OF CANCER	
		NO	PERCENTAGE
Hare <sup>2</sup>	50:2	246	4.87
Ward <sup>3</sup>	3,539	168	4.8
Hinton and Lord <sup>4</sup> (toxic and nontoxic)	184	14	7.6
Cole, Slaughter and Rossiter <sup>5</sup>	100	11	11.0
Anglem and Bradford	50:0	42	7.6

goiter, varying from 9.0 to 24.0 per cent (Table 2).

These authors and many others advocate, on the basis of the figures presented, the principle of pro-

TABLE 2 Incidence of Cancer in Single Nontoxic Adenomas

AUTHOR	CASES OF ADENOMA	CASES OF CANCER	
		NO	PERCENTAGE
Hare	1971	206	12.0
Cole, Slaughter and Rossiter	92	22	24.0
Anglem and Bradford	65	33	9.0

phylactic thyroidectomy for nodular goiter, even though it may be symptomless.

It is recognized that the incidence of cancer in simple diffuse goiter, in primary hyperplasia and

\*Assistant professor of surgery, Boston University School of Medicine, visiting surgeon, Massachusetts Memorial Hospitals and New England Baptist Hospital.

†Assistant in surgery, Boston University School of Medicine, second assistant visiting surgeon, Massachusetts Memorial Hospitals.

in toxic adenomatous goiters is so low as to be of no significance in the general problem. It is also recognized that certain adenomatous goiters require thyroidectomy because of toxicity or because of substernal, retrotracheal or intrathoracic extension productive of serious pressure symptoms. The operation in these cases can in no sense be considered a prophylactic procedure.

The crux of this problem thus revolves about the attitude that should be taken toward the single adenoma and the relatively symptomless and usually small or moderate-sized multinodular nontoxic goiter. The validity of the principle of prophylactic thyroidectomy in such cases has recently been questioned by Rogers, Asper and Williams,<sup>6</sup> who

TABLE 3 Incidence of Cancer in Various Types of Goiter

TYPE OF GOITER	NO OF CASES	NO OF CANCERS	PERCENTAGE
Nontoxic adenomatous	550	42	7.6
Single adenoma	363	33	9.0
(Cancer unsuspected)	(354)	(24)	(6.7)
Multiple adenoma	187	9	4.8
Toxic	811	4	0.49
Toxic adenoma	105	2	1.9
Primary hyperthyroidism	706	2	0.28
Thyroiditis	16	0	0.00
Totals operated	1377	46	
Average			3.3

support their point of view by data obtained from the study of the records of 3221 cases drawn from all services of the Boston City Hospital, the Johns Hopkins Hospital and the Massachusetts General Hospital.

In support of their point of view, Rogers, Asper and Williams lay great emphasis on an alleged discrepancy between the incidence of thyroid cancer in surgical specimens and that in "clinical" and autopsy material, the significance of the factor of variability is the degree of malignancy in thyroid cancer and in the morbidity and mortality associated with thyroidectomy. VanderLaan<sup>7</sup> also stresses the low incidence of thyroid cancer in autopsy material and implies on the strength of this that surgical pathologists are diagnosing as thyroid cancer lesions that are not malignant.

Since nodular goiter is not uncommon, it is highly desirable to arrive at some measure of accord regarding the therapy, if any, that should be recommended to the patient with an otherwise symptomless unimodular or multinodular goiter.

A challenge such as that implied in the paper of Rogers, Asper and Williams serves a useful purpose in compelling a reappraisal of prevailing attitudes and critical re-examination of the bases on which they rest.

With these considerations in mind, we have undertaken a critical and objective review of the data on which the two conflicting points of view rest

and have, in addition, made a study of the records of 1377 patients from the Thyroid Service at the Massachusetts Memorial Hospitals and from our office. All patients having had thyroidectomy or excision of thyroid nodules are included. Patients having had two-stage operations are counted only once. Among the 1377 patients, cancer was encountered in 46 cases, or 3.3 per cent. The incidence of cancer among the various types of goiter is indicated in Table 3.

The types of cancer encountered were as follows: papillary adenocarcinoma (18 cases), adenocarcinoma (11 cases), small-cell carcinoma (5 cases), giant-cell carcinoma (4 cases), Hürthle-cell carcinoma (2 cases), embryonal-cell carcinoma (2 cases), fetal adenoma with blood-vessel invasion (2 cases), fibrosarcoma (1 case), and hemangiosarcoma (1 case). Only 2 cases fell in the borderline group of so-called fetal adenoma with blood-vessel invasion, and in 1 of these the malignant character of the lesion was subsequently confirmed by the development of a metastasis.

Our findings regarding the incidence of cancer fully confirm reports from other surgical clinics in nonendemic areas.

It is our belief that the alleged discrepancy between the incidence of cancer in surgical statistics and that found in "clinical" material does not, in fact, exist. Rogers, Asper and Williams,<sup>6</sup> for example, report an incidence of 1.99 per cent of all patients with goiter, but the total figure on which this calculation is based includes 907 toxic diffuse goiters, 400 nontoxic diffuse goiters, and 377 toxic nodular goiters, all of which play little or no part in this problem. Only 5 of the 74 cases of cancer reported occurred in the toxic group. It is possible from the figures supplied by Rogers, Asper and Williams to calculate the incidence of cancer in the nontoxic nodular group, which, for their entire series, is 4.79 per cent and, for the material that they report from the Johns Hopkins Hospital, 11.2 per cent.

Both VanderLaan<sup>7</sup> and Rogers et al.<sup>6</sup> attach great significance to the infrequency with which carcinoma of the thyroid gland is found as the cause of death in autopsy studies. Jaffé's<sup>8</sup> report of a ratio of 2:1000 is cited by VanderLaan. A ratio of less than 1:1000 in 11,000 autopsies was found at the Massachusetts General Hospital, an incidence of 5 cases in more than 6000 autopsies at the Peter Bent Brigham Hospital, and an incidence of 5 cases in 18,668 cases from the Boston City Hospital. The last figure is so far out of line with the others reported that its accuracy must be questioned.

We believe that this is fallacious reasoning and that the apparent discrepancy is due to the fact that in fatal cases of thyroid cancer the patient has usually had the disease for a long time before the terminal stage is reached and that, except for an

occasional patient who is rushed into the hospital in acute dyspnea and for the rare operative mortality, these patients usually die at home

In a study of 1657 autopsy records from the Department of Pathology of the Massachusetts Memorial Hospitals for the thirteen-year period from January, 1934 to September, 1947, we found confirmation of the low incidence of cancer as a cause of death in this type of material. Thyroid cancer was not found to be the cause of death in a single case (657 of these records were on children under the age of ten years). However, neither did we find a single case of cancer of the tongue, floor of the mouth, gingiva, buccal mucosa, or palate, which as a group are considerably more common than thyroid cancer. We also found that our figures suggested that cancer of the duodenum was half as common as cancer of the cervix, — a patent absurdity.

The significant fact we believe to be this in a period shorter by two years than that covered by the autopsy survey we found 11 patients (from the Massachusetts Memorial Hospitals and from a single private office) who are known to be dead of thyroid cancer. Only 1 of these came to autopsy, and that one at another hospital. It is important to point out that none of the private cases of the remainder of the entire hospital staff are included, and yet their contribution to the autopsy material is included. If a similar situation prevails in other medical centers, and we see no reason to doubt that it does, the actual incidence of death from thyroid cancer is more than ten times greater than autopsy statistics suggest.

Rogers, Asper and Williams<sup>6</sup> emphasize the point that a large percentage of thyroid cancers fall in the group of low or moderate malignancy and suggest that because of this fact a conservative attitude is warranted and that one may wait in dealing with such patients until there is definite objective evidence that cancer is actually present, such as a recent sudden increase in the size of a nodule or the appearance of an increased hardness in the consistency of such a nodule. Against this teaching, it is only necessary to report such end results as those of Ward,<sup>3</sup> who found that when carcinoma of the thyroid gland was diagnosed or suspected on clinical examination, 80 per cent of patients were dead at the end of five years, that when carcinoma was diagnosed at operation, 60 per cent were dead after five years and that when the diagnosis was first made at pathological examination only 20 per cent were dead, it may be pertinent to point out that Cochrane,<sup>9</sup> reporting from the Boston City Hospital on 559 thyroidectomies done between 1925 and 1937, found not a single case of cancer of the thyroid gland diagnosed clinically that was surgically operable.

The mortality and morbidity associated with thyroidectomy is put forward by Rogers, Asper and

Williams<sup>6</sup> as a potent argument against prophylactic thyroidectomy. They cite a 15.3 per cent incidence of complications and 5 fatal cases in a series of 431 patients who had thyroidectomies for nontoxic goiter, diffuse or nodular. At least 4 of the operations in the fatal group could by no stretch of the imagination be called "prophylactic."

It is not at all unreasonable to suggest that prophylactic operations performed five, ten, fifteen or twenty years earlier might have obviated these fatal outcomes as well as many of the graver complications. The 15.3 per cent incidence of complications cited is not the incidence of complications that follow thyroidectomy done as a prophylactic procedure, but for the entire group, which unquestionably contained many complicated surgical problems.

It is well known that in the hands of competent thyroid surgeons the incidence of mortality and serious complications is almost wholly limited to the complicated case — the large goiters with retrotracheal, substernal or intrathoracic extension. To cite such complications as an argument against prophylactic removal of discrete adenomas or small nodular goiters is simply to confuse the issue. Lahey<sup>10</sup> has stated

The mortality of removal, particularly in the type of adenoma that is likely to become malignant, ought to be zero because it is a discrete adenoma and easily removed. These patients are in the hospital not over a week, so why trade the hazards of malignancy in a thyroid adenoma of this type when there is no risk and the hospital stay is so short?

With this we concur.

In our own series of nontoxic nodular goiters we have excluded all cases in which there was a clear-cut complaint of pressure symptoms, all patients who had substernal, retrotracheal or intrathoracic extension, and all whose goiters were estimated to be 7 cm in diameter or larger. The remaining group of 331 cases consisted of 220 single adenomas and 111 small or moderate-sized, essentially symptomless multinodular nontoxic goiters. We believe that the term "prophylactic thyroidectomy" can be applied only to this group. Actually, many of these patients wished to be rid of their goiters and the number of cases in which the operation was truly prophylactic was much smaller than the figure given. There were no deaths. The complications occurring in this entire group consisted of 1 case of deep thrombophlebitis, 2 cases of hypothyroidism, 2 cases of keloidal scars, and 12 cases of serum in the wound, all of which cleared up uneventfully in one month or less.

#### CONCLUSIONS

The high incidence of cancer in single thyroid adenomas from our own study (9.0 per cent) makes obligatory the removal of all single thyroid nodules.

The incidence of cancer in nontoxic multinodular goiters (4.8 per cent) is sufficiently low so that

we concede that the propriety of operating on all such patients might be questioned if there were not other compelling reasons why the growths should be removed. It is our opinion that the multinodular goiter is not a simple benign process, but a progressive disease that goes on, first to develop toxicity in a significant percentage of cases, as indicated by the increasing incidence of toxicity as one ascends the age scale,<sup>11</sup> and secondly, to produce serious mechanical disturbance, chiefly by compression and deviation of the trachea by retrotracheal, substernal and intrathoracic extension. The frequency of such manifestations is indicated by Means's<sup>11</sup> report of an incidence of pressure symptoms in 65 per cent of cases of nontoxic nodular goiter at the Massachusetts General Hospital.

The mortality from operations that can be classed as prophylactic is virtually zero.

The incidence of complications in operations on this class of patient is insignificant, compared with the hazards of leaving the goiter

1180 Beacon Street

#### REFERENCES

- 1 Taylor G W. Fundamentals in cancer problem. *Am. Exp. J. Med.* 215:383-385, 1936
- 2 Hare H F. Cancer of thyroid. *S. Clin. North America* 27:561-563, 1947
- 3 Ward R. Malignant goiter. *Surgery* 16:783-803, 1944
- 4 Hinton J W, and Lord J W Jr. Is surgery indicated in all cases of nodular goiter, toxic and nontoxic? *J. A. M. A.* 129:503, 1941
- 5 Cole W H, Slaughter D P, and Rossett L J. Potential dangers of nontoxic nodular goiter. *J. A. M. A.* 127:883-888, 1941
- 6 Rogers W F Jr, Asper S P Jr, and Williams R H. Clinical significance of malignant neoplasms of thyroid gland. *Am. Exp. J. Med.* 237:569-576, 1947
- 7 VanderLaan W P. Occurrence of carcinoma of thyroid gland in autopsy material. *New Eng. J. Med.* 237:221, 1947
- 8 Jaffe R H. Variation in weight of thyroid gland and frequency of its abnormal enlargement in region of Chicago. *Arch. Path.* 10:351-394, 1930
- 9 Cochrane R C. Thyroid surgery at large municipal hospital. *Am. Exp. J. Med.* 220:7-14, 1939
- 10 Lahey F H. Discussion of Cole et al.<sup>5</sup>
- 11 Means J H. Nodular goiter. In *The Thyroid and Its Diseases* (67 pp). Philadelphia: J. B. Lippincott Co., 1937. Pp. 460-476.

## PENICILLIN IN THE TREATMENT OF DIPHTHERIA AND THE DIPHTHERIA CARRIER STATE

JOHN D CRAWFORD, M D \*

BOSTON

THE importance of diphtheria has been re-emphasized lately by experiences with the disease in foreign countries during the war and its aftermath and by slight but statistically significant increases in the prevalence of diphtheria in this country. The clinical manifestations and complications have been completely described in the older literature. An important aspect of the problem now being developed is the application of antibiotics in treatment. The value of penicillin in diphtheria has been established in extensive clinical trials by Karelitz et al.<sup>1</sup> and by Weinstein.<sup>2</sup> The following investigations confirm their findings in a series of 97 additional penicillin-treated cases and present some clinical evidence bearing on the mode of action of this antibiotic.

#### MATERIAL

The material reported below consists of all patients admitted for diphtheria or the diphtheria carrier state to the 279th United States Army Station Hospital in Berlin, Germany, from July 1 to December 31, 1946. During the period of study diphtheria was constantly at epidemic levels, the troop rate being about 36/10,000 per annum, compared with the over-all rate for the city of 47/10,000 per annum. Cases in which the animal virulence test of the organism cast doubt on the original diagnosis have been eliminated from the study.

For comparison, an analysis was made of 50 consecutive cases of pharyngeal diphtheria admitted in the six months just prior to the study period and to the routine use of penicillin.

The average length of hospitalization of the non-penicillin-treated patients was fifty-seven days. Whereas all patients were hospitalized for a minimum of six weeks after onset, it is seen that 18 per cent of this series were held for a longer period because of minor cardioneurologic complications, and an additional 6 per cent were held for evacuation to the United States for more serious complications. There were 3 deaths in the series, giving a 6 per cent mortality. Omitting the above three categories, the average length of hospitalization of remaining patients rises to sixty-one days. The reason for this prolonged period of hospitalization becomes apparent when one notes that 57 per cent of the patients had to be held beyond the minimum six weeks merely because they continued to harbor virulent organisms in the nasopharynx. Such prolonged hospitalization of asymptomatic carriers represents a tremendous waste of hospital space and manpower.

#### PILOT STUDY

The routine use of penicillin in diphtheria treatment was based upon the results of a study of its effect upon 20 carriers selected on the following criteria: the patients were all asymptomatic convalescents so far as manifestations of acute diphtheria

\*Resident, Children's Medical Service, Massachusetts General Hospital.

were concerned, all had been hospitalized for six weeks or more since clinical onset, and from all, tri-weekly nasopharyngeal cultures were consistently positive for virulent diphtheria bacilli. During the study patients were isolated from new diphtheria contacts, usually 2 patients to a room, both receiving the same type of treatment.

Five cases were treated locally with sprays of a penicillin solution containing 500 units per cubic centimeter, applied to the nasopharynx every three hours day and night for ten days.

Seven cases were treated with 1,000,000 units of penicillin intramuscularly, the dosage schedule being 40,000 units every three hours for twenty-five doses.

Eight cases were treated parenterally with the same total amount of penicillin but given in doses of 20,000 units every three hours for fifty injections.

Cultures were taken three times a week during treatment. The carrier state was considered terminated if, at the completion of treatment, three consecutive

TABLE 1 *Results of Treatment in 20 Carriers Hospitalized for Six Weeks or More after Onset with Positive Cultures but No Symptoms*

TREATMENT	NO OF CASES	PATIENTS WITH NEGATIVE CULTURES %
Local nose and throat sprays of penicillin (500 units per cubic centimeter every 3 hours)	5	20
Parenteral administration of penicillin (40,000 units every 3 hours for 25 doses)	7	28
Parenteral administration of penicillin (20,000 units every 3 hours for 50 doses)	8	87

secutive cultures at forty-eight-hour intervals and a fourth culture one week later were negative.

Local treatment was followed by termination of the carrier state in only 1 patient. Although negative cultures were obtained during and for several days after the short course of parenteral therapy only 28 per cent of the series satisfied the criteria for termination of the carrier state. Excellent results, however, were obtained from the use of the same total dose given in smaller amounts over a longer period, only 1 patient failing to fulfill the criteria for permanent termination of the carrier state (Table 1). The necessity for the four-culture test for termination of the carrier state was demonstrated both in this pilot study and in the material to follow. In many cases the first culture or even the first three failed to show the organisms after penicillin treatment, though later cultures again revealed virulent diphtheria bacilli. On the other hand, no patient who had had the requisite four consecutive negative cultures showed virulent organisms when cultures were obtained on subsequent occasions.

## PROCEDURE BASED ON RESULTS OF PILOT STUDY

The results of the preliminary study were promising enough to warrant trial on a larger scale. In addition, it was presupposed that the value of penicillin was not limited to the treatment of carriers but that in acute cases its use might well be expected to reduce appreciably the number of patients continuing to carry virulent organisms for more than six weeks after clinical onset of the disease. Thus, penicillin was incorporated into the routine treatment of both carriers and acute cases.

Patients suspected of having acute pharyngeal diphtheria were immediately given a single average dose of 60,000 units of diphtheria antitoxin and in addition were started on three hourly doses of 20,000 units of penicillin (40,000 units in more severe cases). Penicillin was continued for seven days (fifty doses) or longer if the pharyngeal mucosa was not yet entirely healed.

Carriers were treated initially with the fifty-dose schedule. Only those who failed to respond to this routine were subjected to tonsillectomy. If cultures were still positive after penicillin and tonsillectomy a second identical course of penicillin was given.

## PENICILLIN TREATMENT IN ACUTE CASES

Forty-five cases of acute diphtheria were treated with penicillin during the six-month period of study. In comparison with the 50 previous cases, the average length of hospitalization was cut from fifty-seven to forty-five days. Two patients (4.4 per cent) developed serious cardioneurologic complications and were returned to hospitals in the United States. One patient (2.2 per cent) was held beyond the six weeks' minimum for minor cardioneurologic complications. There were no deaths. The average period of hospitalization, omitting the

TABLE 2 *Results of Treatment in 45 Cases\**

TREATMENT	NO OF CASES	NEGATIVE CULTURES AFTER TREATMENT NO PERCENTAGE
Penicillin alone (20,000 units every 3 hours)	45	40 80
Penicillin and tonsillectomy	5	4 80
Penicillin — tonsillectomy — penicillin	1	1 100

\*The average contagious period was 26.3 days from the time of admission in the fourth negative culture.

above three categories, dropped from sixty-one to forty-three and one-eighth days. Only three patients were held beyond the six weeks' minimum because of positive cultures, a reduction from 57 to approximately 9 per cent.

Table 2 shows a further analysis, including a summary of methods of treatment. The average "contagious" period — that is from admission to the time of receipt of the fourth negative culture after

treatment — was twenty-six and one-eighth days. All the 45 patients received an initial course of penicillin, usually consisting of fifty doses of 20,000 units each, however, a larger dose was sometimes given for the first three days. Forty patients, or 80 per cent, consistently showed negative cultures after treatment. Five patients regarded as penicillin failures, who still showed positive nasopharyngeal cultures at the end of six weeks, underwent tonsillectomy. Thereafter all but 1 showed negative cultures. This last patient was subjected to a second course of penicillin, 20,000 units every three hours for fifty doses, as a result of which there was a prompt termination of the carrier state.

#### PENICILLIN TREATMENT IN THE CARRIER STATE

During the period of study 52 chronic carriers of virulent *Corynebacterium diphtheriae* were treated. The average period of hospitalization following treatment was sixteen and a half days (Table 3).

TABLE 3 Results of Treatment in 52 Carriers \*

TREATMENT	NO OF CASES	NEGATIVE CULTURE AFTER TREATMENT	
		NO	PER CENTAGE
Penicillin alone (20 000 units every 3 hours for 50 doses)	44	37	87
Penicillin and tonsillectomy	13	12	92
Penicillin (2 courses)	1	1	100
Penicillin — tonsillectomy — penicillin	1	1	100

\*The average period of hospitalization after definitive treatment was 16.5 days.

Forty-four patients received an initial course of penicillin, consisting of 20,000 units every three hours for fifty doses. The carrier state was terminated in 37 cases, or 87 per cent. Six of these "penicillin failures" and 7 previously untreated cases were subjected to tonsillectomy, only 1 patient remaining a carrier after this procedure. One patient who failed to respond to the initial course of penicillin was desirous of undergoing a second treatment before submitting to tonsillectomy. This second course was given in the same manner as the first and resulted in cure. Finally, the patient who failed to respond to the initial tonsillectomy later underwent a course of penicillin. This resulted in clearing of a coexistent sinusitis and adenoid hypertrophy and was followed by four consecutive negative cultures at the prescribed intervals.

#### DISCUSSION

The results of the studies outlined above give further evidence of the value of penicillin as an adjunct in the treatment of diphtheria and the diphtheria carrier state. The present findings are in close agreement with those of Karelitz<sup>1</sup> and Weinstein.<sup>2</sup>

Tonsillectomy has long been recognized as the single most effective procedure in terminating the diphtheria carrier state. Adenoidectomy, the clearing of chronically infected accessory nasal sinuses, corrections of obstructive nasal septal deviation, dental surgery to eliminate foci of infection in the mouth and removal of foreign bodies occasionally found in the nasal passages of children are also well recognized surgical methods of importance in ridding the patient of organisms still obtainable on culture six weeks or more after the clinical onset of acute symptoms.

In general, modern antibiotics are obviating the necessity for much of the surgery of the presulfonamide days in diseases of bacteriologic etiology. This is true of diphtheria. The diphtheria bacillus is relatively resistant to penicillin<sup>3</sup> and quite resistant to sulfonamides.<sup>4</sup> Though it is sensitive to streptomycin,<sup>5</sup> there has been as yet no report of the clinical use of that drug. In the Schick-negative patient the bacillus is characteristically a surface-growing, noninvasive organism depending in large measure on devitalized organic detritus produced by the action of other bacteria to maintain its foothold in the human organism.<sup>6</sup> The surgical measures in common usage in diphtheria are effective because they mechanically eliminate such devitalized tissue. The rationale for the use of penicillin is based as much on its elimination of this detritus as on its specific effectiveness against the diphtheria organism. Here, in contrast to surgery, the site of action of penicillin is the varied organisms giving rise to hypertrophic and devitalized tissue. Three observations support the contention that this is an important factor in the effectiveness of penicillin. A certain class of carriers with necrotic, chronically infected tonsils that do not shrink in size with prolonged use of the antibiotic may confidently be expected to remain carriers until surgery is effected. Secondly, there is a class of patients with acute diphtheria in whom healing of the pharyngeal mucosa is still incomplete at the end of a week of treatment. If penicillin is discontinued according to rigid schedule after seven days (fifty doses), a high percentage of this group of patients will become chronic carriers. If, on the other hand, penicillin is continued a day or two longer until the pharyngeal tissues are re-epithelialized, almost none of the patients will subsequently show positive cultures. Thirdly, large doses of penicillin given over a short period are far less effective than small doses totaling the same amount but given over a longer period in shrinking and returning infected, hyperplastic pharyngeal lymphoid tissue to a healthy state. Corresponding with this is the superior effectiveness of small, longer continued penicillin doses in ending the diphtheria carrier state.

The present study does not suggest that penicillin supplant antitoxin in the treatment of acute diphtheria or replace surgery in the treatment of

he carrier. It indicates that penicillin is a valuable adjunct to antitoxin that should continue to be recognized as the specific form of treatment. Moreover, penicillin decreases the number of cases in which surgery is indicated, but does not lessen the necessity for operation in a selected group of patients.

### SUMMARY

An attempt to demonstrate the value of penicillin as an adjuvant to the treatment of diphtheria and the diphtheria carrier state is made through the presentation of the results of its use in 45 cases of acute diphtheria and 52 cases of carriers of virulent diphtheria organisms. For comparison these results are reported along with those obtained in treating 50 patients during the same epidemic but in the six previous months when penicillin was not used as part of the routine treatment.

The probable mode of action of penicillin is discussed.

It is concluded that penicillin is a valuable adjunct in the treatment of diphtheria and the diphtheria carrier state but that it does not supplant the use of antitoxin in the acute stage or obviate the necessity for surgery in a selected group of carriers.

### REFERENCES

1. Karelitz, S., Wasserman, L. R., and Moloshok, R. E. Penicillin in treatment of diphtheria and diphtheria carriers. *J. Pediat.* 30: 18-28, 1947.
2. Weinstein, L. Treatment of acute diphtheria and chronic carrier state with penicillin. *Am. J. M. Sc.* 213:308-314, 1947.
3. Ercoli, N. Lewis, M. N., and Moench, L. J. Antibacterial activity of penicillin in experimental infections in mice with *C. diphtheriae*. *J. Pharmacol. & Exper. Therap.* 84:120-127, 1945.
4. Kolmer, J. A. Failure of sulfonamide compounds in treatment of experimental *B. diphtheriae* (*Corynebacterium diphtheriae*) infections of guinea pigs. *Proc. Soc. Exper. Biol. & Med.* 48:350, 1941.
5. Palash, E. J., and Sprinz, H. Streptomycin in surgical infections. I. Laboratory studies. *Ann. Surg.* 125:194-202, 1947.
6. Zinsser, H. and Bayne-Jones, S. *A Textbook of Bacteriology: The application of bacteriology and immunology to the etiology, diagnosis, specific therapy, and prevention of infectious diseases for students and practitioners of medicine and public health.* Eighth edition, 990 pp. New York: D. Appleton Century Co., 1942. P. 418.

## SURGERY OF ELEPHANTIASIS OF THE SCROTUM OF FILARIAL ORIGIN\*

CHARLES E. TOWNE, M.D.†

WATERVILLE, MAINE

A NEW interest in tropical diseases has been attained in American medicine because of the widespread contact with exotic diseases by troops in the worldwide conflict that terminated on V-J Day. Among these none is more bizarre than elephantiasis of *Filaria (Wuchereria) bancrofti* origin. This report deals with experience gained with this affliction among natives of Polynesian extraction in the Society Islands in French Oceania. I obtained the material for this paper in my capacity of chief of the Surgical Service of the 8th Station Hospital under the command of Lieutenant Colonel Julius Sobin, who performed the major part of the actual surgery and whose skill contributed in a large measure to the success of the enterprise.

The patients were studied for a period of twenty-six months on one of the Society Islands occupied by United States forces. Although inter-island traffic was limited to a degree by war conditions, blood tests were performed on hundreds of natives, revealing an incidence of microfilariae in some localities as high as 70 per cent. This incidence is about as high as that found anywhere in the world. De Rivas<sup>1</sup> states

In Polynesia, the micro-filariae show no periodicity and are present in the blood in about equal numbers both day and night. In other areas they show a nocturnal periodicity, it being definitely established that they are much more numerous in the peripheral blood at night than during the day.

### GENERAL DESCRIPTION

In filariasis associated with *W. bancrofti*, the adult parasites usually live in the lymph nodes and lymphatic vessels, and in connective tissues. After pairing, the females emit numbers of microfilariae, which reach the blood stream via the thoracic duct and by penetrating the thick walls of the lymphatic vessels into neighboring capillaries. The infection is transmitted from man to man by means of a mosquito, the species varying according to locality. In Polynesia two species, *Aedes variegatus* and *Culex fatigans*, are responsible. When the insect has sucked blood from a person harboring microfilariae, the parasites migrate to the insect's thorax and there undergo considerable development. In fifteen to twenty-one days the microfilariae become mature larvae and migrate to the head and then to the proboscis of the insect. If the mosquito sucks blood at this time, the parasites are able to find their way to the skin of the host and to penetrate it— independently of the wound made by the insect. The larvae, by an unknown process, reach sexual maturity when they find their permanent abode in the lymphatic vessels and lymph nodes within the host. They become adult worms and in a fresh state are

\*From the Thayer Hospital.

†Member surgical staff, Thayer Hospital.

yellowish white and transparent, resembling thin catgut. They frequently coil together, ten or a dozen being found in a single lymph node. The male is 4 to 4.5 cm long and 0.1 mm in diameter, whereas the female is twice as long and thick. The microfilariae are the product of conception of paired adult worms and are found in peripheral blood. Seen in a fresh smear, the microfilariae appear to be snake-like and exhibit twisting and lashing movements, but they do not progress, either laterally or longitudinally.

### PATHOLOGY

The disease evoked by infestation of lymphatic vessels by adult worms is at first a state of lymphangitis with all the signs of acute inflammatory reac-



FIGURE 1 Elephantiasis of the Scrotum in a Polynesian Native

tion. Very frequently secondary invaders, notably streptococci, cause abscess formation. After a few attacks there is a tendency to fibrosis and considerable hypertrophy of the lymphatic vessels. New and irregular formation of lymphoid tissue surrounded by fat succeeds each attack. An elephantoid process forms by repeated attacks, with predilection for the breast in the female and the scrotum in the male. A typical case of scrotal elephantiasis is illustrated in Figure 1. It is my opinion that these organs favor elephantoid development because of their more dependent lymphatic circulation, which in turn encourages the mechanical obstruction that is always the cause of elephantiasis.

### CLINICAL MANIFESTATIONS

Many people infected with filariasis suffer no inconvenience whatever. Thousands of troops stationed in the Pacific became infested with *W. bancrofti*. Between 1942 and 1945 in all theaters of war Saper<sup>2</sup> estimated that 14,000 members of the armed forces contracted filariasis. Predominantly, the infestation was acquired in the Pacific Theater. Had it not been for the marvelous efficiency of service troops in mosquito-control units, there would undeniably have been a much higher incidence of occurrence than that reported. These units operated in areas of malaria, filariasis and other tropical diseases with great efficiency, mainly by ditching, draining, spraying with DDT and other insecticides, screening and by education of both troops and natives in methods of mosquito control. The troops that became afflicted by repeated bites from infected mosquitoes exhibited early signs of the disease, usually either an acute funiculitis or epididymitis or a superficial lymphadenitis.

When the patient was transferred to a nonfilarial area, the entire symptomatology faded away, and follow-up study in all these cases has shown an almost universal recovery, with practically no recurrence.

On the other hand by repeated attacks about 50 per cent of the natives had a large variety of symptoms, and 5 per cent had elephantiasis. The more usual conditions were lymphangitis and adenitis, elephantoid fever and elephantiasis, abscess, inflammation of the spermatic cord and epididymis, hydrocele, cystic enlargements of the skin, lymph nodes and breasts, fistula, chyluria and chylous conditions of the peritoneum and intestine, and chylocele synovitis.

### DIAGNOSIS

The recovery of living or dead calcified parasites in a lymph node or abscess and the occurrence of microfilariae in the blood constitute positive diagnostic data. However, the microfilariae frequently disappear from the blood after elephantiasis has occurred, owing to death of the parent parasites within the body of the host. Matas<sup>3</sup> states that recurrent erysipelatous inflammation with progressive hypertrophy is diagnostic.

Blood studies may be of value. The presence of eosinophilia in the absence of intestinal helminthiasis is suggestive. At the height of the attack the eosinophil count may rise to 25 or 30 per cent. Recently, O'Connor<sup>4</sup> has used x-ray examination to demonstrate the presence of calcified worms, a new aid in diagnosis.

### SURGERY OF SCROTAL ELEPHANTIASIS

There is little in the American medical literature denoting the technic of surgery on the patient with scrotal elephantiasis, because of an almost total lack

of patients with this affliction within the continental limits of the United States. French and South American surgeons have had great opportunity to pioneer in this field and have published reports of successful surgery performed in scattered areas of the globe. Since the pathologic findings vary materially in different locations, the surgeon, perforce, must adapt his technic to suit the conditions. There is no one type of operative procedure that will answer all the needs as found in various locations. A search of the literature discloses exactly the same number of technical approaches as the number of writers. Certain basic features however are constant findings in these reports:

Infection is always present, and precautionary measures must be adopted. Bankoff<sup>5</sup> states that 95 per cent of the cases will suppurate, adding "The complication can be eliminated today by packing sulfonamide powder directly into the wound."

Preservation of the penis and testes is vital. In some locations scrotal elephantiasis is always accompanied by hydrocele, which must be handled with the established surgical procedure of excision.

Hemostasis and control of bleeding are axiomatic. de Savitsch<sup>6</sup> points out the universal need of applying a tourniquet at the base of the scrotum and doubly ligating the large blood vessels found medial to the cord to avoid the serious consequence of hemorrhage.

In this series of 24 cases the scrotum was universally affected on both sides, with concomitant bilateral hydrocele. The hydroceles were usually disproportionate in size, giving the appearance of more scrotal involvement on the side of the larger hydrocele. Since many patients had skin manifestations of yaws as well as filariasis, they were given three intravenous treatments of arsphenamine before hospitalization. This always sufficed to eradicate yaws as a possible contaminating agent.

The average age was thirty-eight years. The scrotal elephantiasis had been present for an average of eight years, and the scrotal redundancy averaged 15 pounds, which does not include the fluid contained within the hydroceles.

Sexual intercourse was impossible for the patients prior to operation because the penis was deeply imbedded within the tumor mass. These people were Polynesians, and whereas this paper is not intended to deal with ethnology, it should be remarked that the male Tahitian is brown-skinned, extremely muscular and well nourished and, despite his filarial infestation, a very healthy being. Under these conditions it was not necessary to build up the patient prior to surgery by the use of hematinics, vitamins, amino acids or chemotherapy. It was enough to rid him of yaws and to sterilize the skin locally.

Under ether anesthesia the patient received his final skin preparation, and an elastic tourniquet was placed tightly around the scrotum and as near the perineum as possible. The penis was located by palpation and held away by the assistant's right hand. The surgeon then located the testicle on one side and exposed it by a lateral incision. The hydrocele, which was always present, was corrected by an inversion procedure. The same surgery was repeated on the other side. It was not necessary to provide a pulley attached to the ceiling to elevate the tumor mass, as reported by de Savitsch.<sup>6</sup> The large blood vessels were isolated, doubly ligated and divided as high as possible.

In the next step the two lateral incisions were extended on each side of the mass in a curvilinear direction, meeting in the midline posteriorly. Anteriorly, the lateral incisions were joined by a long straight flap, which provided skin for a new sheath for the penis in the event that it was found necessary to sacrifice the integument of the old sheath. However, the sheath in each case was found to be resilient — in fact, quite normal — and to have no relation to the extremely fibrotic and thickened skin of the scrotum. The main tumor mass was then amputated distal to the lines of the incisions, and all bleeding vessels were carefully ligated after removal of the elastic tourniquet.

In reports from other localities — notably, the French Congo — the surgeons had to borrow skin from normal sites to provide new sheath and the new scrotum, but in the present report this was not necessary owing to the integrity of the old sheath and to undermining of the skin of the remaining scrotal flaps. The wound was dusted with sulfonamide powder and closed lightly with nonabsorbable suture material. A rubber dam was inserted in the most dependent part of the wound, and a thick gauze was secured by a T binder. Postoperatively the wounds healed rapidly and with only moderate infection. Usually in ten days the patient was discharged from the hospital to resume his usual haunts, unencumbered by his previous disability and once again able to cope with economic and social obligations.

Military horizons were extended. The Army moved on to new shores, and the results could not be observed over a sufficient period for a report on long-term postoperative findings. It was obvious, however, that psychologically the patients were extremely benefited. There were no indications of impending recurrence of elephantiasis in any case.

#### SUMMARY

A description of elephantiasis of the scrotum of filarial origin among natives in Polynesia is presented. The mosquito vectors are named, and a general picture of the resulting pathology is described.

yellowish white and transparent, resembling thin catgut. They frequently coil together, ten or a dozen being found in a single lymph node. The male is 4 to 4.5 cm long and 0.1 mm in diameter, whereas the female is twice as long and thick. The microfilariae are the product of conception of paired adult worms and are found in peripheral blood. Seen in a fresh smear, the microfilariae appear to be snake-like and exhibit twisting and lashing movements, but they do not progress, either laterally or longitudinally.

### PATHOLOGY

The disease evoked by infestation of lymphatic vessels by adult worms is at first a state of lymphangitis with all the signs of acute inflammatory reac-



FIGURE 1 Elephantiasis of the Scrotum in a Polynesian Native

tion. Very frequently secondary invaders, notably streptococci, cause abscess formation. After a few attacks there is a tendency to fibrosis and considerable hypertrophy of the lymphatic vessels. New and irregular formation of lymphoid tissue surrounded by fat succeeds each attack. An elephantoid process forms by repeated attacks, with predilection for the breast in the female and the scrotum in the male. A typical case of scrotal elephantiasis is illustrated in Figure 1. It is my opinion that these organs favor elephantoid development because of their more dependent lymphatic circulation, which in turn encourages the mechanical obstruction that is always the cause of elephantiasis.

### CLINICAL MANIFESTATIONS

Many people infected with filariasis suffer no inconvenience whatever. Thousands of troops stationed in the Pacific became infested with *W. bancrofti*. Between 1942 and 1945 in all theaters of war Saper<sup>2</sup> estimated that 14,000 members of the armed forces contracted filariasis. Predominantly, the infestation was acquired in the Pacific Theater. Had it not been for the marvelous efficiency of service troops in mosquito-control units, there would undeniably have been a much higher incidence of occurrence than that reported. These units operated in areas of malaria, filariasis and other tropical diseases with great efficiency, mainly by ditching, draining, spraying with DDT and other insecticides, screening and by education of both troops and natives in methods of mosquito control. The troops that became afflicted by repeated bites from infected mosquitoes exhibited early signs of the disease, usually either an acute funiculitis or epididymitis or a superficial lymphadenitis.

When the patient was transferred to a nonfilarial area, the entire symptomatology faded away, and follow-up study in all these cases has shown an almost universal recovery, with practically no recurrence.

On the other hand by repeated attacks about 50 per cent of the natives had a large variety of symptoms, and 5 per cent had elephantiasis. The more usual conditions were lymphangitis and adenitis, elephantoid fever and elephantiasis, abscess, inflammation of the spermatic cord and epididymis, hydrocele, cystic enlargements of the skin, lymph nodes and breasts, fistula, chyluria and chylous conditions of the peritoneum and intestine, and chylocele synovitis.

### DIAGNOSIS

The recovery of living or dead calcified parasites in a lymph node or abscess and the occurrence of microfilariae in the blood constitute positive diagnostic data. However, the microfilariae frequently disappear from the blood after elephantiasis has occurred, owing to death of the parent parasites within the body of the host. Matas<sup>3</sup> states that recurrent erysipelatous inflammation with progressive hypertrophy is diagnostic.

Blood studies may be of value. The presence of eosinophilia in the absence of intestinal helminthiasis is suggestive. At the height of the attack the eosinophil count may rise to 25 or 30 per cent. Recently, O'Connor<sup>4</sup> has used x-ray examination to demonstrate the presence of calcified worms, a new aid in diagnosis.

### SURGERY OF SCROTAL ELEPHANTIASIS

There is little in the American medical literature denoting the technic of surgery on the patient with scrotal elephantiasis, because of an almost total lack

direction of research must be based on theory rather than fact. As an example of this, some representative attitudes on cancer chemotherapy have been culled from the recent literature

Woglom<sup>1</sup> has summarized, in a rather caustic fashion, the efforts to treat cancer by means of tumor extracts or autolysates, organ extracts, enzymes, metals, agents interfering with aerobic glycolysis, fever, cold, dyes, snake venoms, vitamins, various chemicals and a number of miscellaneous substances. His review indicates that many thousands of remedies have been tried in the treatment of cancer, that reports of favorable results usually originate from quacks or deluded or ignorant men and that the possibility of finding a cure for cancer is next to impossible.

Haddow<sup>2</sup> has set down more explicitly the difficulties of discovering a specific therapeutic agent against cancer.

It has always been a matter for legitimate doubt whether a therapeutic agent could impair the growth of malignant cells, without equally damaging the normal cells and especially those which are engaged in active division, for example, in the intestinal mucosa, the bone marrow, and the generative organs. An even more serious obstacle is the fact that the malignant variant is to all intents and purposes quite permanent and irreversible. Hence, even if its growth is impeded by any agent save the most specific (so far unknown), it is likely after a longer or shorter interval, to recover and recur. There can be no misunderstanding as to the almost insuperable problem which the chemotherapy of cancer presents, and which, in search of a comparison, we can almost liken to a biological counterpart of the squaring of the circle. It is indeed true that those who have considered the matter most thoroughly are under the least illusion as to its practicability.

In spite of these real impediments, Haddow has formulated his attack on the problem as follows: "the best prospects of success should come from persistent investigation of the mode of action of carcinogens, so that by increasingly exact and quantitative knowledge of the process as it occurs in one direction, we may estimate at any rate the feasibility of its deliberate reversal."

Burk,<sup>13</sup> on a premise elaborated in a recent book by Greenstein,<sup>14</sup> writes more optimistically:

The hope for the (chemical) approach lies mainly in the finding of modern biochemistry that whereas etiologically and morphologically cancer represents a great group of diseases, biochemically it presents a surprisingly uniform metabolic, chemical pattern that is characteristic, and therefore potentially subject to a unique or reasonably small number of chemotherapeutic agents, just as large classes of pathogenic microorganisms now are. The established biochemical "much of a muchness" of cancers may be regarded as a by-pass to an otherwise seemingly endless complexity of the problem.

Algire<sup>15</sup> has stated the belief that a common factor in the neoplastic process is the stimulation to the formation of new capillaries.

It should be emphasized that an outstanding characteristic of the rapidly growing tumor is its capacity continuously to elicit the production of new capillary endothelium from the host. This characteristic of the tumor cell might possibly be the real underlying factor respon-

sible for the autonomous growth inherent within the tumor cell, and from the standpoint of the host this capacity would seem to be a critical if not the critical expression of the neoplastic change. Since in tumor regression this ability to elicit a continuing vascular proliferation is lost, from the broad viewpoint of tumor therapy the study of the mechanism of this continuous vascular proliferation presents a major problem in cancer research.

On this basis, it appears that a study of agents interfering with capillary proliferation might furnish a generally useful chemotherapeutic agent against cancer.

The virus theory of cancer has been most persuasively presented by Oberling.<sup>16</sup> In this theory, however, the ubiquitous, tissue-specific viruses are presumably numerous and different so that it is difficult to imagine a common chemotherapeutic agent acting on all of them. If one can accept the virus hypothesis it does not seem much more

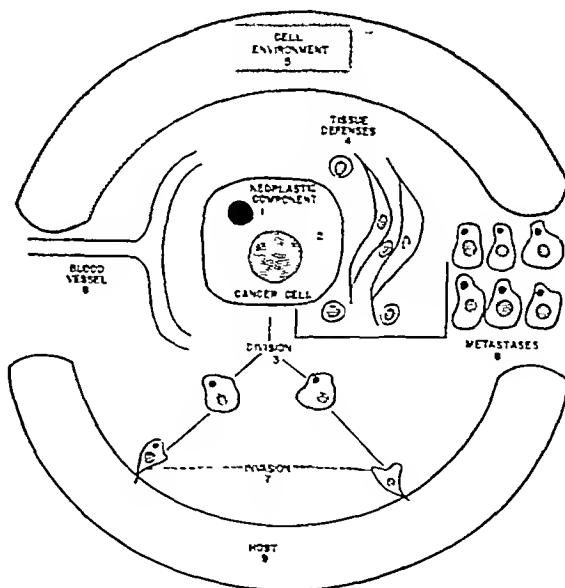


FIGURE 1 Diagram of the Possible Points of Attack by Chemotherapeutic Agents on Cancer and Its Manifestations (Reproduced from Karnofsky<sup>12</sup> by Permission of the Publishers)

difficult to conceive of a single agent or series of agents interfering with the proliferation or activity of these viruses.

Using the broad definition that "cancer chemotherapy is the use of any chemical substance administered systemically which, while relatively nontoxic to the host, will interfere with favorably modify, or destroy a neoplastic growth or alleviate its deleterious effects on the host," Karnofsky<sup>12</sup> has discussed the various possible avenues of chemotherapeutic attack on cancer, these are shown in Figure 1, with examples from agents under current study. The possible effects are as follows.

It is pointed out that veterans who had contracted the infestation during wartime have made virtually 100 per cent recoveries after their return to nonfilarial areas

Drug treatment of filariasis has been attempted with no great success throughout the regions where it occurs. Surgery offers the only benefit to those who have acquired elephantiasis as a result of many repeated bites of infected mosquitoes.

The technic of a surgical approach to the problem of elephantiasis of the scrotum is presented

50 Main Street

## REFERENCES

- 1 de Rivas, D. Filariasis. In *The Cyclopaedia of Medicine, Surgery and Specialties*. Edited by G. M. Pierrel and E. L. Bortz. 15<sup>th</sup> ed. Philadelphia: F. A. Davis Co., 1946. Vol. 6. Pp. 307-314.
- 2 Saper, J. J. Tropical diseases in veterans of World War II. *Am J Med* 235:843-846, 1946.
- 3 Matas, R. Surgical treatment of elephantiasis and elephantoid size dependent upon chronic obstruction of lymphatic and venous channels. *Am J Trop Dis* 1:60-85, 1913.
- 4 O'Connor, F. W., Golden, R. and Auchincloss, H. Roentgen demonstration of calcified *Filaria bancrofti* in human tissue. *Am J Roentgenol* 23:494-502, 1930.
- 5 Bankoff, G. Surgical treatment of elephantiasis. *J. Trop. Med. Hyg* 47:49-53, 1944.
- 6 de Savitsch, E. Surgical treatment of elephantiasis of scrotum and penis. *J. Urol* 45:216-222, 1941.

## MEDICAL PROGRESS

### CHEMOTHERAPY OF NEOPLASTIC DISEASE

#### I. Methods of Approach

DAVID A. KARNOFSKY, M.D.\*

NEW YORK CITY

**I**N RECENT years there has been a remarkable increase in research directed toward the discovery of chemical substances of therapeutic value in neoplastic disease. This endeavor has been stimulated by many factors: the intensification of medical research in general and cancer research in particular, the notable examples set by the development of antibiotics for bacterial infections, public demand for effective methods of controlling the disease, and the ever-present, suffering, doomed, but often lingering, patient with cancer. Recent chemotherapeutic advances — estrogens in prostatic carcinoma, nitrogen mustards in the lymphomas and urethane in the leukemias — have provided some encouragement toward the solution of a problem that has been viewed with unrelieved pessimism by many experienced investigators.<sup>1</sup>

One of the chief objectives of cancer research is the development of effective therapy. With the belief that methods of treatment will follow from an understanding of the disease itself, many investigators concentrate their efforts on the biologic and chemical aspects of cancer. Others, with more faith and often less method, are directly concerned with the therapeutic problem. Investigations in cancer chemotherapy are in progress at the National Cancer Institute<sup>2</sup> and at a number of universities and hospitals. Many projects of this type are sponsored by the American Cancer Society on recommendation of the Chemotherapy Section of the Committee on Growth of

the National Research Council.<sup>3</sup> Some pharmaceutical companies, which routinely test new chemicals against a variety of infectious organisms and in various biochemical systems, now include in these tests the neoplastic cell. In short, a great and direct effort on the problem of cancer chemotherapy is underway. This is evidenced by the numerous reviews that have appeared on the subject since 1945.<sup>4-12</sup>

It seems appropriate to review the basic ideas, the laboratory technics and the methods of clinical evaluation established in the cancer-chemotherapy program, and to discuss the status of the agents that have been proposed, utilized or publicized as having a role in the treatment or management of cancer in man. At present the problem has attracted the attention of most of the scientific disciplines and of many clinical investigators. The modern approach is still in its formative phase, and there is a great deal of room for controversy and differing opinions.

It is hoped that this brief review will help to clarify the several aspects of the complex field of cancer chemotherapy, and substitute concrete expression for what often seems to be wishful thinking.

#### APPROACHES TO THE PROBLEM

It may be assumed that, if the proper approach were known, the attempt to discover curative drugs for cancer would be immensely simplified. Since, unfortunately, there are many conceptions of the chemotherapy problem, none of which is generally acceptable and all of which may be untrue, the

\*Associate Sloan-Kettering Institute for Cancer Research, fellow in medicine, Memorial Hospital Center for Cancer and Allied Diseases, fellow, Jane Coffin Childs Memorial Fund for Medical Research.

are being used, and some of these are briefly described below

The most common methods involve the use of *transplantable solid tumors* in mice or rats

The National Cancer Institute uses the Sarcoma 37, inoculated intramuscularly into the flank of the mouse. The chemotherapy screening technic is described as follows<sup>18</sup>

Injection into mice, bearing a 1-week-old implantation of Sarcoma 37, of a single, maximum tolerated dose. The injection is made into the flank opposite the side bearing the tumor. Sacrifice of the mice at 8, 20, and 48 hours after the injection. Recording of the gross autopsy findings. Fixing of tumor tissue in Zenker-acetic and in acetic-orcein. The wall of the small intestine is taken as control tissue. Evaluation of the cellular changes produced by the treatment.

This test may disclose substances injurious to rapidly dividing cells or to newly formed capillaries, and it may possibly disclose an agent selectively injurious to tumor cells

A somewhat similar method is described by Laszlo and Leuchtenberger<sup>19</sup>. A transplantable tumor, the Sarcoma 180, is inoculated subcutaneously in mice. One week later, when the tumor is definitely palpable, the test material is injected twice daily for two days, and then the tumors are removed and weighed, and the weights compared with appropriate controls

In another type of experiment, a tumor is transplanted subcutaneously and observed for an arbitrary period, or until growth is well established. Treatment may then be instituted in several ways: the agent may be given by mouth<sup>20</sup> or by parenteral injections<sup>21</sup>. The mice may be observed for a standard period, and the size of the treated tumors compared with the controls, or observed indefinitely until the tumor kills the animal or until complete tumor regression occurs. The size of the tumor at death, the incidence of tumor regression or the survival time of the tumor-bearing mice may be used as criteria of effect. The weights of the mice must be observed during therapy, since starvation<sup>22</sup> or nonspecific intoxication may influence tumor growth<sup>23</sup>.

Recently, *transmitted leukemia* has come into more prominent experimental use<sup>24-26</sup>. Susceptible mice are inoculated intraperitoneally or intravenously with a suspension of leukemic cells. Therapy is begun shortly afterward, and is usually continued at the maximum tolerated dose for several weeks. The survival time of the treated as compared with the untreated mice is used as an index of the therapeutic efficacy of the test agent. This procedure will disclose drugs that inhibit rapidly growing cells or selectively inhibit neoplastic cells. It is possible, however, that some drugs increase survival time indirectly by supporting the mice against the systemic consequences of leukemia without acting directly on the neoplastic cells.

Transplanted tumors or leukemia are most practical for the screening of chemotherapeutic agents. In animals bearing transplanted tumors, however, the host-tumor relation usually must be considered abnormal, and a more critical evaluation of chemotherapeutic activity may be conducted in mice with *spontaneous* or *carcinogen-induced* tumors. Suitable groups of these mice are often difficult to obtain. It must also be realized that each spontaneous tumor has its own characteristic properties and rate of growth, survival time and tumor regression studies must therefore be carried out on larger numbers of mice than are necessary with the standardized method in which the disease is transmitted. Usually, if an agent is effective against transplanted tumors, confirmatory tests are run on spontaneous or carcinogen-induced tumors.

A *cytotoxic technic* for determining the dosage of a chemical necessary to inactivate tumor cells *in vivo* has been described by Burchenal<sup>27</sup>. This method is applicable to drugs that do not kill the test animal immediately, even when given at several multiples of the LD<sub>50</sub>\*. Mice with established transmitted leukemia are injected with various multiples of the LD<sub>50</sub> of the test substance. At an arbitrary period after injection, or just before death, the animal is sacrificed and a suspension of its leukemic cells (usually a splenic suspension) is injected into susceptible mice to determine their viability. This method is also applicable to solid tumors<sup>28</sup>. A drug that causes no obvious cytologic effects in a tumor at sublethal doses may produce significant effects when given at supralethal doses.

An *egg-culture method* has been described in which the test object is the Sarcoma 180 (a mouse tumor) growing on the chorioallantoic membrane of the chick embryo<sup>28</sup>. The tumor fragment is implanted on the eight-day embryo, when the presence of an active growth is demonstrated four days later, the maximal dose of the test chemical tolerated by the egg is injected into the yolk sac. Five days after injection the Sarcoma 180 is removed and examined for size, histologic appearance and viability, by transplantation into mice. The method, although limited in application, permits a comparison of the effects of chemicals on a variety of actively growing embryonic and tumor tissue, it may also reveal differences in the inherent susceptibilities of mouse and chick tissues.

Tumors in fowls are usually associated with a filtrable agent. The Rous sarcoma virus has most frequently been used in chemotherapeutic studies. It may be implanted in young chicks<sup>29</sup> or on the chorioallantoic membrane of the chick embryo<sup>30</sup> and the number of "takes" and rate of tumor growth measured. Another technic is the determination of the concentration of the test substance *in vitro* that is necessary to inactivate the infectivity

\*The smallest amount of the drug necessary to kill 50 per cent of the animals within the test period.

1 On the neoplastic component of the cell, which may be a single substance or a physiologic process occurring primarily anywhere in the cell

2 On the normal cell, which is the portion of the neoplastic cell that retains the functional and chemical characteristics of normal tissues and the tissue of origin — for example, nitrogen mustards, urethane and radioactive iodine

3 On the dividing cell, mitosis being essential for the manifestations of the neoplastic process — for example, colchicine

4 On the tissue defenses, suggesting that in some cases the tissues develop a defensive reaction against cancer

5 On the cell environment, on the basis that the growth of certain normal tissues depends on the presence of specific substances in their environment — for example, estrogens

6 On damage to the blood supply, on the basis that cancer tissue requires a good blood supply for growth — for example, Shear's polysaccharide

7 Stopping the invasiveness of cancer

8 Preventing the development of cancer metastases

9 Protecting or strengthening the host against the systemic derangements produced by certain types of tumors

In the absence of any known method of attacking the neoplastic process directly, any substance that may indirectly injure or influence the cancer cell should be considered suitable for clinical trial. Since the possibility of achieving a universal cancer cure seems to lie in the far distant future, "the cancer chemotherapist has progressively lowered his objectives from finding substances which will cure only certain types of cancer, to substances which will control cancer or certain types of cancer or certain manifestations of cancer, and, finally, to substances that have only a temporary palliative effect on the disease"<sup>12</sup> Most of the agents that have been considered suitable for inclusion in this review belong to the last group

#### LABORATORY TECHNICS

Special laboratory technics, involving the use of neoplastic cells and tissues, have been developed to test substances in a preliminary and general fashion for any selective activity against cancer (screening methods), to examine the mechanisms whereby certain substances affect the growth of tumors and to compare quantitatively the chemotherapeutic activity of different members of a given group of substances. In principle, these methods have much in common with those used in bacterial chemotherapy. However, they are more complicated and require more time than antibacterial methods, the results are less reproducible, and the data obtained are, consequently, more difficult to analyze. Further-

more, the validity of conclusions drawn from these data, in terms of the efficiency of an agent in affecting neoplastic as compared with normal cells, is often open to question. Because these methods are in current use<sup>17</sup> and represent an important part of any chemotherapeutic program, it is necessary to review them briefly.

The tumor-bearing mouse is the most commonly used tool in cancer chemotherapeutics, the rat, rabbit and chicken are employed to a lesser extent. Mice can be inbred with relative ease to the point of being homozygous, and strains of mice have been inbred for selected characteristics such as a high incidence of spontaneous leukemia and mammary carcinoma. Tumors of certain types may also be regularly induced by carcinogenic compounds. Within appropriate strains of mice, tumors may be easily and consistently transplanted, and a host of different transplantable tumors are available.

This variability of material and also of testing procedure must be carefully considered in any chemotherapeutic screening program. For example, the sex, strain, degree of inbreeding or homogeneity, age and nutritional and reproductive status of mice may vary. Tumors may be spontaneous, carcinogen induced or transplanted, and they may differ in their site of origin, histologic structure, rate of growth, ability to metastasize, sensitivity to various procedures and ability to grow in heterozygous mice. In the performance of a chemotherapeutic experiment on tumor-bearing mice, the test substance may be given orally, subcutaneously, intraperitoneally or intravenously, it may be given in the maximum tolerated dose, or at a fraction of this dose, or administered as a single dose, or given repeatedly over a period, and it may be administered in combination with other agents. Therapy may be started when the tumor is transplanted or when it is first palpable, or when it reaches a certain size, or a certain number of days after transplantation. In examination of the mouse for evidence of chemotherapeutic effect, tumor injury may be measured by evidence of histologic damage, by change in the size of the tumor or by the survival time of the tumor-bearing mouse.

In vitro tests, egg culture and tissue culture are additional methods currently in use. Thus, an almost infinite variety of chemotherapeutic experiments is possible. Since it is not "logistically" feasible to run all possible variations of these methods for each compound, it is conceivable that the activity of a highly specific drug, effective against a certain tumor in a certain strain of mouse under certain conditions of administration, would be missed in arbitrarily selected procedures. It is more reasonable to assume, however, that a therapeutically active substance will have a broad range of activity, even though its effectiveness within this range may vary considerably. On the latter basis a number of arbitrarily designed testing technics

- The Research Attack on Cancer. A report on the American Cancer Society Research Program by the Committee on Growth of the National Research Council.* 16 pp Washington D C 1946
- Haddow A. Note on chemotherapy of cancer *Brit M Bull* 4 417-426 1947
- A A A S Research Conference on Cancer. A conference of papers and discussions presented at the summer meeting of the American Association for the Advancement of Science at Gibson Island, Maryland, July 31-August 4, 1944.* Edited by F R Moulton 333 pp Washington D C American Association for the Advancement of Science 1945
- Approaches to Tumor Chemotherapy.* Edited by F R Moulton 442 pp Washington, D C American Association for the Advancement of Science, 1947
- Hoggins C. Chemotherapy of cancer *Surg, Gynec & Obst* 85 660-662 1947
- Reinhard E H Artificially prepared radioactive isotopes as means of administering radiation therapy *Am J Roentgenol* 58 757-770 1947
- Brues A M and Jacobson L O Comparative therapeutic effects of radioactive and chemical agents in neoplastic diseases of hematopoietic system. *Am J Roentgenol* 58 774-782 1947
- Klyceva, N G Paths of cancer biotherapy *Am Rev Soviet Med.* 4 40-414 1947
- Spurr C L, Smith, T R., and Jacobson L O Chemotherapy in human lymphomas leukemias and allied disorders of hematopoietic system *Radiology* 50 387-393 1948
- Karnofsky D A Bases for cancer chemotherapy *Stanford M Bull* 6 257-269 1948
- Burk, D Foreword. *Approaches to Tumor Chemotherapy*
- Greene J P *Biochemistry of Cancer* 389 pp New York Academic Press Inc., 1947
- Algire G H Transparent chamber technique as tool in experimental tumor therapy. In *Approaches to Tumor Chemotherapy* p 19
- Oberling C. *The Riddle of Cancer* Translated by William H Woglom. 196 pp New Haven Yale University Press 1944
- Sack, C C, and Rhoads C P Experimental evaluation of chemotherapeutic agents in cancer. *Bull New York Acad Med* (in press)
- Shear M J Some aspects of joint institutional research program on chemotherapy of cancer: current laboratory and clinical experiments with bacterial polysaccharide and with synthetic organic compounds. I. Scope of program. In *Approaches to Tumor Chemotherapy* p 236-247
- Larzel D., and Leuchtenberger C. Rapid test for tumor growth inhibitors. *Cancer Research* 3 401-410 1943
- Boyland, E., and Mawson E H. Experiments on chemotherapy of cancer II. Effect of aldehydes and glucosides. *Biochem J* 32 1982-1987 1938
- 21 Bowland E. Experiments on chemotherapy of cancer I. Effect of certain antibacterial substances and related compounds. *Biochem J* 32 1207-1213 1938
- 22 Sugura K., and Benedict, S R. Influence of insufficient diets upon tumor recurrence and growth in rats and mice. *J Cancer Research* 10 509 518 1926.
- 23 Bass A D., and Freeman, M L H. Regression of lymphosarcoma produced by interperitoneal administration of 90% ethyl alcohol. *Science* 107 114 1948
- 24 Flory, C M, Furth J., Saxton J A., Jr., and Reiner L. Chemotherapeutic studies on transmitted mouse leukemia. *Cancer Research* 3 729-743 1943
- 25 Flory C M. Effects of therapeutic agents on human and mouse leukemia. In *A A S Research Conference on Cancer* p 291-709
- 26 Burchenal J H, Lester R A., Riley J B., and Rhoads C P. Studies on chemotherapy of leukemia. I. Effect of certain nitrogen mustards and carbamates on transmitted mouse leukemia. *Cancer* (in press)
- 27 Burchenal, J H Personal communication.
- 28 Karnofsky D A, Burchenal, J H., Ormsbee R A., Cornman I., and Rhoads C P. Experimental observations on use of nitrogen mustards in treatment of neoplastic diseases. In *Approaches to Tumor Chemotherapy* p 293-305
- 29 Little, P H, Sampath A., Paganelli V, Locke E., and Subbarow V. Effect of folic acid and its antagonists on Rous chicken sarcoma. *Tr New York Acad Sc* (Spec No Ser 11) 10 91-98 1948
- 30 Karnofsky D A, Parsette, L M, Patterson P A., and Jacques, J A. Behavior and growth of homologous and heterologous normal and neoplastic tissues on chick embryo and influence of various agents on tumor growth. *Fourth International Cancer Research Congress* September 1947 p 86
- 31 Johnson E P. Nitrogen mustards in fowl leukosis. *Science* 107 40-42, 1948
- 32 Ormsbee R A, Cornman I and Berger R E. Effect of podophyllin on tumor cells in tissue culture. *Proc Soc Exper Biol & Med* 66 586-590 1947
- 33 Sugura, K. and Chesley L C. Effect of heavy water (deuterium oxide) on viability of mouse sarcoma and melanoma. *Proc Soc Exper Biol & Med* 31 659-661 1934
- 34 Cohen A L, Borsook, H., and Dubnoff J W. Effect of *procarbazone* preparation on tumor cells *in vivo*. *Proc Soc Exper Biol & Med* 66 440-444 1947
- 35 Singher H O, Kensler C J, and Rhoads C P. Effect of various agents on normal and malignant tissues. In *A A S Research Conference on Cancer* p 310-320
- 36 Karnofsky D A and Burchenal J H. Clinical evaluation of chemotherapeutic agents in cancer. *Bull New York Acad Med* (in press)

## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

TRACY B MALLORY, M D, *Editor*

BENJAMIN CASTLEMAN, M D, *Associate Editor*

EDITH E PARRIS, *Assistant Editor*

### CASE 34321

#### PRESENTATION OF CASE

A fifty-five-year-old businessman entered the hospital because of abdominal pain and vomiting. One night six weeks before admission the patient awoke feeling nauseated and subsequently vomited several times. There was no pain. Business and family worries had been plaguing him and for several months he had felt tense and nervous. After this episode he remained in bed four days and then returned to work. Late at night, following days on which financial problems had been particularly trying, spells of painless vomiting would recur. Two weeks before admission he left work. The nocturnal

vomiting became more frequent and began to be accompanied by severe cramps, starting in the back and radiating around to the midline in a vise-like manner. He was given pills and put on a bland diet without relief. Two days before admission the frequency of vomiting increased to every two or three hours, no food or fluid was retained. The vomitus consisted of food, fluid and mucus without blood. The bowels had been moving only with laxatives or with enemas. The stools were of normal color. During this illness there was a 25-pound weight loss.

During examination the patient was tense and uncomfortable, constantly shifting position in an effort to relax. When activity reached a peak, he vomited. The speech was rambling, and he had difficulty recalling dates and time. The heart was normal. There was dullness over the left lower lobe posteriorly and in the left axilla, breath sounds and tactile fremitus being reduced in the same areas. The abdomen showed tenderness and spasm throughout the epigastrium. Peristalsis was active. There were no masses.

The temperature was 98.6°F, the pulse 88 and the respirations 20. The blood pressure was 135 systolic, 90 diastolic.

Examination of the blood revealed a white-cell count of 9600. The hemoglobin was 14.6 gm. There was a + test for albumin in the urine, and rare casts were found. The icteric index was 13.

of the virus. Similar studies have been conducted with fowl leukosis in chicks.<sup>31</sup>

Several types of technics have been used *in vitro* to measure the toxicity of certain agents to neoplastic cells, or to detect a selective toxicity to neoplastic tissue by comparison with normal tissue of similar origin. These procedures are particularly useful when only small amounts of the test substance are available.

**Tissue culture.** Normal and neoplastic cells are explanted under similar conditions, and the effects of the test substances, as measured by their lethal effect or a specific type of cellular injury to the explant, are determined. The susceptibility of normal and neoplastic cells to the test substance is compared, and the procedure may reveal an agent selectively injurious to neoplastic cells. Ormsbee, Cornman and Berger<sup>32</sup> have described a method of grading the condition of explanted tissues, so that a numerical index of injury can be obtained. The ratio between the injury produced by a given agent in the neoplastic and in the normal tissue is known as the "selective index."

**Chemical toxicity.** Sugiura<sup>33</sup> and others have placed small pieces of mouse tumor in a solution of the test agent for a prescribed period at certain temperatures (one test is run at 2 to 4°C for twenty-four hours), after which the fragments are assayed for viability in susceptible mice. The index of effect is the percentage of "takes" and their rate of growth. This method measures the toxicity of chemicals to cells, but it provides no evidence for a selective effect on tumor cells. Another variation in this method is to place slices of tumor tissue and of normal liver tissue in serum containing the test substance at 37°C for twenty-four hours and then to examine the tissues histologically.<sup>34</sup> A selective effect is shown if the normal tissue appears unaltered in the presence of damaged neoplastic tissue.

**Metabolic studies *in vitro*.** Suspensions or slices of normal and neoplastic tissue are placed in the Warburg apparatus, and the test substances are added. Selective inhibition of the tissue respiration of the neoplastic compared with the normal tissue is the measure of effect.<sup>35</sup>

None of the methods in use appear to be entirely satisfactory in disclosing agents that have a selective action on tumor cells. One of the important fields in cancer research is the development of more precise methods for testing substances in the laboratory for chemotherapeutic activity.

#### CLINICAL TESTING OF CHEMOTHERAPEUTIC AGENTS

The clinical investigation of various substances for therapeutic activity in cancer still remains, in large part, a program distinctly separate from the laboratory "screening procedures." Most of the laboratory procedures are designed to disclose substances that are selectively injurious to tumor cells,

either temporarily damaging, or inhibiting, or destroying neoplastic cells in the presence of normal cells. The discovery of such substances in the laboratory and subsequent proof of their effectiveness in patients with cancer would be of extreme importance to the clinician. In the meantime, the clinician is faced with the problem of palliating or attempting to control definite clinical entities that fall in the category of neoplastic diseases. He cannot depend entirely on the laboratory "screening" results to give him substances for therapeutic trials; he must be able to borrow from the fields of biochemistry, pathology, physiology, pharmacology, endocrinology and toxicology. For example, certain cancers may be controlled by influencing the non-neoplastic properties of cells persisting from their tissue of origin; this technic is particularly effective if the tissue from which the cancer arises is not essential to life. Without undue injury to the organism, the prostate may involute almost completely, in some cases, with stilbestrol therapy, or the thyroid gland may be severely damaged by radioactive iodine through its ability to concentrate iodine selectively, if cancers, arising from these tissues, retain their characteristic physiologic properties; they will also be adversely affected by these agents. General cell poisons may depress certain neoplastic cells to a greater degree and for a longer period than they depress the normal tissue of their origin and, thereby, produce some clinical benefit. Secondary manifestations of tumor growth may be combated by general therapeutic measures appropriate for the organ or system involved or for the physiologic derangement present. The clinician will therefore obtain suggestions for clinical trials from many sources, of which a relatively limited one, at present, is the laboratory screening program.

If a compound is to be studied clinically, pharmacologic data and, if obtainable, the mechanism of action *in vivo* should be available before the treatment of patients is begun. It is apparent that a more complete, coherent and critical clinical study can be carried out if there is some indication of how the patient and disease will be affected by the agent. Experience has shown that the clinical evaluation of an agent producing only palliative effects may be an extremely difficult project, an effective form of therapy may be overlooked owing to an inadequate clinical trial, and ineffective treatments have been used for many years because of the lack of a convincing body of negative data. These problems are well known to clinicians familiar with cancer, and they have recently been discussed in detail.<sup>36</sup>

#### REFERENCES

1. Woglom, W. H. General review of cancer chemotherapy. In *Approaches to Tumor Chemotherapy*. Pp. 1-12.
2. Shimkin, M. Research activities of National Cancer Institute. *J Nat Cancer Inst* 5:77-88, 1944.

rampy' pains in the back suggest penetration of an ulcer in the pancreas. The tenderness in the epigastrium can again be caused by a penetrating ulcer. Many hold an opinion that tenderness does not occur with a duodenal ulcer until there is penetrating involvement of either the pancreas or peritoneal surface of the duodenum. So much for the ulcer. It will not explain such things as the fluid in the chest, the mass in the midepigastrium, and probably the jaundice.

What next? Gallstones should be considered. The patient had recurrent pains in the back and whenever one elicits this fact one must think of gallstones as well as peptic ulcer. Moreover, with this recurrent periodic pain there was associated nausea and vomiting. If jaundice appears, it is even more suggestive of gallstones obstructing the common duct. Unfortunately, there should have been fever and leukocytosis for the diagnosis of gallstones. Unless there were complications from the gallstones, he should not have had this mass in the midepigastrium and the fluid. One could suggest that the gallstone had perforated into the lesser omental cavity, and that the patient then developed an abscess of the lesser omental cavity. It could then cause inflammatory obstruction of the common duct and perhaps extension of fluid through the left leaf of the diaphragm. We might even consider that because of this mass the splenic vein had been involved with thrombosis and, ergo, a large spleen. It is a good story but we have no elevation of the white-cell count and no fever to go with it.

Another possibility is that a person with severe pain in this region and a mass, which might be a pancreatic cyst, could have chronic recurrent pancreatitis or acute pancreatitis. So far as acute pancreatitis is concerned, this man was sick enough but he did not have a high white-cell count, he did not have a high temperature, he had no board-like abdomen—in fact, nothing to go with acute pancreatitis except for the serum amylase of 78 units. In this hospital the serum amylase is so variable that we cannot put much emphasis on a single determination. If we had had another determination, either twelve or twenty-four hours before that, and if it had been approximately 30 units, or another twenty-four hours later and had it been around 125 to 150 units, we could say that the serum amylase was significant. This 78 units was an isolated reading. A determination of 50 or 55 units is considered the upper limit of normal. With an amylase of 78 units if we wanted to "go out on a limb," we could say that this man had pancreatitis. So we are left somewhat in a quandary.

I have covered the essentials of my differential diagnosis and I still have not considered one point, that is, the rambling speech and difficulty in recalling dates and time. I am frankly stumped as to how to explain these neurologic changes. It is possible that excessive electrolyte depletion due to the

vomiting was the basis for this neurologic manifestation. We know that some decompensated cardiac patients, who are treated intensively with salt restriction and dehydration, are "out in left field" because of hyponatremia.

I am sure I shall be wrong but I am going to say that he had carcinoma of the pancreas, with possible involvement of the splenic vein and thrombosis to explain the enlarged spleen, metastases to the left pleura to explain the fluid in the left chest and that he developed a cyst of the pancreas, secondary to the cancer.

#### CLINICAL DIAGNOSIS

Acute pancreatitis?

#### DR CULVER'S DIAGNOSES

Carcinoma of pancreas

Pancreatic cyst.

Metastatic cancer of left pleura

Splenomegaly due to thrombosis of splenic vein

#### ANATOMICAL DIAGNOSES

*Carcinoma of pancreas, with extension to stomach, transverse colon, and spleen, with metastases to retroperitoneal lymph nodes, lungs and kidney*

Hydrothorax, bilateral

Pulmonary atelectasis, left lower

Operations cholecystostomy and jejunostomy

#### PATHOLOGICAL DISCUSSION

DR BENJAMIN CASTLEMAN. The preoperative diagnosis was acute pancreatitis. The surgeon found a large amount of bloody fluid in the abdomen and extensive induration of fat, especially along the lesser curvature of the stomach, with small nodules more suggestive of fat necrosis than carcinoma. The liver appeared normal. The spleen was twice the normal size to palpation, but it was not visualized. The gastroduodenal omentum was opened and the pancreas carefully palpated. It was enlarged and indurated throughout. The gall bladder seemed thick, but he did not believe that it was diseased. A cholecystostomy and a jejunostomy were done—the latter for feeding purposes.

A biopsy of one of the nodules that the surgeon thought might be fat necrosis turned out to be carcinoma, but we could not tell where the tumor was primary.

The patient died a few days later, and at autopsy we found the stomach fairly well fixed. On the lesser curvature and the posterior wall was a large mass that extended to the left, up to the hilus of the spleen. All the retroperitoneal nodes along the aorta and beneath the stomach were involved with tumor. On opening the stomach we found that the mass adherent to the posterior wall did not involve the mucosa and was entirely extrinsic. The mass proved to be the pancreas involved from head to tail with

The patient was tense and frequently nauseated but appeared to obtain considerable relief from hot baths so that he stopped vomiting and was able to drink water. On the third hospital day the skin and scleras were slightly jaundiced. A surgical consultant found a tender mass in the epigastrium, extending to both sides of the midline but slightly more to the left. The edges of the mass were indefinite, the whole mass was about 15 cm in diameter. Rectal examination was negative. On the same day the gastrointestinal series showed some thickening of the gastric folds, and there was evidence of pressure along the lesser curvature and the posterior wall. The duodenal loop was enlarged, the second portion was displaced to the right and showed evidence of somewhat lobulated compression from the region of the pancreas, which also displaced the third portion of the duodenum downward. There were several diverticula in the colon. The spleen was enlarged. There was considerable fluid in the left pleural cavity. Linear areas of atelectasis showed in both lower lobes of the lungs, and motion of both leaves of the diaphragm was slightly limited. On the following day the icteric index was 25, and the serum amylase was 78 units per 100 cc. Three hundred and fifty cc of opaque, amber fluid, which proved to be sterile, was removed from the left chest. The temperature remained normal.

An operation was performed on the fifth hospital day.

#### DIFFERENTIAL DIAGNOSIS

**DR PERRY CULVER** In discussing this case I shall start with certain features that stand out as signposts toward arriving at a diagnosis. The first is a mass in the upper abdomen, in the region of the pancreas, if we can believe what the x-ray examination appeared to show. Perhaps at this time we should view the films to see if my conception of this mass is true.

**DR STANLEY M WYMAN** The films of the chest show rather definite pleural effusion on the left. The left main bronchus is perhaps displaced slightly downward. One can see no definite defect in its lumen. There is some atelectasis at the right base, and the changes in the left are probably partially the result of considerable atelectasis in the left lower lobe. The heart shadow does not appear definitely abnormal. The most striking change in this patient's examination lies in the duodenal loop, which is displaced laterally in the second portion and manifests a fairly constant contour in this region. Two spot films of that area confirm this impression and show what appears to be a somewhat lobulated mass pressing into the lumen at this point. Downward displacement of the third portion of the duodenum is seen. The displacement of the stomach I cannot see on these films but it may have been seen by the fluoroscopist. The large spleen extends downward

to this point. I can see no evidence of actual bony destruction.

**DR CULVER** Can you see evidence of metastases anywhere in the lung to account for the fluid?

**DR WYMAN** No, simply fluid, without definite evidence of intrinsic disease except for atelectasis.

**DR CULVER** The discovery of this mass three days after the initial physical examination when no mass had been found makes one wonder if this tender mass in the midepigastrium appeared suddenly overnight.

The second salient point is the sudden appearance of jaundice. Since the mass is in the general region of the common bile duct, the possibility of obstruction of the duct is suggested.

The third point that one has to bring into the picture is the rather marked weight loss of 25 pounds in approximately six weeks. Apparently the patient had retained most of the ingested food until two days before admission, so that he did not lose the 25 pounds because of limited food intake or from vomiting.

The fourth point is the fluid in the left chest. These four facts have to be reconciled with what was apparently a consistently normal temperature, a normal white-cell count, and no anemia. We also have to try to fit the enlarged spleen into the picture.

When I read this abstract over, I immediately thought that the mass, the jaundice and the marked weight loss were the three salient points for carcinoma of the pancreas. One can add to such possibilities that of fluid in the left chest from metastasis to the pleura. Then, because of the sudden appearance of the mass in the midepigastrium, where no mass had been felt three days before, one could postulate that there was sudden development of a cyst of the pancreas. It is rather common for a cyst of the pancreas to develop on the basis of carcinoma. I would like to speculate that there had been a hemorrhage or bleeding into the cyst to account for its rapid increase in size. While carcinomas of the pancreas are statistically one of the common causes of painless jaundice, approximately 50 per cent of all carcinomas of the pancreas cause pain. Many cause back pain, which is most severe. Often an erroneous diagnosis of psychoneurosis is made because no one can explain the back pains until the diagnosis finally becomes evident post mortem.

If these were all the facts, the diagnosis would be easier, but we have to consider other things. What is the relation of his mental status to the symptomatology? The business and family worries gave this man a perfect background for peptic ulcer. The psychosomatic experts on duodenal ulcer say that people with the ulcer type of personality remain asymptomatic as long as either their business or their family life runs smoothly. When both are disturbed ulcers develop. This man had both things to plague him. The fact that he had a recurrence under stress also suggests an ulcer. In addition, the

ampy pains in the back suggest penetration of an ulcer in the pancreas. The tenderness in the epigastrium can again be caused by a penetrating ulcer. Many hold an opinion that tenderness does not occur with a duodenal ulcer until there is penetrating involvement of either the pancreas or peritoneal surface of the duodenum. So much for the ulcer. It will not explain such things as the fluid in the chest, the mass in the midepigastrium, and probably the jaundice.

What next? Gallstones should be considered. The patient had recurrent pains in the back and whenever one elicits this fact one must think of gallstones as well as peptic ulcer. Moreover, with this recurrent periodic pain there was associated nausea and vomiting. If jaundice appears, it is even more suggestive of gallstones obstructing the common duct. Unfortunately, there should have been fever and leukocytosis for the diagnosis of gallstones. Unless there were complications from the gallstones, he should not have had this mass in the midepigastrium and the fluid. One could suggest that the gallstone had perforated into the lesser omental cavity, and that the patient then developed an abscess of the lesser omental cavity. It could then cause inflammatory obstruction of the common duct and perhaps extension of fluid through the left leaf of the diaphragm. We might even consider that because of this mass the splenic vein had been involved with thrombosis and, ergo, a large spleen. It is a good story but we have no elevation of the white-cell count and no fever to go with it.

Another possibility is that a person with severe pain in this region and a mass, which might be a pancreatic cyst, could have chronic recurrent pancreatitis or acute pancreatitis. So far as acute pancreatitis is concerned, this man was sick enough but he did not have a high white-cell count, he did not have a high temperature, he had no board-like abdomen—in fact, nothing to go with acute pancreatitis except for the serum amylase of 78 units. In this hospital the serum amylase is so variable that we cannot put much emphasis on a single determination. If we had had another determination, either twelve or twenty-four hours before that, and if it had been approximately 30 units, or another twenty-four hours later and had it been around 125 to 150 units, we could say that the serum amylase was significant. This 78 units was an isolated reading. A determination of 50 or 55 units is considered the upper limit of normal. With an amylase of 78 units if we wanted to "go out on a limb," we could say that this man had pancreatitis. So we are left somewhat in a quandary.

I have covered the essentials of my differential diagnosis and I still have not considered one point, that is, the rambling speech and difficulty in recalling dates and time. I am frankly stumped as to how to explain these neurologic changes. It is possible that excessive electrolyte depletion due to the

vomiting was the basis for this neurologic manifestation. We know that some decompensated cardiac patients, who are treated intensively with salt restriction and dehydration, are "out in left field" because of hyponatremia.

I am sure I shall be wrong but I am going to say that he had carcinoma of the pancreas, with possible involvement of the splenic vein and thrombosis to explain the enlarged spleen, metastases to the left pleura to explain the fluid in the left chest and that he developed a cyst of the pancreas, secondary to the cancer.

#### CLINICAL DIAGNOSIS

Acute pancreatitis?

#### DR. CULVER'S DIAGNOSES

Carcinoma of pancreas

Pancreatic cyst.

Metastatic cancer of left pleura

Splenomegaly due to thrombosis of splenic vein

#### ANATOMICAL DIAGNOSES

*Carcinoma of pancreas, with extension to stomach, transverse colon, and spleen, with metastases to retroperitoneal lymph nodes, lungs and kidney*

Hydrothorax, bilateral

Pulmonary atelectasis, left lower

Operations: cholecystostomy and jejunostomy

#### PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: The preoperative diagnosis was acute pancreatitis. The surgeon found a large amount of bloody fluid in the abdomen and extensive induration of fat, especially along the lesser curvature of the stomach, with small nodules more suggestive of fat necrosis than carcinoma. The liver appeared normal. The spleen was twice the normal size to palpation, but it was not visualized. The gastrocolic omentum was opened and the pancreas carefully palpated. It was enlarged and indurated throughout. The gall bladder seemed thick, but he did not believe that it was diseased. A cholecystostomy and a jejunostomy were done—the latter for feeding purposes.

A biopsy of one of the nodules that the surgeon thought might be fat necrosis turned out to be carcinoma, but we could not tell where the tumor was primary.

The patient died a few days later, and at autopsy we found the stomach fairly well fixed. On the lesser curvature and the posterior wall was a large mass that extended to the left, up to the hilus of the spleen. All the retroperitoneal nodes along the aorta and beneath the stomach were involved with tumor. On opening the stomach we found that the mass adherent to the posterior wall did not involve the mucosa and was entirely extrinsic. The mass proved to be the pancreas involved from head to tail with

cancer The tumor had extended into the spleen and what was believed to be a large spleen was spleen plus tumor The tumor had also extended to the transverse colon and microscopically there were metastases to the lung and kidney The shadow in the left-lower lung field seen on the x-ray examination was 2 liters of clear fluid with compression atelectasis of the left lower lobe There was also a liter of fluid in the right pleural cavity An interesting incidental finding microscopically was an islet of Langerhans in the pancreas about five times the normal size It may have been a section through a small adenoma that was not recognized grossly because of the widespread carcinomatous invasion

Unfortunately we were not permitted to examine the brain, but it is not uncommon for patients with carcinoma of the pancreas to have mental symptoms without evidence of cerebral metastases Why, no one knows

A PHYSICIAN Was a blood sugar done?

DR CASTLEMAN No The urine did not contain any sugar

A PHYSICIAN How about the nonprotein nitrogen?

DR CASTLEMAN It was normal I believe that the elevated amylase can be explained by the extensive involvement of the pancreas by tumor

DR CULVER The more of these cases we see, the more I am impressed with how varied and bizarre the symptomatology can be I remember one case that I saw in consultation as a problem in vitamin deficiency because the patient had numbness and tingling of the toes He had been treated with larger and larger doses of vitamins without relief of his peripheral neuritis He also had pain in the back No one paid any attention to it When he died a year later a carcinoma of the pancreas was found at autopsy as the probable cause of the difficulty A great many of these people who have carcinoma of the pancreas are diagnosed as psychoneurotics for a period of time They have vague backaches, the x-ray films are normal, and they have all sorts of symptoms, but no one is able to fit them into any syndrome One should become sensitized to the possibility of carcinoma of the pancreas How to prove it is another story

DR CASTLEMAN It is interesting that the man who interpreted these x-ray films originally concluded "The findings are those of a mass in the region of the pancreas I would think that the entire pancreas was involved and although carcinoma cannot be definitely excluded, pancreatitis with involvement of the lesser omentum would be my first choice" That is what probably influenced the surgeon in making the preoperative diagnosis

DR CULVER Was the mass cystic or solid?

DR CASTLEMAN It was a very necrotic tumor

DR CULVER That is probably the reason it was tender

## CASE 34322

### PRESENTATION OF CASE

A thirty-seven-year-old Negro was admitted to the hospital complaining of progressive blindness, proptosis of the left eye and pain in the left supraorbital region

One month prior to entry he was admitted to another hospital with similar complaints of about one week's duration A note from that hospital concerning the patient reported that x-ray examination had revealed sinusitis X-ray studies of the skull were negative A spinal puncture revealed normal pressure and cell count, with a negative globulin reaction The gold-sol curve was 0000000000 The Wassermann reaction was positive A blood culture was negative Two weeks following admission to the other hospital an acute epididymitis developed and he was subsequently transferred to this hospital

On physical examination the patient was obviously acutely ill There were proptosis of the left eye and complete bilateral nasal obstruction, with a cheesy purulent material in the vestibules A left external ethmoid incision was present, and the sinuses were dark to transillumination The soft palate was pushed downward and forward, and the soft and hard palate were both swollen and indurated A Caldwell-Luc incision was present on the left side The chest and abdomen were negative The left testicle was enlarged to about the size of a small orange and did not transmit light Examination in the Eye Clinic revealed retention of ability to project light accurately in the right eye, with total blindness on the left Impairment of ability to move the eyes laterally and some loss of power to move the muscles supplied by the seventh nerve were also noted

The temperature was 103.4°F The blood pressure was 90 systolic, 60 diastolic

Examination of the blood showed a red-cell count of 3,680,000, with 11.8 gm of hemoglobin, and a white-cell count of 6300, with 75 per cent neutrophils The urine sediment contained 8 to 10 white cells per high-power field Spinal puncture revealed an initial pressure equivalent to 170 mm of water, with a total protein of 172 mg per 100 cc The sugar was 63 mg per 100 cc, and a cell count showed 480 white cells per cubic millimeter, with 39 per cent polymorphonuclears and 61 per cent lymphocytes A gold-sol curve was 0011233210 X-ray films of the chest were normal Those of the skull disclosed no enlargement of the sella turcica X-ray examination of the sinuses revealed that the cell partitions of the ethmoid sinuses were gone and all sinuses showed a soft-tissue density A large nasopharyngeal mass extended anteriorly into the nasal cavities All sinuses, including the sphenoid, were full Cultures from the nose, throat and left ethmoid showed *Staphylococcus aureus*

Following admission the patient's condition grew steadily worse, he became disoriented, and x-ray therapy was started. The patient improved somewhat for a short time but after about two weeks began to suffer from abdominal distention. He became steadily weaker and died after approximately one month in the hospital.

#### DIFFERENTIAL DIAGNOSIS

DR GRANTLEY W TAYLOR I am probably here because I know very little about tumors of the nose and throat and eye. This is fairly obviously a problem of neoplasm. It is worth while to make a few general remarks on the subject because I cannot go into the elaborate details of histology in these cases.

This thirty-seven-year-old man had a rather acute course. The first evidence of anything wrong, from his viewpoint, was progressive loss of vision and proptosis of the eye and pain in the superior orbital area that initially took him to another hospital, where, I presume, a diagnosis was made of chronic infection involving the accessory sinuses, probably primarily the ethmoid. We see this evidence of ethmoid disease in an occasional case, namely, disturbance of vision and proptosis of the eye and headache. It is consistent with a diagnosis of infection. However, the findings at the other hospital were not consistent with the diagnosis of infection primarily. He had a normal chart and a normal leukocyte count, and even if it was obvious that the disease was more in the nature of a chronic non-inflammatory process, the evolution was rapid after he entered the other hospital. He had two operations, one, we know, was an ethmoid operation, the scar of which was visible when he came here. The other was a Caldwell-Luc incision. By the time he arrived here there was no question that he had tumor of marked extent. The palate was pushed downward, the nares were obstructed, and there were blindness of the left eye and proptosis. Obviously he had a tumor mass originating in the general vicinity of the nasopharynx or the ethmoid area, with probable direct extension into the orbit and probable further extension through the orbital foramen into the base of the skull. When he came here he had a great deal of evidence of neurologic disturbance around the head and base of the skull, which could be interpreted not so much as due to pressure from the tumor as probably the result of direct invasion. He had no elevation of white-cell count but he had a temperature. He had a gold-sol curve and white cells

in the spinal fluid, and we must assume that he had a direct local meningitis due to progress of the tumor and introduction of infection through the base of the skull.

I should like to look at the x-ray films and have Dr Wyman point out the soft-tissue masses that are described. Interpretation of x-ray films of the sinuses is a highly specialized art.

DR STANLEY M WYMAN The soft-tissue thickening in the posterior nasopharynx is best seen in the lateral view and is confined chiefly to the roof of the nasopharynx in this area. There is soft-tissue density extending upward and obliterating the normal ridges of the sphenoid and wiping out completely the normal cell partitions in the ethmoid sinuses. With a strong light one can see soft tissue extending far forward into the posterior nares. There is probably some haziness in the frontal sinuses, although this is less definite. A frontal projection shows density in both ethmoid sinuses, with complete loss of the cell walls and probably some hazy density in the frontal sinuses. This position shows a soft-tissue density overlying the left orbit, a fairly definite mass extending upward where the left eye is being pushed forward. A view of the floor of the skull shows density in both ethmoid sinuses of rather uniform, hazy character, showing only a small airway far posteriorly. I can see no definite bone destruction, however.

DR TAYLOR We are confronted with a rapid evolution of a large tumor mass that fills the nasal passages, the nasopharynx and the accessory sinuses and that has destroyed bone, and it seems to me that the only conclusion one can derive is that we are dealing with a rapidly growing and highly malignant neoplasm. What is the nature of it? When this point is reached all one can say is that the answer is something the microscope alone can give. We have a number of rapidly growing and highly malignant tumors that may occur in this area. They may be primarily carcinoma, ordinarily either in the sinuses or in the pharynx, and there are also sarcomas seen in this area. Which of these we are dealing with in this case is largely a matter of guess. It is interesting that although there is no specific description of the neck, we can probably assume that there is nothing in the way of metastases to the regional lymph nodes. We know that these rapidly growing carcinomas in this general area are prone to form early bilateral cervical-lymph-node metastases. We have an x-ray examination of the

chest during the terminal illness, which showed no evidence of dispersion of the disease. Both these factors, I think, argue considerably against a carcinoma and in favor of a sarcoma. It is largely a matter for the pathologist to decide.

The clinician was confronted in this case with the problem of what to do about it. Quite obviously with disease as extensive as that described here in the physical examination and as revealed by x-ray study, the only hope was that we were dealing with a tumor highly sensitive to radiation. Accordingly, this method of treatment was undertaken, in spite of which there was no particular improvement. It seems to me that if this sarcoma, as I have said, was of the lymphocytic series, Hodgkin's disease or lymphoblastic type, there would probably have been an initial very gratifying and rapid response. Such does not seem to have been the case. It seems, therefore, more reasonable to say that this is perhaps a sarcoma of the neurogenic group — a neurofibrosarcoma or a glioma or one of those tumors.

I cannot go very much farther than that, Dr Mallory. The lesson, I think, is that when anybody has a bizarre cold with sinus infection that does not respond to ordinary, reasonable measures, the possibility of a diagnosis of neoplasm should be entertained. The more we look for this the more likely we are to find it at an early stage. In this case even if the diagnosis had been made initially, the man's "goose was cooked."

DR TRACY B MALLORY: I think the abstract is misleading. There is a note to the effect that the local tumor had responded fairly well to radiation, but two days later the patient died.

DR TAYLOR: I still will be glad to hear what you found.

A PHYSICIAN: How about the possibility of tumor primary in the testicle with metastasis to the brain, such as a chorioepithelioma?

DR TAYLOR: It is nice of you to bring it up. I wondered if we should discuss the possibility of metastatic carcinoma. It is highly unlikely. We have, in a few cases, seen that occur — localized metastatic neoplasm. I did not consider this necessarily a tumor of the testis, even though it did not transmit light. He had an acute epididymitis two weeks after admission to the other hospital. In other words, we could say that the testicle was innocent at the time of the initial physical examination, when the disease in the nasopharynx was well along. That is the only physical finding other than the local

one that could be implicated. One could also say that he had a renal-cell carcinoma with a solitary metastasis and never showed anything in the kidney. That is also possible, but we would not be dealing with the facts as presented.

A PHYSICIAN: Can you rule out gumma in view of the positive Wassermann test?

DR TAYLOR: I gave some thought to gumma but was inclined to pay not a great deal of attention to it. I do not believe that a gumma would evolve so rapidly and give rise to such an extensive soft-tissue mass as he had. I am not expert enough in relation to the gold-sol test and that sort of thing to say that the gold-sol curve is not consistent with a syphilitic disease. But it seems to me that he suffered from probable pyogenic localized invasion of the meninges around the base of the brain, which accounted for some of the seventh-nerve weakness and the impaired ocular motor functions on the other side and so forth.

DR JOSEPH C AUB: I did not see this patient but I am intrigued by Dr Taylor's discussion of the metastases. Are not tumors in this area prone to go to the brain? Do you not believe that this was a metastasis to the brain?

DR TAYLOR: I would say direct extension rather than metastasis.

DR AUB: The x-ray therapy might well have been of influence.

DR TAYLOR: You mean on the ground that x-ray treatment might have made it worse?

DR AUB: Yes, it may have facilitated the spread of infection.

DR TAYLOR: He had this ethmoid trouble before x-ray treatment was started. As I read it I thought that the infection was already there. Whether x-ray therapy would facilitate the transmission of infection, I do not know.

DR WYMAN: It is quite consistent, as Dr Taylor said, with a malignant lesion in the posterior nasopharynx invading the sinuses, and from the point of view of x-ray therapy one can go no farther than to say that it is probably malignant neoplasm.

#### CLINICAL DIAGNOSIS

Malignant tumor involving nasal chambers, ethmoid and sphenoid sinuses, left lateral and anterior nasal walls, nasopharynx, hard and soft palate and left periorbital tissue.

## DR TAYLOR'S DIAGNOSIS

Sarcoma, type undetermined

## ANATOMICAL DIAGNOSES

*Malignant lymphoma (stem-cell type), with involvement of nasopharynx, air sinuses, left orbit, base of skull, retroperitoneum, left testicle, left kidney and pancreas*  
*Extradural abscess, right middle fossa*

## PATHOLOGICAL DISCUSSION

DR MALLORY A biopsy of this tumor was done before x-ray treatment was started. I did not consult Dr Taylor with that because our report on it was that the tumor was extremely variable in appearance. In some areas it suggested plasma-cell myeloma, in other areas neuroblastoma, and in still other areas lymphoblastoma. We were unable on the biopsy to make any diagnosis more specific than extremely malignant neoplasm.

At autopsy we found this large tumor mass involving the entire nasopharyngeal region and the sinuses. It had partially eroded and markedly thinned the bone at the base of the skull, particularly the wings of the sphenoid, and extended into the orbit and the nares. The blindness was due to a direct involvement of the optic nerve. We also found considerable tumor elsewhere in the body. The testis was involved with tumor and all the retroperitoneal tissues were a massive sheet of tumor. Tumor infiltration had obliterated all the retroperitoneal lymph nodes surrounding the aorta, had encapsulated both adrenal glands, invaded the kidneys at one spot, and surrounded and invaded the pancreas. The only suggestion of this extensive abdominal involvement in the physical examination was the vague description of distention of the

abdomen. There was enough tumor in the retroperitoneal tissues to explain the distention, and I imagine no isolated tumors could be felt.

From the histologic appearance of the tumor, the diagnosis is still, I think, a matter of some question. The distribution puzzled us quite a bit, it was essentially the distribution of lymphomatous tumor and the histology is consistent with that. We finally called it a reticulum-cell sarcoma of a very undifferentiated type. The possibility of plasma-cell myeloma was seriously considered at autopsy because the nasopharynx is the one spot in the body where plasma-cell myeloma or plasmacytomas are common outside the bone marrow. There was, incidentally, diffuse involvement of the bone marrow with multiple small foci of tumor.

DR TAYLOR He did not have an anemia so marked as to suggest that type of disease?

DR MALLORY The anemia may have progressed during his stay in the hospital. I think we have very little evidence on that. During all the early period in the first hospital, and even for several days in this hospital, this was considered to be an inflammatory process. The possibility of sinus thrombosis was seriously considered and the thought of neoplasm occurred a little bit later. There was secondary infection of the tumor and this infectious process had extended through the sphenoid and produced a localized, extradural abscess, but there was no true meningitis.

DR BERNARD M JACOBSON Was the spleen involved?

DR MALLORY No.

DR TAYLOR The superficial lymph nodes of the neck were entirely free?

DR MALLORY Yes.

# The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established 1828

Official Organ of

THE MASSACHUSETTS MEDICAL SOCIETY

and

THE NEW HAMPSHIRE MEDICAL SOCIETY

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND

PUBLISHED WEEKLY UNDER THE JURISDICTION OF THE

COMMITTEE ON PUBLICATIONS

James P. O'Hare, M.D. Richard M. Smith, M.D., Chairman  
Oliver Cope, M.D. Conrad Wesselhoef, M.D.  
John Fallon, M.D.

Joseph Garland, M.D., Editor

ASSOCIATE EDITORS

Thomas H. Lanman, M.D. Donald Munro, M.D.  
Henry Jackson, Jr., M.D.

Clara D. Davies, EXECUTIVE EDITOR

Robert O'Leary, ASSISTANT EDITOR

EDITORIAL BOARD

C. Guy Lane, M.D.	Maxwell Finlan, M.D.
Henry R. Viets, M.D.	James M. Faulkner, M.D.
Robert M. Green, M.D.	Carroll B. Larson, M.D.
Dwight O'Hara, M.D.	Francis D. Moore, M.D.
Fletcher H. Colby, M.D.	C. Stuart Welch, M.D.
Robert L. Goodale, M.D.	Vernon P. Williams, M.D.
Chester M. Jones, M.D.	Benjamin Castleman, M.D.
Harvey R. Morrison, M.D.	Hugh R. Leavell, M.D.

SUBSCRIPTION TERMS \$7.00 per year in advance, postage paid for the United States (medical students, \$4.00 per year), Canada \$8.00 per year (Boston funds) \$9.50 per year for all foreign countries belonging to the Postal Union

MATERIAL should be received not later than noon on Thursday three weeks before date of publication

THE JOURNAL does not hold itself responsible for statements made by any contributor

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts Telephone KE 6-2094

NEW ENGLAND ADVERTISING REPRESENTATIVE Edwin B. Tyler 89 State Street Boston Massachusetts Telephone LA 3-5516

## THE THYROID NODULE

MUCH of the recent literature concerning the thyroid gland has emphasized the conflicting opinions that exist regarding the incidence of carcinoma of this structure, and the interpretation of the nodule in the gland as precancerous. On the one hand reports from surgical clinics where an aggressive attitude is followed disclose that carcinoma is discovered in a large percentage of apparently innocent nodules, opposed to this are the analyses of routine autopsy material indicating a very low incidence of thyroid carcinoma as a cause of death. A further complication enters the picture with the disagreements among pathologists in interpretation of borderline conditions, adenomas with blood-vessel invasion, carcinoma in aberrant thyroid tissue and benign metastasizing goiter. The impartial observer is brought to the conclusion that a wide

disparity exists between histologic character and clinical behavior or, alternatively, that carcinoma of the thyroid gland is readily curable in the earliest stages, when the disease is not recognizable clinically.

Currently, evidence of cancer is found in about 20 per cent of the single nontoxic nodules that are removed surgically at the Massachusetts General Hospital. This high incidence of thyroid cancer may be contrasted with the experience at the Pondville Hospital, where only 46 cases have been encountered in twenty years, or approximately 1 case among every 300 cases of all types of cancer.

There is general agreement that the highest incidence of cancer is found in the single nontoxic adenoma, although all types of thyroid disease have been associated with carcinoma. At the Pondville Hospital more than 10 per cent of the thyroid carcinomas have arisen in toxic goiters.

The paper of Anglem and Bradford published elsewhere in this issue of the *Journal* offers further evidence of the incidence of carcinoma in thyroid nodules, and also sheds some light on the apparently low incidence in autopsy statistics. The study emphasizes the frequency with which carcinoma may be found in an apparently benign nodule. It seems probable that with the increasing employment of medical measures in the management of hyperthyroidism, the incidence of carcinoma in the remaining group submitted to surgery will increase. There is also the possibility that the drugs used in the treatment of hyperthyroidism may in some cases precipitate the development of carcinoma.

Regardless of the role of the nontoxic adenoma, whether it is precancerous or merely indistinguishable from cancer in its earliest stages, there is sufficient evidence to justify prompt surgical intervention in all cases with single nontoxic nodules. Carcinoma discovered at this early stage is curable in a high percentage of cases. The decision to keep such a lesion under observation, and to resort to surgery only when the lesion by rapid growth or fixation raises the probability of malignant degeneration, is a serious one and not in the best interests of the patient. Operation performed when the diagnosis of cancer is obvious results in fewer cures. With thyroid carcinomas as with those of other regions, prompt intervention is likely to be successful. The nature of the nodule should be decided in the laboratory, not on its future course in the neck of the patient.

## THE BOSTON EYE BANK

THE Boston Eye Bank, affiliated with the Eye-Bank for Sight Restoration, Incorporated, of New York City, has been in operation for the past year and a half. The wisdom and foresight of those responsible for its establishment are attested by the number of people who have benefited from corneal transplantation through its services.

Naturally, the dramatic element in corneal transplantation has great popular appeal, and this has been reflected by the gratifying interest demonstrated by the public and lay press in the activities of the Eye Bank. Numerous requests are received daily for donation forms bequeathing eyes. However, at present it is not practical to obtain eyes from other than patients dying in a hospital. It is precisely in this connection that the medical profession, including hospital administrators, can do much to ensure success of this worthy project. Literature is available for reception rooms in hospitals and doctors' offices explaining the noble aims and purpose of the Eye Bank. At the time that permission for post-mortem examination is sought, a proper appeal could well be made, for the eyes.

No exact figures are available regarding the number of blind persons throughout the country who could be aided. The best estimates have been placed at 10,000 to 15,000. Obviously, it will take time and many high-minded persons to provide a sufficient number of eyes to restore that most precious gift, sight, to these unfortunate victims.

If, for some reason, an eye is not suitable for corneal transplantation, it is used in research, particularly in problems that do not lend themselves to solution by the use of animal eyes. For example, studies of the vitreous and the possibilities of vitreous transplantation are currently the object of much research.

In its short span, The Boston Eye Bank has proved a most valuable ally in the fight against blindness. The future is contingent upon the continuing support of the general public and the medical profession.

---

## CHLOROMYCETIN

IN THE field of virus and rickettsial diseases the therapeutic results of the use of chemotherapeutic and antibiotic agents have not been comparable to those obtained in infections with bacterial agents.

However there is accumulating evidence of progress in this field.<sup>1</sup> The sulfonamides and penicillin have been shown to be active against certain viruses of the psittacosis-lymphogranuloma group. Certain rickettsias have proved susceptible to para-aminobenzoic acid, and therapy with this agent has given favorable results in some diseases caused by this group of agents. Streptomycin has also been found to have some rickettsiostatic effect in fertile hens' eggs and also in guinea pigs. Thus far no really effective agent has been found that affects the smaller viruses such as those responsible for the encephalitides and influenza.

Interest at the moment is focused on a new antibiotic, chloromycetin.<sup>2-8</sup> This agent has been obtained in crystalline form from cultures of a *Streptomyces* similar to the ones that produce streptothricin. It is particularly noteworthy in that a large portion of the weight of chloromycetin is in the form of nonionic chlorine. One of the chief drawbacks of chloromycetin is its low solubility in water, but it is soluble in many solvents that can be used clinically, including propylene glycol. It is highly stable in water over a wide range of reaction and resists boiling.

In vitro this agent appears to be effective in fairly small concentrations against a large range of gram-positive and gram-negative organisms, but moderately high concentrations are required for certain mycobacteria and for a few gram-negative bacilli. It is not effective against fungi, protozoa or rabbit syphilis, but at least one strain of *Borellia* is extremely sensitive. In vivo it has been shown to be markedly effective against various strains of rickettsias in mice and eggs. It has also been found effective against some strains of psittacosis in eggs and mice, but not against most other viruses. It appears to be inferior quantitatively to streptomycin in mice against many infections and does not seem to have any effect against pneumococcal infections.

One of the great virtues of chloromycetin is that it seems to be effective in mice and dogs when given by mouth. It appears to have relatively low toxicity and, from the results obtained in mice, to be effective even late in the disease. Clinical trials have been undertaken in the treatment of epidemic typhus and in scrub typhus.<sup>9-12</sup> The early results as judged from press reports seem to be favorable, and the details will be awaited with considerable interest.

There is reason to believe that other chemotherapeutic and antibiotic agents with similar or greater effects against many viral and rickettsial diseases will become available in the not too distant future and with those already available will tend to bring under control another large group of serious infections

### REFERENCES

- 1 Rivers T M Recent advances in treatment of viral and rickettsia diseases *J A M A* 136 291, 1948
- 2 Ehrlich, J., Bartz, Q R, Smith R. M and Joslyn D A Chloromycetin new antibiotic from soil actinomycete *Science* 106 417, 1947
- 3 Smadel J E., and Jackson E B Chloromycetin, antibiotic with chemotherapeutic activity in experimental rickettsial and viral infections *Science* 106 418 1947
- 4 Carter H E Gottlieb D and Anderson H W Chloromycetin and streptomycin *Science* 107 113 1948
- 5 Bartz Q R Isolation and characterization of chloromycetin *J Biol Chem* 172 445-450 1948
- 6 Gottlieb, D. Bhattacharya P K, Anderson H W and Carter H E Some properties of antibiotic obtained from species of streptomycetes *J Bact* 55 409-417, 1948
- 7 Smith R M et al Chloromycetin biological studies *J Bact* 55 425-448 1948
- 8 Smadel, J E., and Jackson, E. B Chemotherapeutic effect of chloromycetin on experimental infection with psittacosis and lymphogranuloma venereum viruses *Fed Proc* 7 280, 1948
- 9 Army to test new drug against scrub typhus in Malaya *J A M A* 136 409, 1948
- 10 Payne E. H Knaudt J A., and Palacios S Treatment of epidemic typhus with chloromycetin *J Trop Med* 51 68-71, 1948
- 11 Smadel J E, LeSne, A P, Ley, H L Jr and Varela G Chloromycetin in treatment of patients with typhus fever *Proc Soc Exper Biol & Med* 68 12-19, 1948
- 12 Woodward T E, Smadel, J E, Ley H L Jr, Green R and Manikar, D S Preliminary report on beneficial effect of chloromycetin in treatment of typhoid fever *Ann Int Med* 29 131 134, 1948

### THROUGH THE LOOKING GLASS

THE lonely heart may find its mate in unfrequented byways, trees grow in Brooklyn, stars fell, of all places, on Alabama Romance emerges where one least expects it Thus, in the *Bulletin of the United States Army Medical Department*, among such subjects as "Venereal Disease Anxiety" and "The Suddenness with which the Bowel Can Fill with Gas," appears the title, "Veterinary Inspection of Oysters"

And we had thought that the Army, by now, was fully mechanized

The term "veterinary," we had been led to believe through all these years by Webster (Noah), is "of or pertaining to the art of healing or treating the injuries and diseases of domestic animals" If by any stretch of the imagination this category can be expanded to include marine or aquatic life we should certainly expect the first candidate for veterinary attention to be the sea horse (genus *Hippocampus*), and its picket lines to be serviced by the Marine Corps, or at least the Navy — or perhaps the whole purpose of the project is to provide occupation for veterans

That there may be some reason, however, for believing that the oyster leads a double life, rising

from the relatively inert existence of a marine bivalve mollusk to an amphibious plane on which it attains a considerable degree of mobility, we can quote no less an authority than the late Lew Carroll

Whether or not it was veterinary inspection that they were anticipating, oysters have apparently been known to behave in an extraordinary manner, according to the observations of this great naturalist

Four other Oysters followed them,  
And yet another four,  
And thick and fast they came at last,  
And more, and more, and more —  
All hopping through the frothy waves,  
And scrambling to the shore

The method of locomotion of the succulent bivalve (genus *Ostrea*) is also somewhat reminiscent of the method by which horseflesh gets from one place to another, or wherever it happens to be going

"It seems a shame," the Walrus said,  
"To play them such a trick.  
After we've brought them out so far,  
And made them trot so quick!"

Nor is this zeal for clinical oceanology confined to the Army Medical Department According to the report of a special commission investigating the edible shellfish of the Commonwealth of Massachusetts, "both natural and artificial propagation of soft shell clams is necessary and feasible, and there is great need of reclaiming a greater number of shellfish from areas determined to be contaminated"

It might be the better part of wisdom to decide once and for all that areas so resolutely bent on their own contamination should be abandoned altogether, at least for the purposes of raising shellfish

Further inquiry into the veterinary inspection of oysters, however, reveals that hydrogen ion concentration, not hoof and mouth disease, is the subject of investigation

### MASSACHUSETTS MEDICAL SOCIETY

#### INFORMATION FROM VETERANS ADMINISTRATION

##### CERTAIN FEES INCREASED

On April 19, 1948, the Massachusetts Medical Society renegotiated its contract with the Veterans Administration. This contract became effective July 1, 1948 and is similar in every way to the previous contract, except that certain fees have been increased, for example, the Veterans Administration will now pay \$3.00 for an office visit, instead of the previous maximum of \$2.50. The fee for specialist treatment, except neuropsychiatric treatment, has been increased from \$3.00 to \$5.00.

### \$6000 MAXIMUM PAYMENT

During the fiscal year 1948 which ended on June 30, many doctors' earnings from the Veterans Administration were very near the \$6000 maximum limit allowed by law. With the new increase in fees as described in the previous paragraph, these doctors run the risk of exceeding their \$6000 limitation, if they order the same amount of service during the coming fiscal year. They should, therefore, maintain a fairly accurate record of work accomplished each month. In order to insure that the \$6000 maximum will not be exceeded, the doctor should limit his veterans' practice to a total earning of \$500 per month.

Reimbursement for services rendered in excess of \$6000 per year cannot be made. The salary limitation is based upon earnings during the fiscal year, from July 1, to June 30, and not based upon the payments made.

### REFERRAL OF PATIENTS

Occasionally during the course of treating a veteran, a doctor finds it necessary to refer his patient to another doctor for consultation or laboratory work. Whenever this is necessary, the Veterans Administration should always be notified in advance. Unless the Veterans Administration is so notified, authorization cannot be given and the veteran may have to pay the consultation fee.

### INFORMATION PHONE FOR DOCTORS

Two telephones at the V A Regional Office have been set aside for the use of physicians phoning for information. Trained clerks will be on duty from 8 30 a m to 5 15 p m each Monday through Friday. Call LA 3-7500, extensions 751 and 752.

### TREATMENT PROCEDURE INAUGURATED IN MASSACHUSETTS NOW USED IN OTHER STATES

On July 1, 1947 a new form of treatment authorization and a simplified procedure was tried out in Massachusetts. The response and co-operation received from Massachusetts physicians has been very gratifying. The reduction in the amount of paper work required of each doctor has elicited many favorable comments and has enabled many doctors who formerly were unable to cope with the excessive amount of paper work to participate in the Veterans Care Program. The procedure has also resulted in a net saving of 4,697 clerical man-hours per month at the Boston Regional Office, or the equivalent of twenty-six full-time employees. This is an excellent illustration of co-operation and teamwork eliminating many of the irritating problems frequently encountered in the administration of a large scale program.

On the first of May, the new form and procedure was introduced in Rhode Island, Connecticut, New Hampshire and Vermont, where it also has been favorably received.

### INFORMATION FOR NEWLY DESIGNATED FEE BASIS PHYSICIANS

Within the past few months, over 2000 new fee basis physicians have been approved for appointment by the Massachusetts Medical Society, consequently it is felt that a brief outline of Veteran Administration treatment requirements are in order.

- 1 The Veterans Administration authorizes out-patient treatment only for disabilities that have been adjudicated as service connected.
- 2 Except in an emergency the veteran should be required to present the physician with an authorization from the Veterans Administration office, before treatment is begun. If emergency treatment is rendered to a veteran it should be reported to this office within fifteen days.
- 3 Authorizations are for one calendar month only. If the veteran requires treatment during the following month, authorization should be requested on the yellow third page of the treatment form.
- 4 The veteran should be treated only for the specific disability covered by the authorization.
- 5 All reports of treatment and completed invoices must be submitted no later than the fifteenth of the month following the month in which treatment was rendered.
- 6 If medicine is prescribed the prescription blanks that are part of the second or pink page must be used. The veteran may have the prescription filled by any druggist who is a

member of the Massachusetts Pharmaceutical Association. The druggist in turn will be reimbursed by the Veterans Administration, through the State Association.

7 Prescribe only for the service connected disability shown on the authorization and only during the treatment period.

8 When forwarding completed reports to this office, retain the upper portion of the yellow or third copy for your files.

9 To identify payments received, the number listed on the reverse side of the voucher form, which accompanies the check, should be compared with the large number appearing on the yellow copy of the treatment authorization, retained by the doctor, in the box headed Fiscal Symbols.

10 If a physician believes that the number of treatments authorized is not sufficient for the month, or if the number of treatments authorized is less than the number requested, this office should be advised, giving a summary of treatment to date and a plan of future treatment, together with prognosis. The doctors authorizing these cases seldom see the patient and must rely almost entirely upon the reports submitted by the contracting physician.

11 All forms must be prepared in ink, typewriter or indelible pencil.

12 All reports of treatment and invoices must be personally signed by the doctor.

VETERANS ADMINISTRATION  
REGIONAL OFFICE

17 Court Street  
Boston 8, Massachusetts

### DEATHS

LEDBURY — John W Ledbury, M D, of Uxbridge, died on February 20. He was in his seventy-third year.

Dr Ledbury received his degree from College of Physicians and Surgeons of Baltimore in 1905. He was an affiliate fellow of the American Medical Association.

His widow, a daughter and two grandsons survive.

STRONG — Richard P Strong, M D, of Boston, died on July 4. He was in his seventy-sixth year.

Dr Strong received his degree from Johns Hopkins University School of Medicine in 1897. He was professor of tropical medicine, emeritus, at Harvard Medical School and was a member of the Association of American Physicians and a fellow of the American Medical Association.

A sister survives.

## MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

### RHEUMATIC FEVER FELLOWSHIPS

The United States Children's Bureau has made available through the Massachusetts Department of Public Health and the Harvard Medical School two fellowships in Rheumatic Fever at the House of the Good Samaritan of the Children's Medical Center, Boston, for the year beginning July 1, 1948.

Trainees should be interested in working eventually in the field of rheumatic fever in public health or in teaching, rather than in private practice.

Work under these fellowships will probably be acceptable for credit by the Board of Internal Medicine or the Board of Pediatrics.

Application should be made to Dr Benedict F Massell at the House of the Good Samaritan, 25 Binney Street, Boston 15, or BE 2-3002.

## MISCELLANY

### AMERICAN COLLEGE OF CHEST PHYSICIANS

Dr Richard H Overholt, of Brookline, took office as president of the American College of Chest Physicians at the fourteenth annual meeting of the College, June 17-20

## CORRESPONDENCE

### MORE ON ADOPTION

To the Editor I am delighted to see the editorial in the *Journal* of June 17 commending the work of the Boston Children's Friend Society on adoption and so indicating the importance of more and more care in this matter

The New England Home for Little Wanderers has been receiving into custody and placing children for adoption since 1865. With the passing of the years we have become more and more conscious of the importance of great care in procedure. We are sure that physicians, public-health officers and hospitals with whom we have co-operated have realized the protection we can give both children and family in the adoption process. Our staff is equipped with pediatrician, psychologist and psychiatrist, as well as with social workers, to assure a thoroughgoing service. During the past twelve months we have placed with a view to adoption 24 children and have completed the adoption of 35 children who had been placed for a year or more. We are acquainted with many fine young men and women who were placed for adoption as long as twenty-five or thirty years ago. Our experience confirms your statement "Few decisions require more tact and skill than the suitable placing of a child unwanted under one roof, so badly wanted under another."

CHENEY C JONES  
Superintendent

New England Home for Little Wanderers  
Boston, Massachusetts

## BOOK REVIEWS

*Stethoscopic Heart Records*. By George D Geckeler, M D. An album of four double-faced twelve-inch phonograph records. New York: Columbia Records, Incorporated, 1948. \$8.00.

While a book of records does not suggest the type of literature that is customarily reviewed in medical journals or elsewhere, stranger things are taking place in our brave new world where the electric impulse is used to convey both visual and auditory sensations, and the printed word may yet become the archaic symbol of another forgotten civilization.

This new issue of *Stethoscopic Heart Records*, ably presented by Dr Geckeler, provides a most satisfactory reproduction of a wide range of heart sounds, both normal and abnormal, including the arrhythmias and a variety of commonly encountered murmurs.

Although they are intended primarily for the practicing physician who wishes to keep his stethoscope ear in practice, these recordings will fill a variety of academic needs as well.

*Human Gastric Function. An experimental study of a man and his stomach*. By Stewart Wolf, M D, and Harold G Wolff, M D. With a foreword by Walter B Cannon, M D. Oxford Medical Publications. 8°, cloth, 262 pp., with 55 illustrations. New York: Oxford University Press, 1947. \$5.00.

The first and second editions of this book are continuations of the studies begun by Beaumont one hundred years ago on Alexis St. Martin, through a gastric fistula, on digestion in the stomach, the composition of gastric juice and the contraction and emptying of the stomach, but are far more complete and easy to read than Beaumont's "Observations on the Effects of the Mind on the Secretions of the Stomach and the Effect of the Mind on the Secretions of the Stomach and the Effect of the Mind on the Secretions of the Stomach."

Great care and skill and ingenuity have been shown in this study. The changes in appearance of the gastric mucus in severe emotion, the great increase in gastric secretions when the patient was worried, excited or obstinate, the rate of emptying of the stomach and the rapidity with which these changes came and went are described in a clear, simple and convincing way.

The influence of many agents—foods, drugs, coffee, tobacco, alcohol, acids, antacids, atropine, nitrites, histamine, epinephrine, methylcholine, prostigmin, pitressin, benadryl, emetics and others that have been used to change the gastric function—are critically examined, and it is shown that their action on the stomach may be modified or reversed by the effect of the mental state present at the time, previous data about the length of time food remains in the stomach must be revalued in the light of the great changes that occur in emotional states. It is interesting that no effect from tobacco smoking on the motor activity, acid secretion or vascularity of the stomach was formed in the patient unless nausea appeared.

The wide range of the appearance of the healthy gastric mucosa is important in relation to the diagnosis of gastritis. The authors found the difference between hyperfunction of the stomach, however caused, and hypertrophic gastritis mainly one of degree. The protective action of gastric mucus is well shown. Some valuable and fundamental applications of this research are made in the treatment of gastritis and ulcer.

Three chapters have been added to the first edition of 1943, including further data on the effects of chemical agents and other influences on gastric function and the gastric mucosa, further correlation of gastric function with life situations (causing depression, resentment, anger, worry, fear, frustration and so forth) and a timely chapter on gastric studies of a patient with fistula both before and after vagotomy.

The book is very interesting, and no internist, practitioner or psychologist can afford to miss it. It ranks as a medical classic, and its significance has already been widely recognized.

## BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

*Minor Surgery*. By Frederick Christopher, M D, associate professor of surgery, Northwestern University Medical School, and chief surgeon, Evanston (Illinois) Hospital. Sixth edition. 8°, cloth, 1058 pp., with 937 illustrations. Philadelphia: W B Saunders Company, 1948. \$12.00.

This standard textbook, first published in 1929 and last revised in 1944, has been again thoroughly revised, and many sections have been entirely rewritten and new sections added. The material on the use of penicillin and other antibiotics and the sulfonamides has been thoroughly revised in the light of present-day usage. The sections on thrombophlebitis and phlebotrombosis have been extensively revised and include consideration of anticoagulant therapy and femoral-vein ligation in the prophylactic treatment of pulmonary embolism. The sections on burns and varicose veins, pilonidal sinus, and methods of artificial respiration have been revised in the light of the knowledge gained from World War II. New material includes the control of hemorrhage by the gelatin sponge, or oxidized cellulose, early postoperative ambulation, Lund table of skull areas, procaine and serum sickness, plastic cast in burns, lumbar sympathetic block in thrombophlebitis, intra-arterial injection of penicillin and infections of the extremities, excision and encasement of bedsores, treatment of malignant melanoma, prosthetic restoration of amputate, finger, refrigeration anesthesia and the use of aluminum hydroxide paste in bowel fistula. The following sections have been amplified: wound healing, diet and burns, injection of novocain, and subacromial bursitis, Colles fracture, fracture of the carpal scaphoid, glomus tumors, novocain injection for ankle sprains, march fractures, sternal puncture, the

iting, the Rh factor, shock, fluid and electrolyte administration after operation, hypoproteinemia, use of the Miller-bott tube and pulmonary atelectasis. A selected bibliography is appended to each chapter, and a good index condenses the volume. The work is well published in every way and is recommended for all medical libraries and should prove of value to all persons interested in surgery.

*Sulfonamides and Allied Compounds*. By Elmore H. Orthner, Ph.D., administrative director, Stamford Research Laboratories, American Cyanamid Company, Stamford, Connecticut. 8°, cloth, 660 pp., with 323 tables. New York: Reinhold Publishing Corporation, 1948. \$12.50.

This essential reference work covers the chemical side of the sulfonamide derivatives, simple and complex, the sulfones and their derivatives and other allied compounds. The structure and activities of the compounds are considered extensively. There are special chapters on the experimental evaluation and relation to structure of chemotherapeutic activity, pharmacology, theories of the mechanism of action and the clinical action of the drugs. In this fast expanding field over 300 new compounds have been synthesized, and in 1943 the United States produced over 10,000,000 pounds of sulfonamides. The first two chapters deal briefly with the history of antetarial chemotherapy and nomenclature, classification and synthesis. A comprehensive bibliography of 2668 references concludes the text. The appendices give a key of organisms and diseases, and the trade names for sulfanilamide, its derivatives and related compounds. The volume is well published in every way and is recommended for all medical libraries and to all physicians interested in chemotherapy.

*A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology*. By Torald Sollman, M.D. Seventh edition. 4°, cloth, 1132 pp. Philadelphia: W. B. Saunders Company, 1948. \$11.50.

This standard work on pharmacology, first published in 1917, has been thoroughly revised to bring it up to date. In this revision the author has eliminated material no longer considered of real importance or interest. The text is printed in two columns and in two sizes of type. The large type presents material that should be known by all students, and the small type contains data for reference purposes. Since the publication of the last edition in 1942, there have been great advances in the field of pharmacology. Much material has been added throughout the volume, including the new antibiotic agents, the anti-infective sulfonamides, antimalarials, the antitumoral drugs, the insecticides and rodenticides, the toxins and weed killers. The antithyroids, anticonvulsants, antihistamines, anticholine acetylases, folic acids, standardized curare, digitoxin, nitrogen mustards and B.A.L. are considered in the text. The extensive bibliography of 112 pages appended to the text comprises references to the pertinent literature published since January 1, 1926. The volume is well published and is recommended for all medical libraries and as a reference work for physicians.

*The Industrial Environment and Its Control*. By J. M. Dallavalle. 8°, cloth, 225 pp. New York: Pitman Publishing Corporation, 1948. \$4.50.

This monograph in a new field of public health is well written, and the material well organized. Although technical in parts the text is kept as simple as possible and understandable to the average person. The monograph deals with engineering methods for the control of health hazards in factories. The first chapter discusses problems and trends, including the importance of industrial hygiene to the industrial physician and public-health administrator and the need for adequate reporting of morbidity and mortality. The various chapters consider psychrometry (the relation between temperature and humidity), air and its contamination, illumination and radiant energy, noise, vibration and fatigue, industrial ventilation in all its aspects, and industrial dust collection. An appendix discusses the general principles of industrial sanitation. Each chapter is documented with a list of pertinent references. The monograph is recommended for all public-health collections in medical and general libraries, in industrial plants and in health-department libraries of estates and cities, and to all persons interested in industrial sanitation. The printing is well done with a good type on good paper.

*Hernia: Anatomy, etiology, symptoms, diagnosis, differential diagnosis, prognosis and treatment*. By Leigh F. Watson, M.D. Third edition. 8°, cloth, 732 pp., with 323 illustrations. St. Louis: The C. V. Mosby Company, 1948. \$13.50.

This authoritative work, first published in 1924, has been thoroughly revised in the third edition, and the type entirely reset. Chapters have been added on the complications of hernia, internal supravescical and epigastric hernias, hernia into the broad ligament, recurrent inguinal hernia and industrial hernia. Cooper's ligament operation, Babcock's operation for inguinal hernia using stainless steel wire and Harrington's operation for diaphragmatic hernia are described and illustrated in detail. Material has also been added on early rising after operation, suture materials, embolism and thrombosis, preoperative and postoperative treatment and new statistics on the rarer types of hernia. Much space has been devoted to a thorough consideration of nonoperative treatment by the injection method, including its use in inguinal, femoral, umbilical epigastric and ventral hernias. The bibliography has been brought up to date and appended to each chapter. Comprehensive indexes of authors and subjects conclude the volume. Many illustrations have been added. The printing is well done with a good large type on good coated paper. This paper is probably necessary to ensure adequate reproduction of the fine illustrations, but it makes the volume rather heavy to handle. The book is recommended as an essential reference work for all medical libraries and to all surgeons.

*The Case Book of a Medical Psychologist*. By Charles Berg, M.D. (Lond.), D.P.M., fellow of the British Psychological Association, physician at the British Hospital for Functional Mental and Nervous Disorders and physician to the Institute for the Scientific Treatment of Delinquency. 8°, cloth, 260 pp. New York: W. W. Norton and Company, Incorporated, 1948. \$3.50.

Dr. Berg, in this second edition of his case book, has made a few minor changes and has substituted a long analytical case report for the three last articles in the section on war neuroses. All the papers were published originally in medical and psychologic periodicals. The text is written in a semi-popular style and presents 34 cases, illustrative of the practical application of clinical psychology. Four cases of war neuroses are included for the purpose of demonstrating that these cases do not differ in any essential particular, except the ease of curability, from the average case treated by the clinical psychologist. The theoretical explanations attached to each case have been reduced to a minimum, but enough has been included to interest the general reader and prove of value to the practitioner of clinical psychology. In the last chapter the author discusses the theory and practice of psychoanalysis. The book is well published and should prove of value to all physicians interested in nervous and mental diseases.

*Operative Gynecology*. By Harry S. Crossen, M.D., consulting gynecologist to the Barnes Hospital, St. Louis Maternity Hospital, St. Luke's Hospital, de Paul Hospital and Jewish Hospital, and Robert J. Crossen, M.D., assistant professor of clinical gynecology and obstetrics, Washington University School of Medicine, assistant gynecologist and obstetrician to the Barnes Hospital and the St. Louis Maternity Hospital and gynecologist to St. Luke's Hospital and de Paul Hospital. Sixth edition. 4°, cloth, 999 pp., with 1534 illustrations. St. Louis: The C. V. Mosby Company, 1948. \$15.00.

The first edition of this standard textbook was published in 1915, and the last edition in 1938. This new edition has been revised to bring it up to date, and to accommodate the large number of new data it was necessary to eliminate much of the historical material. This will make it essential for libraries interested in medical history to retain the fifth edition (1938) in their collections. Included in the new material are measures for the prevention of cancer, made a part of the sections on the various organs, and the development of measures for giving more effective relief to patients with general handicaps contraindicating operative removal of serious pelvic lesions. The volume is well published in every way. The many fine illustrations necessitate the use of a heavy paper, a fact to be deplored. The book is recommended for all medical libraries and should be in the collections of all gynecologists.

## MISCELLANY

### AMERICAN COLLEGE OF CHEST PHYSICIANS

Dr Richard H. Overholt, of Brookline, took office as president of the American College of Chest Physicians at the fourteenth annual meeting of the College, June 17-20

## CORRESPONDENCE

### MORE ON ADOPTION

To the Editor: I am delighted to see the editorial in the *Journal* of June 17 commending the work of the Boston Children's Friend Society on adoption and so indicating the importance of more and more care in this matter.

The New England Home for Little Wanderers has been receiving into custody and placing children for adoption since 1865. With the passing of the years we have become more and more conscious of the importance of great care in procedure. We are sure that physicians, public-health officers and hospitals with whom we have co-operated have realized the protection we can give both children and family in the adoption process. Our staff is equipped with pediatrician, psychologist and psychiatrist, as well as with social workers, to assure a thoroughgoing service. During the past twelve months we have placed with a view to adoption 24 children and have completed the adoption of 35 children who had been placed for a year or more. We are acquainted with many fine young men and women who were placed for adoption as long as twenty-five or thirty years ago. Our experience confirms your statement: "Few decisions require more tact and skill than the suitable placing of a child unwanted under one roof, so badly wanted under another."

CHENEY C. JONES  
Superintendent

New England Home for Little Wanderers  
Boston, Massachusetts

## BOOK REVIEWS

*Stethoscopic Heart Records*. By George D. Geckeler, M.D. An album of four double-faced twelve-inch phonograph records. New York: Columbia Records, Incorporated, 1948. \$8.00.

While a book of records does not suggest the type of literature that is customarily reviewed in medical journals or elsewhere, stranger things are taking place in our brave new world where the electric impulse is used to convey both visual and auditory sensations, and the printed word may yet become the archaic symbol of another forgotten civilization.

This new issue of *Stethoscopic Heart Records*, ably presented by Dr. Geckeler, provides a most satisfactory reproduction of a wide range of heart sounds, both normal and abnormal, including the arrhythmias and a variety of commonly encountered murmurs.

Although they are intended primarily for the practicing physician who wishes to keep his stethoscope ear in practice, these recordings will fill a variety of academic needs as well.

*Human Gastric Function. An experimental study of a man and his stomach*. By Stewart Wolf, M.D., and Harold G. Wolff, M.D. With a foreword by Walter B. Cannon, M.D. Oxford Medical Publications. 8°, cloth, 262 pp., with 55 illustrations. New York: Oxford University Press, 1947. \$5.00.

The first and second editions of this book are continuations of the studies begun by Beaumont one hundred years ago on Alexis St. Martin, through a gastric fistula, on digestion in the stomach, the composition of gastric juice and the contractions and emptying of the stomach, but are far more complete and interesting and easy to read than Beaumont's "Observations and Experiments" and more useful at present, when men are interested in the causes of ulcer and gastritis, the reasons for their recurrence and the effect of the mind on the stomach.

Great care and skill and ingenuity have been shown in this study. The changes in appearance of the gastric mucosa in severe emotion, the great increase in gastric secretion when the patient was worried, excited or obstinate, the rate of emptying of the stomach and the rapidity with which these changes came and went are described in a clear, simple and convincing way.

The influence of many agents—foods, drugs, tobacco, alcohol, acids, antacids, atropine, nitrates, histamine, epinephrine, methylcholine, prostigmin, pituitrin, benadryl, emetics and others that have been used to change the gastric function—are critically examined, and it is shown that their action on the stomach may be modified or reversed by the effect of the mental state present at the time, previous data about the length of time food remains in the stomach must be revalued in the light of the changes that occur in emotional states. It is interesting that no effect from tobacco smoking on the motor activity, acid secretion or vascularity of the stomach was found in the patient unless nausea appeared.

The wide range of the appearance of the healthy gastric mucosa is important in relation to the diagnosis of gastritis. The authors found the difference between hyperfunction of the stomach, however caused, and hypertrophic gastritis mainly one of degree. The protective action of gastric mucus is well shown. Some valuable and far-reaching mental applications of this research are made in the treatment of gastritis and ulcer.

Three chapters have been added to the first edition of 1943, including further data on the effects of chemical agents and other influences on gastric function and the gastric mucosa, further correlation of gastric function with emotional situations (causing depression, resentment, anger, worry, fear, frustration and so forth) and a timely chapter on gastric studies of a patient with fistula both before and after vagotomy.

The book is very interesting, and no internist, practitioner or psychologist can afford to miss it. It ranks as a medical classic, and its significance has already been widely recognized.

## BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

*Minor Surgery*. By Frederick Christopher, M.D., associate professor of surgery, Northwestern University Medical School, and chief surgeon, Evanston (Illinois) Hospital. Sixth edition. 8°, cloth, 1058 pp., with 937 illustrations. Philadelphia: W. B. Saunders Company, 1948. \$12.00.

This standard textbook, first published in 1929 and last revised in 1944, has been again thoroughly revised, and many sections have been entirely rewritten and new sections added. The material on the use of penicillin and other biotics and of the sulfonamides has been thoroughly revised in the light of present-day usage. The sections on thrombophlebitis and phlebothrombosis have been extensively revised and include a consideration of anticoagulant therapy and femoral-vein ligation in the prophylactic treatment of pulmonary embolism. The sections on burns and varicose veins, pilonidal sinuses and methods of artificial respiration have been revised in the light of the knowledge gained from World War II. New material includes the control of hemorrhage by the gelatin sponge, oxidized cellulose, early postoperative ambulation, Lund's table of skin areas, procaine and serum sickness in thrombophlebitis, in burns, lumbar sympathetic block in thrombophlebitis, intra-arterial injection of penicillin and infections of the extremities, excision and enclosure of bedsores, treatment of malignant melanoma, prosthetic restoration of amputated finger, refrigeration anesthesia and the use of aluminum hydroxide paste in bowel fistula. The following sections have been amplified: wound healing, diet and burns, injection of novocain, and subacromial bursitis, Colles fracture, fractures of the carpal scaphoid, glomus tumors, novocain injections for ankle sprains, march fractures, sternal puncture, skin

ing, the Rh factor, shock, fluid and electrolyte administration after operation, hypoproteinemia, use of the Miller-Ritt tube and pulmonary atelectasis. A selected bibliography is appended to each chapter, and a good index concludes the volume. The work is well published in every way and is recommended for all medical libraries and should prove valuable to all persons interested in surgery.

*Sulfonamides and Allied Compounds*. By Elmore H. Thyer, Ph.D., administrative director, Stamford Research Laboratories, American Cyanamid Company, Stamford, Connecticut. 8°, cloth, 660 pp., with 323 tables. New York: Knol Publishing Corporation, 1948. \$12.50.

This essential reference work covers the chemical side of the sulfonamide derivatives, simple and complex, the sulfones and their derivatives and other allied compounds. The structure and activities of the compounds are considered extensively. There are special chapters on the experimental evaluation and relation to structure of chemotherapeutic activity, pharmacology, theories of the mechanism of action and the clinical action of the drugs. In this fast expanding field over 30 new compounds have been synthesized, and in 1945 the United States produced over 10,000,000 pounds of sulfonamides. The first two chapters deal briefly with the history of sulfonamide chemotherapy and nomenclature, classification and synthesis. A comprehensive bibliography of 2668 references concludes the text. The appendixes give a list of organisms and diseases, and the trade names for sulfanilamide, its derivatives and related compounds. The volume is well published in every way and is recommended for all medical libraries and to all physicians interested in chemotherapy.

*Manual of Pharmacology and Its Applications to Therapeutics and Toxicology*. By Torald Sollman, M.D. Seventh edition. 4°, cloth, 1132 pp. Philadelphia: W. B. Saunders Company, 1948. \$11.50.

This standard work on pharmacology, first published in 1917, has been thoroughly revised to bring it up to date. In this revision the author has eliminated material no longer considered of real importance or interest. The text is printed in two columns and in two sizes of type. The large type presents material that should be known by all students, and the small type contains data for reference purposes. Since the publication of the last edition in 1942, there have been great advances in the field of pharmacology. Much material has been added throughout the volume, including the new antiparasitic agents, the anti-infective sulfonamides, antimalarials, the antitumor drugs, the insecticides and rodenticides, the anxiants and weed killers. The antithyroids, anticonvulsants, antihistamines, anticholinergic acetals, folic acids, standardized curare, digitoxin, nitrogen mustards and BAL are considered in the text. The extensive bibliography of 112 pages appended to the text comprises references to the pertinent literature published since January 1, 1926. The volume is well published and is recommended for all medical libraries and as a reference work for physicians.

*The Industrial Environment and Its Control*. By J. M. Dallavalle. 8°, cloth, 225 pp. New York: Pitman Publishing Corporation, 1948. \$4.50.

This monograph in a new field of public health is well written, and the material well organized. Although technical in parts the text is kept as simple as possible and understandable to the average person. The monograph deals with engineering methods for the control of health hazards in factories. The first chapter discusses problems and trends, including the importance of industrial hygiene to the industrial physician and public-health administrator and the need for adequate reporting of morbidity and mortality. The various chapters consider psychrometry (the relation between temperature and humidity), air and its contamination, illumination and radiant energy, noise, vibration and fatigue, industrial ventilation in all its aspects, and industrial dust collection. An appendix discusses the general principles of industrial sanitation. Each chapter is documented with a list of pertinent references. The monograph is recommended for all public-health collections in medical and general libraries, in industrial plants and in health-department libraries of estates and cities, and to all persons interested in industrial sanitation. The printing is well done with a good type on good paper.

*Hernia: Anatomy, etiology, symptoms, diagnosis, differential diagnosis, prognosis and treatment*. By Leigh F. Watson, M.D. Third edition. 8°, cloth, 732 pp., with 523 illustrations. St. Louis: The C. V. Mosby Company, 1948. \$15.50.

This authoritative work, first published in 1924, has been thoroughly revised in the third edition, and the type entirely reset. Chapters have been added on the complications of hernia, internal supravesical and epigastric hernias, hernia into the broad ligament, recurrent inguinal hernia and industrial hernia. Cooper's ligament operation, Bahcock's operation for inguinal hernia using stainless steel wire and Harrington's operation for diaphragmatic hernia are described and illustrated in detail. Material has also been added on early rising after operation, suture materials, embolism and thrombosis, preoperative and postoperative treatment and new statistics on the rarer types of hernia. Much space has been devoted to a thorough consideration of nonoperative treatment by the injection method, including its use in inguinal, femoral, umbilical epigastric and ventral hernias. The bibliography has been brought up to date and appended to each chapter. Comprehensive indexes of authors and subjects conclude the volume. Many illustrations have been added. The printing is well done with a good large type on good coated paper. This paper is probably necessary to ensure adequate reproduction of the fine illustrations, but it makes the volume rather heavy to handle. The book is recommended as an essential reference work for all medical libraries and to all surgeons.

*The Case Book of a Medical Psychologist*. By Charles Berg, M.D. (London), D.P.M., fellow of the British Psychological Association, physician of the British Hospital for Functional Mental and Nervous Disorders and physician to the Institute for the Scientific Treatment of Delinquency. 8°, cloth, 260 pp. New York: W. W. Norton and Company, Incorporated, 1948. \$3.50.

Dr. Berg, in this second edition of his case book, has made a few minor changes and has substituted a long analytical case report for the three last articles in the section on war neuroses. All the papers were published originally in medical and psychology periodicals. The text is written in a semi-popular style and presents 34 cases, illustrative of the practical application of clinical psychology. Four cases of war neuroses are included for the purpose of demonstrating that these cases do not differ in any essential particular, except the ease of curability, from the average case treated by the clinical psychologist. The theoretical explanations attached to each case have been reduced to a minimum, but enough has been included to interest the general reader and prove of value to the practitioner of clinical psychology. In the last chapter the author discusses the theory and practice of psychoanalysis. The book is well published and should prove of value to all physicians interested in nervous and mental diseases.

*Operative Gynecology*. By Harry S. Crossen, M.D., consulting gynecologist to the Barnes Hospital, St. Louis Maternity Hospital, St. Luke's Hospital, de Paul Hospital and Jewish Hospital, and Robert J. Crossen, M.D., assistant professor of clinical gynecology and obstetrics, Washington University School of Medicine, assistant gynecologist and obstetrician to the Barnes Hospital and the St. Louis Maternity Hospital and gynecologist to St. Luke's Hospital and de Paul Hospital. Sixth edition. 4°, cloth, 999 pp., with 1354 illustrations. St. Louis: The C. V. Mosby Company, 1948. \$15.00.

The first edition of this standard textbook was published in 1915, and the last edition in 1938. This new edition has been revised to bring it up to date, and to accommodate the large number of new data it was necessary to eliminate much of the historical material. This will make it essential for libraries interested in medical history to retain the fifth edition (1938) in their collections. Included in the new material are measures for the prevention of cancer, made a part of the sections on the various organs, and the development of measures for giving more effective relief to patients with general handicaps contraindicating operative removal of serious pelvic lesions. The volume is well published in every way. The many fine illustrations necessitate the use of a heavy paper a fact to be deplored. The book is recommended for all medical libraries and should be in the collections of all gynecologists.

**Modern Cosmetology** By Ralph G. Harry, F.R.I.C., certificate of the Royal Institute of Chemistry in the Chemistry and Microscopy of Foods, Drugs and Waters, Pharmacognosy, Pharmacology and Therapeutics, and head of the Cosmetic Department, Beecham Research Laboratories, Ltd. With a foreword by P. B. Mumford, M.D., F.R.C.P. Third revised edition 8°, cloth, 515 pp., illustrated. Brooklyn, New York: Chemical Publishing Company, Incorporated, 1947. \$12.00.

This third edition of an unusual book has been enlarged and completely revised. The work deals with the practical and scientific aspects of cosmetic preparations and includes special investigations by the author and others in this field. In addition to skin preparations there is included material on dental, hair, nail and eye preparations. The sections on skin nutrition, sunburn and sun-tan preparations, allergy and dermatitis, histology and physiology of the nails and hair, diet and skin health should prove valuable to physicians. There are hundreds of formulas for the preparations described in the text, making the book invaluable to the dermatologist. The text is documented throughout with pertinent references. A good index concludes the work. The material is well organized, and the text well written in a simple, clear style. The type and printing are excellent. The heavy coated paper could have been dispensed with, since the few plates are inserts. The book is recommended for all medical and general libraries, and as a reference work for dermatologists and physicians.

**Treatment by Diet** By Clifford J. Barborka, M.S., M.D., D.Sc., F.A.C.P., assistant professor of medicine, Northwestern University Medical School, attending physician, Passavant Memorial Hospital, and consultant in gastroenterology and gastroscopy, Diagnostic Centre, Hines Veterans Hospital. Fifth edition 4°, cloth, 784 pp., with 14 plates. Philadelphia: J. B. Lippincott Company, 1948. \$10.00.

This standard work, first published in 1934, and last revised in 1939, has been again brought up to date. More than half the volume has been rewritten, expanded or revised. Chapters on protein and amino acids, deficiency diseases, diet and skin diseases and on preoperative and postoperative dietary care have been added. New material on folic acid and on fat-soluble and water-soluble vitamins has been incorporated in the text. The chapter on liver disease has been rewritten to include the up-to-date use of protein, choline and other food factors in cirrhosis, chronic hepatic diseases and hepatocellular jaundice. In the chapter on diabetes mellitus the low carbohydrate diets have been eliminated and replaced by diets allowing up to 250 gm. A series of colored plates has been added to demonstrate the comparative servings of all types of foods recommended by the Food and Nutrition Board of the National Research Council. A long bibliography of thirty-eight pages is appended to the text, and there is a good index. The volume is well published and should be in all medical libraries and in the libraries of physicians interested in the subject.

**Animal Genetics and Medicine** By Hans Grüneberg, Ph.D., M.D., reader in genetics, University College, London. With a foreword by Sir Henry Dale, O.M., G.B.E., F.R.C. 12°, cloth, 296 pp. New York: Paul B. Hoeber, Incorporated, Medical Book Department of Harper & Brothers, 1947. \$5.50.

Dr. Grüneberg has confined his subject to the inherited diseases of laboratory rodents, omitting the domesticated animals, both large and small, because of the amount of space it would require for adequate coverage of the whole subject. Likewise, the subject of animal tumors has been omitted because it has been adequately covered in recent publications on cancer. The material is arranged according to the systems of the body, with special sections on the relation of animal to human congenital conditions. The beginning chapters discuss inherited diseases in general, the advantages and limitations in etiologic studies and the principles of developmental genetics. The two last chapters consider serology, including blood grouping, and disease resistance. A long bibliography concludes the text, and an attempt has been made to include wartime literature of Continental Europe. There are good author and subject indexes. The book is well published. The sheets were printed in Great Britain and bound in the United States. The author makes a plea for the proper utilization of material of interest to medicine now lying dormant in genetical periodicals seldom consulted by physicians. This unusual monograph should be in all medical reference collections.

## NOTICES

### ANNOUNCEMENTS

Dr. Robert B. Holden announces the opening of his office for the practice of internal medicine at 520 Commonwealth Avenue, Boston.

Dr. William D. Rowland announces the removal of his office from 180 Commonwealth Avenue to 140 Marlborough Street, Boston.

### NEW ENGLAND CONFERENCE OF INDUSTRIAL PHYSICIANS AND SURGEONS

The next meeting of the New England Conference of Industrial Physicians and Surgeons will be held at the Copley Plaza Hotel, Boston, on September 22.

### AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY, INC.

A number of changes in Board requirements and regulations were made at the annual meeting of the Board held in Washington, D. C., May 16 to May 22. New bulletins are now available for distribution upon application and give details of all new regulations. These relate both to candidates and to hospitals conducting residency services for training.

The next written examination and review of case histories (Part I) for all candidates will be held in various cities of the United States and Canada on Friday, February 4, 1949.

Application may be made until November 1, 1948. Application forms and bulletins will be sent on request to the American Board of Obstetrics and Gynecology, 1015 Highland Building, Pittsburgh 6, Pennsylvania.

### FEDERAL SECURITY AGENCY

Public Health Service  
Washington, D. C.

#### EXAMINATION FOR REGULAR CORPS

A competitive examination for appointment in the Regular Corps of the United States Public Health Service in the grade of assistant surgeon (first lieutenant) and senior assistant surgeon (captain) will be held in October. The written examination will be conducted October 4, 5, and 6 at places convenient to the candidates. The oral examination will be held at various points throughout the country.

All applicants must be at least twenty-one years of age and citizens of the United States, must present a diploma of graduation from a recognized medical school and satisfactorily pass a physical examination performed by Public Health Service officers.

Physicians beginning internship on July 1, 1948, will be admitted to the examination. Successful candidates will be placed on active duty in the Regular Corps upon completion of internship on July 1, 1949.

Applicants for the grade of assistant surgeon must have had at least seven years of educational and professional training or experience, exclusive of high school. Applicants for the grade of senior assistant surgeon must have had at least ten years of educational and professional training or experience, exclusive of high school.

Entrance pay for an assistant surgeon with dependents is \$5011 a year and for senior assistant surgeon with dependents \$5551 a year. This includes the additional pay of \$1200 for medical officers, as well as subsistence and rental allowance. Provisions are made for promotions at regular intervals up to and including the grade of senior surgeon (lieutenant colonel) and for selection for promotion to grade of medical director (colonel) at \$9751 a year. Retirement is authorized at either completion of thirty years' service or at the age of sixty-four. Full medical care including disability retirement at three-fourths pay is provided.

Application forms may be obtained from Public Health Service Hospitals, District Offices or by writing to the Surgeon General, United States Public Health Service, Washington 25, D. C.

(Notices concluded on page xv)

NOTICES (Concluded from page 244)

CITY MEETINGS AND CONFERENCES

LENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING  
THURSDAY, AUGUST 12

FRIDAY AUGUST 13

\*10:00 a.m. - 12:00 m. Medical Staff Rounds. Peter Bent Brigham Hospital  
12:00 m. - 1:00 p.m. Clinicopathological Conference (Boston Floating Hospital) Joseph H. Pratt Diagnostic Hospital.

WEDNESDAY AUGUST 17

\*12:15-1:15 p.m. Clinicoradiological Conference. Peter Bent Brigham Hospital.  
\*1:30-2:30 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.

THURSDAY AUGUST 18

\*12:00 m.-1:00 p.m. Clinical Conference. (Children's Hospital) Amphitheater Peter Bent Brigham Hospital

Open to the medical profession

AUGUST 11-21 International Congress on Mental Health Page 344  
issue of March 4

AUGUST 23-26. International Society of Hematology Page 419, issue  
of March 18

AUGUST 26-28 American Association of Blood Banks Page 420 issue  
of March 18

SEPTEMBER 7-11 American Congress of Physical Medicine. Page 582  
issue of April 15

SEPTEMBER 7-11 American Occupational Therapy Association Page  
xv issue of July 8

SEPTEMBER 9 Some of the Advances in Surgery Dr. Frank H. Lahey  
Pentucket Association of Physicians 8:30 p.m. Haverhill.

SEPTEMBER 13-15 American Academy of Pediatrics Olympic Hotel  
Seattle, Washington

SEPTEMBER 16-18 Vermont State Medical Society Annual Meeting  
Burlington.

SEPTEMBER 20-23 American Hospital Association Page 310 issue of  
February 26

SEPTEMBER 22 New England Conference of Industrial Physicians and  
Surgeons. Page 244

SEPTEMBER 29 Mississippi Valley Medical Editors' Association.  
Page 170 issue of January 29

OCTOBER 6-9 American Board of Ophthalmology Page 170 issue of  
January 29

OCTOBER 18-22. American College of Surgeons. Page 34 issue of  
July 1

OCTOBER 27 New England Obstetrical and Gynecological Society  
Annual Meeting Hotel Somerset, Boston

NOVEMBER 1-3 American Clinical and Climatological Association  
Page 582 issue of April 15

NOVEMBER 8-12 American Public Health Association Page 420 issue  
of March 18

NOVEMBER 10-13 Association of Military Surgeons of the United  
States. Page 722 issue of May 13

NOVEMBER 20-23 American Academy of Pediatrics. Annual Meeting  
Chaumont Haddon Hall Hotel Atlantic City New Jersey

DECEMBER 7-9 Southern Surgical Association. Annual Meeting  
Page 543 issue of April 8

DECEMBER 9 and 10 New York State Society of Anesthesiologists.  
Page 34 issue of July 1

FEBRUARY 4 1949 American Board of Obstetrics and Gynecology Inc.  
Page 244

MARCH 28-APRIL 1 1949 American College of Physicians. Page 158  
issue of July 22

NOVEMBER 11-17 1949 Third Inter American Congress of Radiology  
Page 153 issue of July 22

Valleyhead Hospital

CONCORD, MASSACHUSETTS

For the treatment of psychoneuroses, alcoholism, mild mental disorders and chronic diseases Pleasant pastoral setting near historic Concord Accepted modern therapies used Complete occupational and recreational facilities available including outdoor swimming pool and tennis court

S GAGNON, M D J BUTLER TOMPEINS, M D  
Supintendent Director of Clinical Psychiatry  
J P THORNTON M D IRVING KAUFMAN, M D  
Consultant in Neuro-psychiatry Psychiatrist

Post Office, Box 151, Concord Mass Tel Concord 1600

Washingtonian Hospital

41-43 WALTHAM STREET, BOSTON, MASS  
Incorporated 1859

Conditioned Reflex, Psychotherapy, Semi-Hospitalization  
For Rehabilitation of Male Alcoholics  
Treatment of Acute Intoxication and Alcoholic Psychoses  
Included  
Outpatient Clinic and Social-Service Department for  
Male and Female Patients

JOSEPH THIMANN, M D, Medical Director  
Visiting Psychiatric and Neurologic Staff  
Consultants in Medicine, Surgery and the Other Specialties  
Telephone HA 6-1750

Tablets Ferglate-B with C

High in vitamin B complex content to quicken hemoglobin response to iron therapy

EACH TABLET CONTAINS  
Ferrous Gluconate (5 grains) 0.375 gm Pyridoxine HCl 0.15 mg  
Thiamin HCl 3 mg Calcium Pantothenate 0.5 mg  
Riboflavin 2 mg Ascorbic Acid 30 mg  
Niacinamide 20 mg Yeast-Liver Base q.s

INDICATIONS  
Iron deficiency and nutritional anemias as a source of iron and B complex factors

Write Department N-12 for Professional  
Sample and Literature

KENMORE PHARMACAL CO.  
500 COMMONWEALTH AVENUE  
BOSTON 15 MASS

The Boston  
Children's Friend Society

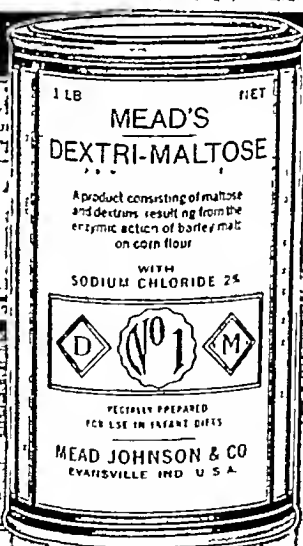
offers its services to physicians for the care of a limited number of unmarried mothers arranging for the adoption of their infants

Address communications to  
GENERAL SECRETARY  
BOSTON CHILDREN'S FRIEND SOCIETY  
123 Marlborough Street, Boston 16, Massachusetts  
Telephone KE 6-8070

# BACKGROUND

The use of cow's milk, water and carbohydrate mixtures represents the one system of

infant feeding that consistently, for over three decades, has received universal pediatric



recognition No carbohydrate employed in this system of infant feeding enjoys so rich and enduring a background of authoritative clinical experience as Dextri Maltose

# The New England Journal of Medicine

Copyright, 1948 by the Massachusetts Medical Society

Volume 239

AUGUST 12, 1948

Number 7

## DIAGNOSTIC AND THERAPEUTIC PROBLEMS IN DIVERTICULITIS\*

C P LEROYER, JR, M D,† AND BENJAMIN V WHITE, M D‡

HARTFORD, CONNECTICUT

DIVERTICULOSIS and diverticulitis are relatively common in persons past the age of forty-five. Ochsner and Bagen<sup>1</sup> discovered that in all the patients registered at the Mayo Clinic in 1933, x-ray study showed diverticulosis in 0.4 per cent, and 7 per cent of all autopsies revealed the presence of diverticula. This corresponds with Morton's<sup>2</sup> figure of 6.5 per cent in 8500 autopsies at the University of Rochester. Among 24,620 cases in which barium enemas were performed Rankin and Brown<sup>3</sup> found diverticulosis in 5.6 per cent.

Diverticulitis occurs at some time in 17 to 27 per cent of all cases of diverticulosis. Rankin and Brown<sup>3</sup> reported the incidence to be about 17 per cent in 1300 cases of diverticulosis, and Abell<sup>4</sup> found it to be 10 to 20 per cent. Ochsner and Bagen<sup>1</sup> observed an incidence of 27 per cent, Smithwick<sup>5</sup> one of 25 per cent, and Willard and Bockus<sup>6</sup> one of 22 per cent.

Most of these analyses of diverticulosis and diverticulitis are concerned with the incidence, etiology and pathological features of the disease. For this reason these aspects are given only brief consideration in the review of the case material that forms the basis of this communication. Emphasis is placed, rather, upon the difficulties of diagnosis that arise from confusion with diseases affecting neighboring organs, and upon the complications.

During the twenty-year period, 1927-1946, 200 cases of diverticulitis were seen at the Hartford Hospital. Of these, 50 were complicated by perforation or obstruction. This incidence is much higher than that in the community at large, because many patients are selected for hospital admission because of symptoms attributable to the complications rather than to the disease itself.

Most of the cases of diverticulitis were seen in persons over forty-five with an antecedent history of spastic constipation or diarrhea. The inflammation in the diverticula was often accompanied by

chills and fever, crampy lower abdominal pain with localized soreness, and a recent change in bowel habits. On physical examination, there was almost invariably tenderness in the lower abdomen to the left of the midline, and a palpable, tender mass or muscle spasm was often found. The temperature was elevated in 60 per cent of the cases, and in 36 per cent there was a white-cell count of over 11,000. The erythrocyte sedimentation rate was frequently increased. Diverticula were evident on barium enema, and spasm was usually present. Sigmoidoscopic examination was seldom helpful. The treatment was medical unless complications arose.

### SIGNS AND SYMPTOMS

The diagnosis of diverticulitis was made by the clinical picture in addition to the x-ray findings in 161 cases, at operation in 32, by the clinical picture alone in 5, and at autopsy in 2. Of the 32 patients in whom the diagnosis was made at operation, 15 were suspected primarily to have acute appendicitis, and 17 were operated on with such preoperative diagnoses as pelvic inflammatory disease, acute cholecystitis, intestinal obstruction and ruptured ovarian cyst. In none of the 32 cases was a barium enema performed.

The leading symptoms and signs were similar to those described by other authors and need no comment (Table 1). However, there are two symptoms due to diverticulitis that bear more consideration—back pain and melena.

Pain in the lower back was noted in 20.5 per cent of the cases. Heretofore little emphasis has been placed on this symptom. By applying irritant solutions to the mucosa of the rectosigmoid through a sigmoidoscope, White and Jones<sup>7</sup> demonstrated that pain could be referred from the colon to the lumbosacral region. This radiation of pain is also encountered in mucous colitis and ulcerative colitis, both of which involve essentially the same portion of the sigmoid as diverticulitis. Thus, there is experimental evidence for back pain in lesions of the rectosigmoid. In diverticulitis this symptom is often part of the clinical picture.

\*From the Medical Service and the Gastroenterologic Clinic, Hartford Hospital.

†Assistant physician, Middlesex County Sanatorium, Waltham, Massachusetts; formerly assistant resident in medicine, Hartford Hospital.

‡Assistant professor of clinical medicine, Yale University School of Medicine; assistant visiting physician, Hartford Hospital.

Another symptom, often the presenting complaint, is the passage of blood by rectum. This may appear as free blood or as flecks on the fecal material. Melena occurred in 16.5 per cent of the cases, a figure that is consistent with those of other authors (Table 1). Ochsner and Bagen,<sup>1</sup> Smithwick<sup>5</sup> and Morton<sup>2</sup> showed that bleeding occurs in diverticulitis more often than is generally believed. Rankin and Brown<sup>3</sup> found that melena was present

times when great confusion exists. Smithwick<sup>5</sup> found that an incorrect diagnosis was made in 26 of 64 cases of acute diverticulitis, a 40.5 per cent of error on initial diagnosis. The three conditions most often confused with diverticulitis are appendicitis, carcinoma of the sigmoid colon and masses involving the structures of the genitourinary tract.

Acute appendicitis is often difficult to differentiate from diverticulitis, and in our series 15 patients

TABLE 1 *Leading Symptoms and Signs in Cases of Diverticulitis*

AUTHOR	NO. OF CASES	AVERAGE AGE	SEX RATIO	CONSTIPATION	DIARRHEA	BACK PAIN	MELANA	FEVER	CRAMPY ABDOMINAL PAIN	WHITE CELL COUNT PER 11,000
Ochsner and Bagen <sup>1</sup>	151	yr 45.0	275:100	58%	26%	5%	22.0%	26%	—	—
Morton <sup>2</sup>	111	44.5	10:10	45	37	—	32.0	29	94	79
Smithwick <sup>5</sup>	333	50-60	10:10	—	—	—	15.7	—	—	—
Willard and Bockus <sup>4</sup>	72	55	10:10	44	15	—	7.0	—	—	—
LeRoy and White	200	60	10:10	50	31	20.5	16.5	59	80	36

in 39 of 142 cases, an incidence of 27 per cent. In discussing Smithwick's<sup>5</sup> paper, C. C. Lund cited a case at the Boston City Hospital in which the chief complaint was severe melena. Soon after admission 1500 cc. of blood was expelled in a bedpan. The patient was operated on as an emergency, and a ruptured diverticulum was found to have involved a large blood vessel, causing extensive intraluminal hemorrhage. In our series, melena was the chief complaint in 6 cases, and in 1 of these the bleeding was extensive enough to require a transfusion.

#### ROENTGENOLOGIC FINDINGS

Spriggs and Marxer<sup>8</sup> pointed out the roentgenologic findings of a prediverticular state that could be recognized before full-blown diverticula had formed. They also described irritability, spasm and narrowing of the lumen as indications of diverticulitis.

Of the 200 Hartford Hospital cases, 161 had barium enemas that showed diverticulosis in the colon, and 133 of these demonstrated definite spasm of the sigmoid, with narrowing of the lumen. The 28 cases of diverticulosis with no spasm had a clinical picture that, with the finding of diverticula by x-ray study, was consistent with the diagnosis of diverticulitis. The X-Ray Department demonstrated a mass by barium enema in 33 of the 161 cases, and the mass was invariably in the sigmoid region. However, the appearance of a mass on x-ray examination is not necessarily diagnostic, since it may be seen with multiple noninflamed diverticula, or it may indicate an unrelated carcinoma or other pathologic process.

#### DIFFERENTIAL DIAGNOSIS

Whereas diverticulitis is often a clear-cut disease that presents no diagnostic difficulties, there are

were operated on with this preoperative diagnosis. In all the appendix was found to be normal, and on exploration an acute, inflammatory diverticulitis of the sigmoid was discovered. In 2 cases the sigmoid loop was to the right of the midline, so that with the findings of crampy abdominal pain, tenderness in the right and middle portions of the abdomen, slight fever and leukocytosis, the diagnosis of acute appendicitis was made. Both patients were found to have normal appendixes.

The following case illustrates the difficulty in differential diagnosis between appendicitis and diverticulitis.

**CASE 1.** A 68-year-old man had been well until 10 hours before admission, when he suddenly developed a rather sharp constant pain in the lower back. After several hours the pain worked around to the right lower quadrant. The last bowel movement had occurred several hours before onset of the pain, and the patient vomited three times. His bowel habits had been normal, and there were no urinary symptoms.

The past history was noncontributory.

Physical examination revealed a well developed, well nourished man in moderate abdominal pain. The pertinent findings were confined to the abdomen, where there was persistent spasm, with rebound tenderness in the right lower quadrant and in the midline. Rectal examination revealed slight soreness on the right.

The temperature was 99.6°F. Urinalysis was negative. The white-cell count was 13,000, with 88 per cent neutrophils and 12 per cent lymphocytes.

At operation a normal appendix was found, and further exploration was carried out. In the midsigmoid there was an area of spasm and induration, and several diverticula were seen. Appendectomy was then performed. On the 9th post-operative day a barium enema showed a localized spastic area in the sigmoid, with numerous diverticula.

The only symptom unusual for appendicitis in this case was the initial pain in the lower back, a finding that was present in 20.5 per cent of the 200 cases of diverticulitis.

Carcinoma of the sigmoid is frequently confused with diverticulitis. The clinical diagnosis is often impossible even with the help of barium enemas,

nd at operation under observation and palpation is sometimes very difficult to differentiate the two lesions. The final diagnosis in this type of case usually rests with the pathologist. The association of carcinoma and diverticulitis has evoked considerable discussion in the literature. Rankin and Brown<sup>2</sup> found carcinoma to be present in 4 of 227 cases of diverticulitis. Smithwick<sup>5</sup> encountered the same lesion in 2.9 per cent of 309 cases of diverticulitis. It is now generally believed that the two conditions may exist coincidentally and that carcinoma of the sigmoid rarely, if ever, develops from pre-existing diverticulosis.

Narrowing of the rectosigmoid or evidence of a mass was demonstrated by barium enema in 33 of the 200 cases of diverticulitis under consideration. In none of the 33 could a differential diagnosis be made on the radiographic findings alone. Schatzki<sup>9</sup> states that the differential diagnosis of carcinoma of the sigmoid and diverticulitis by x-ray study is easy in most, difficult in some and impossible in a few cases.

The following case demonstrates the difficulty in differentiating carcinoma of the sigmoid from diverticulitis.

**CASE 2** A 67-year-old housewife was admitted to the hospital for cramp-like, lower abdominal and rectal pain of 2 weeks' duration, which was worse during defecation. She also noted bright-red blood with mucus in the stools, and she had moderate tenesmus with a desire to defecate three or four times a day. Her appetite was poor, and she had lost 16 pounds of weight in 2 years. She had had no nausea, vomiting or urinary complaints.

Physical examination showed a well developed but poorly nourished woman who appeared anemic. Tenderness without spasm was noted in the middle-lower portion of the abdomen and in the right lower quadrant. No masses were palpable. Rectal examination was negative. Sigmoidoscopy revealed one small area of discolored bowel just above the third valve, and there was a mass that prevented further observation. No blood was seen.

Examination of the blood disclosed a red-cell count of 3,700,000 with a hemoglobin of 12 gm. and a white-cell count of 10,000. Two stools showed strongly positive benzidine tests. A barium enema was not performed.

On the 11th hospital day the patient was explored with the preoperative diagnosis of carcinoma of the rectosigmoid. The mass that was found in the rectosigmoid was to the right of the midline and seemed to involve the lumen of the bowel. The surgeon believed it was carcinoma. A colostomy was made. Four weeks later, when resection was performed, the mass, which had been obstructing the bowel, was found to be smaller, and several diverticula were encountered. After excision an end-to-end anastomosis was performed. The colostomy was not closed at that time. The specimen consisted of a portion of colon 50 cm. in length. There were a few small diverticula lined by normal colonic mucosa, but no evidence of neoplasia was found.

The patient was readmitted 5 months later, and a barium enema revealed no obstruction between the rectum and the colostomy, but showed multiple diverticula and considerable spasm of the sigmoid. At that time the colostomy was closed, and the patient made an uneventful recovery.

This case is significant because of the difficulty in differential diagnosis. Carcinoma was originally considered because the chief complaint was melena. This symptom is more common in acute diverticulitis than has generally been realized. The

appearance of the lesion at operation was also misleading. The similarity of such an inflammatory mass to carcinoma on inspection and palpation is so great that not infrequently the final diagnosis rests with the pathologist.

Diverticulitis may be confused with diseases of the lower genitourinary system. The primary complaints may be dysuria, frequency and burning on urination, and the patient may first be studied from a genitourinary point of view. Pressure on the uri-



**FIGURE 1** Cystogram Showing a Soft-Tissue Mass Producing Pressure on the Posterior Wall of the Bladder and Rotating It Slightly to the Right.

The barium-filled diverticula in that region indicate that the mass probably represented an inflammatory diverticulitis.

nary bladder by an inflammatory mass, secondary to an acute or recurrent diverticulitis, accounts for the bladder symptoms (Fig 1). Such a mass may be found by rectal examination. Extrinsic pressure defects of the urinary bladder may be observed cystoscopically and may be attributed to neoplasm of the rectum or internal genitalia. The following case illustrates the diagnostic confusion that exists when signs and symptoms referable to the bowel and urinary bladder are present.

**CASE 3** A 51-year-old office worker had been entirely well until 1 year before admission, when he began to have pain on defecation. At the time of admission it was relatively severe and he had three to five bowel movements daily, with increasing pain at each successive stool. There had been no diarrhea. Bright-red blood had been present in the stools on several

occasions. In addition, the stools had often been covered by mucus. Recently there had been intermittent, dull, aching lower abdominal pain and urinary frequency.

Physical examination revealed a well developed, slightly thin man in no distress. On rectal examination, there was a firm, rounded mass occupying a position practically in the midline and yet extending well out on each side in the region of the seminal vesicles. It did not suggest a tumor of one or the other seminal vesicles. Distally, it extended down to and was apparently confluent with the prostate.

The temperature, pulse and respirations were normal.

Several urinary specimens were normal, and a culture was negative. The hematocrit was 47 per cent, and the serum protein 6.2 gm per 100 cc.

On proctoscopy a mass was seen above the prostate. The mucosa of the rectum was intact but puckered down at the junction of the mass with the prostate.

Several needle-punch biopsies were taken. Microscopical examination showed hyalinized strands of fibrous tissue in

sigmoid with an end-to-end anastomosis was carried out. Microscopical study of the sections revealed many diverticula, two of which showed infected sinus tracts into the sigmoid mass. Another section demonstrated that the seminal vesicles were surrounded by chronic inflammatory tissue.

The final diagnosis was diverticulitis of the sigmoid, with secondary seminal vesiculitis.

This case demonstrates how an acute, inflammatory diverticulitis can drain to the rectovesical pouch, with formation of a secondary inflammatory mass closely associated with the internal genitalia and bladder wall.

In the series reviewed, 18 patients with diverticulitis had urinary symptoms, and of these, 3 developed bladder fistulas.

### COMPLICATIONS

The complications of diverticulitis are of interest in terms of incidence and of surgical management. Smithwick<sup>5</sup> found that 19.2 per cent of 333 cases of

TABLE 2 Complications in Cases of Diverticulitis

COMPLICATION	No. of Cases
Perforations	45
Local abscess	32
Peritonitis, with ileus	1
Mechanical obstruction	4
Fistula formation	6
Rectovaginal	3
Rectovesical	3
Mechanical obstruction due to local inflammation	7
Total	100

diverticulitis required surgery and that the incidence of such surgical complications in persons over the age of forty was 1/2500.

Perforation may lead to localized abscess formation, peritonitis with ileus, mechanical obstruction or fistula formation. These are the most common complications. However, mechanical obstruction

TABLE 3 Location of Abscess in 32 Cases

LOCATION	No. of Cases
Abdominal	18
Pelvic	14
Rectovesical	9
Rectovaginal	2
Colonovesical	1
Rectosigmoidal	1
Broad ligament (left)	1
Total	32

which there was a chronic inflammatory reaction. No evidence of a neoplastic process was made out.

On the 4th hospital day, cystoscopy was performed. The trigone was elongated, and the ureteral orifices were farther apart than normal. At a level 1.0 cm above the orifices, a band of trabeculation was seen, which persisted on distention. The bladder mucosa was normal. X-ray films of the pelvis, after the bladder had been injected with an opaque medium, showed the ureters and the floor of the bladder to be pushed forward. The upper urinary tract was normal.

The patient was explored extraperitoneally through a suprapubic incision. A lemon-sized, inflammatory mass was found in the rectosigmoid attached to the posterior aspect of the bladder. This mass seemed to bulge into the bowel. On palpation, deep in the pelvis, a second mass of equal size was found. This occupied the region of the seminal vesicles and extended distally under the trigone of the bladder to the prostate. Frozen sections proved that this mass surrounded the seminal vesicles and was not primary in them. The primary lesion was in the bowel, and the indurated inflammatory mass was secondary (Fig. 2). A wide resection of the lesion in the

due to narrowing of the bowel lumen by a local inflammatory mass may be found in a smaller portion of patients. Twenty-five per cent of the 200 Hartford Hospital cases developed a complication. Local abscesses secondary to perforation were by far the most common (Table 2). Smithwick<sup>5</sup> reported local

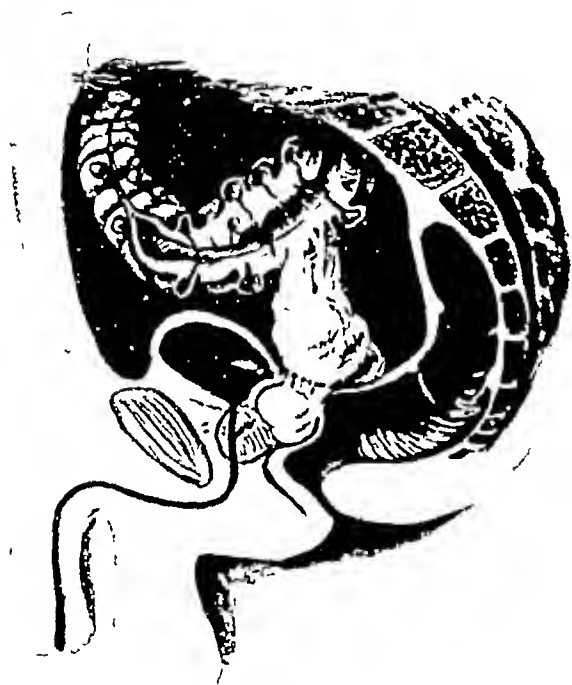


FIGURE 2 Diagrammatic Sketch of the Findings at Operation in Case 3, Showing a Diverticulitis of the Sigmoid, with a Large Inflammatory Mass.

A second mass can be seen above the prostate compressing the trigone of the bladder and bulging into the rectum.

abscesses in 11.9 per cent of 506 cases, with a mortality of 9.3 per cent.

Table 3 indicates the location of the abscesses in the Hartford Hospital series. Of 18 abdominal abscesses, 13 were drained with no further complications. Four led to intestinal obstruction, and 1 resulted in death from generalized peritonitis. However, of 14 pelvic abscesses, 6 developed into fistulas. Three of these drained into the bladder, and 3 into the vagina. The over-all incidence of fistulas was 3 per cent. Morton<sup>2</sup> found 22 cases of fistula formation in 83 complicated cases of diverticulitis. Smithwick<sup>5</sup> records an incidence of 13.1 per cent of spontaneous bladder fistulas in 611 complicated cases. Higgins<sup>10</sup> noted that of 160 cases of vesico-colonic fistula, 57.5 per cent were secondary to diverticulitis.

Mechanical obstruction in the rectosigmoid by an inflammatory mass due to diverticulitis occurred

other neoplastic lesions, and complicates the differential diagnosis.

The 25 per cent incidence of perforations and inflammatory obstructions is undoubtedly much higher than that in the community at large, because such complications serve as indications for admission to a hospital. Among 18 patients with abscesses within the peritoneal cavity, there was 1 with generalized peritonitis, and 4 others had intestinal obstruction secondary to localized inflammation. On the other hand, among 14 patients with abscesses in the pelvis, fistulas were encountered in 6. Hence, it appears that inflammatory masses within the peritoneum often lead to intestinal obstruction, whereas those in the pelvis frequently result in fistulas.

### SUMMARY

The clinical features of 200 cases of diverticulitis treated at the Hartford Hospital between 1927 and 1946 are reviewed.

The relative incidence of the leading symptoms and signs was essentially similar to those generally reported. A notable exception was the occurrence of pain in the lower back as a prominent feature in 20.5 per cent of the cases. A finding in accord with other authors' experiences, but worthy of special emphasis, was the presence of melena in 16.5 per cent.

Diagnostic confusion occurred most frequently in cases that presented signs suggestive of acute appendicitis, and in those in which masses in the lower abdomen or pelvis could not be differentiated clinically from carcinoma of the bowel or from genitourinary lesions such as ruptured ovarian cyst and carcinoma of the seminal vesicles or prostate.

Complications were encountered in 50 cases, or 25 per cent. These included 7 of obstruction secondary to ligneous induration of the affected sigmoid and 43 perforations. Thirty-two of the latter led to local abscesses, 6 to fistulas, 4 to mechanical obstruction, and only 1 to generalized peritonitis.

### REFERENCES

1. Ochsner H. C. and Bagen J. A. Diverticulosis of large intestine: evaluation of historical and personal observations. *Ann. Int. Med.* 9:282-296, 1915.
2. Morton J. J. Diverticulitis of colon. *Ann. Surg.* 124:722-745, 1946.
3. Rankin F. W. and Brown P. W. Diverticulitis of colon. *Surg., Gynec. & Obst.* 50:836-847, 1910.
4. Abell I. Diverticulosis of colon. *Ann. J. Surg.* 46:158-161, 1929.
5. Smithwick R. H. Experiences with surgical management of diverticulitis of sigmoid. *Ann. Surg.* 118:969-985, 1942.
6. Willard J. H. and Boekus H. L. Clinical and therapeutic status of cases of colonic diverticulosis seen in office practice. *Am. J. Digest. Dis.* 3:580-584, 1916.
7. White B. V., Jr. and Jones C. M. Effects of irritants and drugs affecting autonomic nervous system upon mucosa of normal rectum and rectosigmoid with especial reference to mucous colitis. *Ver. Erg. J. Med.* 218:791-797, 1918.
8. Spriggs E. I. and Marxer O. A. Intestinal diverticula. *Quart. J. Med.* 19:1-4, 1925.
9. Schatzki R. I. Roentgenologic differential diagnosis between cancer and diverticulitis of colon. *Radiol. C.* 34:611-662, 1940.
10. Higgins C. C. Vesico-intestinal fistula. *J. Urol.* 36:694-709, 1916.

TABLE 4 Types of Operations on Patients with Diverticulitis

OPERATION	No. of Cases
Diagnostic	
Appendectomy	15
Laparotomy (only)	3
Hysterectomy	1
Incidental	
Herniorrhaphy (ventral)	1
Cholecystectomy	2
Posterior gastroenterostomy	2
Hemorrhoidectomy	1
Therapeutic	
Irrigation and drainage of abdominal (or pelvic) abscess	17
Colostomy	4
Cecostomy	7
Mikulicz (stages I and II)	3
Colostomy with resection	2
Resection with anastomosis	5
Total	63

in 7 cases, an incidence of 3.5 per cent. All patients recovered after operation.

Table 4 indicates that among the 200 Hartford Hospital cases 63 operations were carried out, 19 of them for diagnostic purposes. In all there was acute diverticulitis of the sigmoid. Six patients were operated on for other conditions (Table 4), and acute diverticulitis was found incidentally. Thirty-eight surgical procedures were carried out.

### DISCUSSION

Most of the findings of this review of 200 cases of diverticulitis are in accord with those of other authors. From the diagnostic point of view two features are striking: the relatively high incidence of back pain and the frequency of bleeding from the rectum. The latter is somewhat disconcerting because it detracts from the significance of blood in the rectosigmoid as an indication of polyps or

## RELAPSING KALA-AZAR\*

## Report of a Case with Cure Effected by Stilbamidine

PAUL R. WILNER, M.D.,† AND MAJOR THOMAS A. HAEDICKE, M.C., A.U.S.‡

WASHINGTON, D. C.

THERE have been many reports concerning the increased incidence of certain tropical diseases in the United States during the postwar period. Service personnel were exposed to and contracted more tropical diseases than any previous group of citizens. There were many cases of dysentery, malaria and dengue among the armed forces. However, the incidence of more exotic tropical diseases, such as leishmaniasis, relapsing fever, cholera and trypanosomiasis, was fortunately much less.

During the immediate postwar period, it became apparent that no widespread outbreaks of tropical diseases in this country would occur chiefly because of the climate, housing and sanitation and the absence of certain vectors. Relapsing and delayed primary attacks of malaria have not been uncommon, and there is no doubt that amebiasis is more evident. Other tropical diseases may be seen sporadically, not only because of a residual focus in returned veterans but also because of increased air travel.

Kala-azar may be encountered. On the basis of a preliminary account of Army medical records, approximately 56 cases of visceral leishmaniasis were reported among Army troops during the period 1942-1945. The diagnosis should be considered in every obscure illness since the over-all untreated mortality throughout the world is 95 and the treated mortality less than 5 per cent. A recent review of the disease in the United States by Ecker and Lubitz<sup>1</sup> emphasizes that kala-azar demands a higher index of suspicion among physicians in the United States.

The clinical picture and course of kala-azar are usually typical. The disease is characterized by an irregular fever, chronicity, splenomegaly, emaciation, anemia and leukopenia. However, the disease may be quite mild and vague. Armstrong<sup>2</sup> has shown that patients may be ill with kala-azar and still have very few obvious complaints. The clinical course varies with the geographic origin of the disease. We have found the disease acquired in the Sudan to be most severe.

The diagnosis of kala-azar is sometimes very difficult. The history and physical examination may be typical, but the demonstration of the causative

organism, *Leishmania donovani*, is necessary for diagnosis. Packchianian<sup>3</sup> believes that the diagnosis may be made only by culture of *L. donovani* from the blood, bone marrow, spleen or liver. Scovell<sup>4</sup> does not consider a positive culture necessary. We have not found the peripheral blood cultures of much value in establishing the diagnosis in Americans. The material aspirated from the spleen and bone marrow produces 95 per cent of positive smears and cultures.

Other tests, such as those using aldehyde, antimony and distilled water, may be useful. Feldman<sup>5</sup> has found the formol-gel test of help in suggesting the diagnosis. As this test is based upon the hyperglobulinemia present in kala-azar, it is positive in any condition producing hyperglobulinemia. It was negative in the case reported below.

Antimony preparations, especially neostibosan and urea-stibamine, are the present drugs of choice for therapy. The response to treatment, like the severity, depends on the geographic origin of the disease. Burchenal and Woods<sup>6</sup> reported 3 cases acquired in the Mediterranean area, 2 of which responded poorly to the antimonials. The patients of Waud and Kruger<sup>6</sup> responded to a relatively small amount of antimony. However, their follow-up study was probably of too short duration to meet the criteria for cure of visceral leishmaniasis brought out in a recent review by Marple.<sup>7</sup> It should be emphasized that these patients cannot be considered cured unless they are followed for a minimum of six months.

Hargreaves<sup>8</sup> reported several cases from Italy and Sicily that did not respond to antimony and were treated with urea-stibamine and stilbamidine. His results were satisfactory in the treatment of all cases of Indian and Mediterranean kala-azar. May and Baker,<sup>9</sup> of London, recommend pentamidine for the treatment of patients who relapse after antimonial therapy. It is possible that some kala-azar patients develop resistance to all forms of chemotherapy. In a case recently published, which was complicated by severe anemia and finally cured by splenectomy, the patient received large amounts of antimonials and stilbamidine over a period of two years with only temporary improvement.<sup>10</sup>

Stilbamidine was first brought into clinical prominence by the work of Napier and Sen Gupta<sup>11</sup> at the London School of Tropical Medicine in an effort to find a drug that would cure antimony-resistant kala-azar. It became apparent that all patients not

\*From the Medical Service, Walter Reed General Hospital, Army Medical Center.

†Instructor in clinical medicine, Georgetown University School of Medicine.

‡Lecturer in tropical diseases, Georgetown University School of Medicine, chief, Tropical Disease Section, Walter Reed General Hospital, Army Medical Center.

responding to antimony therapy were cured with stilbamidine

The administration of stilbamidine presents several problems, and a detailed discussion is therefore presented. The di-isethionate form of the drug is more soluble and easier to prepare. A maximum of 15 mg per pound of body weight is given in any one day. The entire dose should be mixed with approximately 250 cc of physiologic saline solution or distilled water to prevent thrombosis of veins. An initial dose of 40 mg is given to each patient, and this is followed every day with a higher dose until the maximum dose has been attained. A fresh preparation of the solution should be made daily, and it should be given intravenously. Oastler and Fidler<sup>12</sup> demonstrated that stilbamidine is much more hepatotoxic and nephrotoxic in dogs when exposed to light prior to administration. A fresh preparation prevents the occurrence of liver damage sometimes noted in patients. A total dose of approximately 4 gm is considered adequate. Napier and Sen Gupta<sup>11</sup> administered as little as 15 gm to patients with kala-azar who had previously relapsed after treatment with antimony.

Patients seem to tolerate stilbamidine well, but a few toxic vasomotor manifestations should be mentioned. Various subjective symptoms, usually of a transient nature, include flushing of the face, giddiness, breathlessness, faintness, nausea, vomiting, epigastric discomfort, salivation, sweating, tachycardia and occasionally collapse. After the

tom complex generally begins three or four months after administration has been completed and may last for several years.

The following case is presented because of several interesting features in diagnosis and treatment. The patient had malaria and amebiasis in addition to kala-azar and presented an apparent cure when treated with quinine, quinacrine (atabrine) and emetine. One sternal-marrow puncture was negative, and the *L. donovani* bodies were found on only two of the nine slides made from the second puncture. Two courses of neostibosan failed to cure the infection. One course of stilbamidine was successful.

### CASE REPORT

A 36-year-old former Army officer was overseas in India, upper Assam and China from March, 1944, to November, 1945. In August, 1944, he had an acute attack of tertian malaria treated with quinine and atabrine. Intermittent diarrhea was present and was occasionally treated with small amounts of sulfaguanidine and diodoquin.

The patient felt well on his return to the United States until the onset of his present illness on March 3, 1946. This was characterized by chilliness, fever, sweats and malaise. He was first seen on March 6, when the temperature was 102°F, the spleen was palpable three fingerbreadths below the costal margin and the liver was tender, its edge being palpable two fingerbreadths below the costal margin. A blood smear revealed *Plasmodium vivax*. Atabrine therapy was followed by an apparent response. Quinine sulfate (0.6 gm daily) was prescribed as a maintenance dose.

On March 25 the patient reported a recurrence of malaise, chilliness, fever and sweats and was confined to bed at home. His temperature fluctuated widely, readings of 104° and 105°F being reported and the minimum being 99°F. Drenching sweats were prominent, and insomnia was troublesome. There was no frank chill. An increased looseness and frequency of

TABLE 1 Pertinent Laboratory Data\*

DATE	RED-CELL COUNT	HEMO- GLOBIN	WHITE CELL COUNT	NEUTRO- PHILS	LYMPHO- CYTES	MONO- CYTES	EOSINO- PHILS	BLOOD CULTURE	STOOL EXAMINATION
1946	x10 <sup>6</sup>	gm/100 cc	x10 <sup>3</sup>	%	%	%	%	at 48 hr	
March 30	3.20	11 (67%)	5.8	58	40	4	0	—	—
March 31	—	—	—	—	—	—	—	No growth	—
April 1	3.35	10 (60%)	5.5	62	33	3	2	—	Negative
April 2	—	—	—	—	—	—	—	No growth†	Negative
Apr 13	—	—	—	—	—	—	—	—	Cysts of <i>Endamoeba histolytica</i>

\*Agglutinations for *Eberthella typhosa* (strains A and B), *Proteus vulgaris* (strains O12 and O19) and *Brucella abortus* were negative in all dilutions on March 31.

†Penicillinase added.

first few injections of the drug there is usually a fall in blood pressure, which is frequently marked. As the blood pressure returns to its normal level, most of the symptoms disappear, usually within half an hour or so. These reactions may be controlled or prevented by an injection of epinephrine.

Nervous symptoms, including paresthesia, peripheral neuritis, paraplegia and trigeminal neuropathy, may develop after treatment has been continued for some time, suggesting a cumulative action. The most important of these is an unexplained bilateral trigeminal neuropathy in which light touch is absent and pain and temperature sensation is preserved along the course of the fifth cranial nerve. Numbness and tingling over this entire area may be a real complaint. This symp-

stools was noted, which continued for several weeks. At times, the patient was incontinent. A pasty type of pallor was present.

The spleen was hard and palpable three or four fingerbreadths below the costal margin. The liver edge was palpable two fingerbreadths below the costal margin and was tender and sharp. On March 28 examination of the blood disclosed a red-cell count of 4,090,000, with a hemoglobin of 11.5 gm (76 per cent), and a white-cell count of 3700, with 49 per cent neutrophils, 10 per cent band forms, 39 per cent lymphocytes and 12 per cent monocytes. Malaria smears were negative. Urinalysis was negative. Quinine sulfate (0.6 gm three times a day) was administered from March 25 to 29, with no response objectively or subjectively.

On March 29 the patient was admitted to a hospital. His course was stormy. Chills, fever, vomiting, diarrhea, drenching sweats, apprehension and disorientation were prominent. His temperature had a tendency to double daily spikes. Six to eight liquid stools occurred daily. Vomiting occurred two or three times daily. The physical findings remained the same. The patient began to look emaciated. The results of laboratory studies performed from March 30 to April 2 are presented

in Table 1 Urinalysis was negative. A sternal puncture on April 3 was negative for *L. donovani*. Specific treatment with atabrine (12 gm) and penicillin (640,000 units), in addition to supportive measures, was ineffective.

He was transferred to Walter Reed General Hospital on April 4. The white-cell count was 2100, with 60 per cent

ulins of 1.74 gm. The formol-gel test was negative. An x-ray film of the chest was normal.

The patient failed to respond to emetine, and his temperature rose to 104°F. It was believed that he had either an abscess of the liver that was not responding to emetine or kala-azar, which had not been proved. Fluoroscopic study

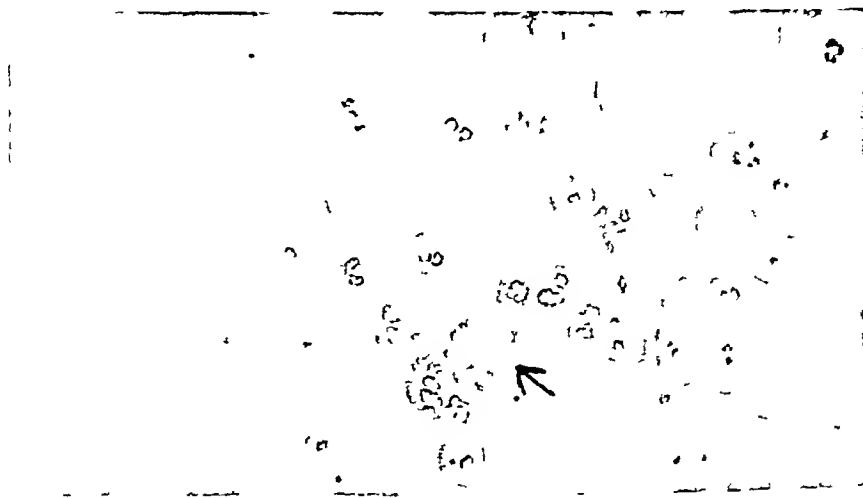


FIGURE 1 Endothelial Cell Containing Leishman-Donovan Bodies (Arrow)  
The dark objects within the red cells are artefacts

neutrophils, 38 per cent lymphocytes and 2 per cent monocytes. The total protein was 5.75 gm per 100 cc, with an albumin of 3.8 and a globulin of 1.95 gm per 100 cc. A blood

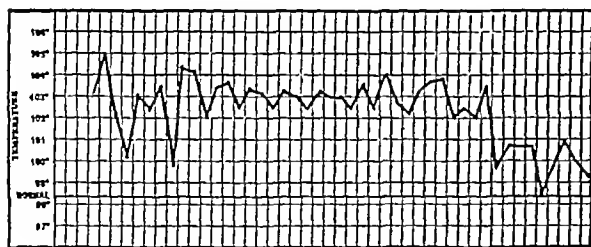


FIGURE 2 Temperature from March 29 to April 5

culture, complement-fixation test for amebiasis, Widal test on the stools and stool culture were negative, as was the formol-gel test.

The differential diagnoses were amebic hepatitis, visceral leishmaniasis and typhoid fever. Because cysts of *E. histolytica* were found in the stools and the liver was enlarged and tender, a course of emetine (0.55 gm) was administered. A dramatic response to emetine was noted. The temperature dropped to normal levels, and the appetite improved, the red-cell count rose to 4,000,000, and the white-cell count to 5000. The patient felt well. He was discharged on April 14 and he continued to improve. The size and tenderness of the liver decreased, but the spleen remained the same size.

This apparent cure continued for approximately 2 weeks, when he began running a low-grade fever, which gradually increased. Malaise recurred, and he was readmitted to Walter Reed General Hospital on May 1 for further treatment of what was thought to be an amebic abscess. The entire picture was identical with that during the previous episode with splenomegaly, hepatomegaly and the following laboratory studies: negative malarial smears, a red-cell count of 2,440,000, with a hemoglobin of 43 per cent, and a white-cell count of 2750, with 59 per cent neutrophils, 38 per cent lymphocytes, and 2 per cent monocytes. The total protein was 5.65 gm per 100 cc, with an albumin of 3.91 and a glob-

ulin of 1.74 gm. The formol-gel test was negative. An x-ray film of the chest was normal.

The patient failed to respond to emetine, and his temperature rose to 104°F. It was believed that he had either an abscess of the liver that was not responding to emetine or kala-azar, which had not been proved. Fluoroscopic study

of the right leaf of the diaphragm demonstrated good mobility on inspiration and expiration. The white-cell count remained low. In view of these findings, abscess of the liver or diffuse amebic hepatitis was deemed unlikely. A repeated sternal puncture revealed *L. donovani* organisms on two of the smears, and a culture of the aspirated blood from the sternal marrow was later reported positive for *L. donovani* (Fig 1). This confirmed the diagnosis of kala-azar. A good response was brought about with a total of 2.7 gm of neostibosan, and he was discharged on May 20, afebrile and well. The red-cell count was 3,830,000, with a hemoglobin of 60 per cent, and the white-cell count was 5250.

The patient was followed during the months of June and July periodically. Toward the beginning of July, it was apparent that he was not cured of his disease. Although he ate well and led a restful life, he did not fully regain his strength. His color was pasty. His liver and spleen continued to be palpable. The hemoglobin and red-cell count dropped from 85 per cent and 4,390,000 on June 27 to 70 per cent and 3,580,000 on July 10. It was believed that another course of neostibosan should be instituted. This was carried out from July 15 through 26. He received a total of 3.45 gm. of neostibosan at home with apparent complete remission. There

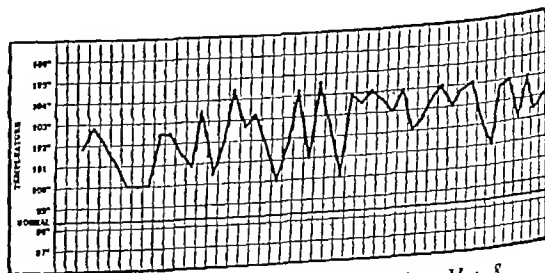


FIGURE 3 Temperature from May 1 to May 8

was a reduction in the size of the liver and spleen, although they still remained palpable.

After 1 month of apparent cure, a recurrence of fever and malaise began on August 24. This continued, and he was

mitted for the third time to Walter Reed General Hospital on August 30, remaining until September 20.

On admission it was evident that the patient was markedly icteric. The temperature was 101°F, the spleen was palpated three fingerbreadths below the left costal margin on deep inspiration (one and a half fingerbreadths at rest) but as not tender. The liver was not palpable.

On August 31 examination of the blood revealed a red-cell count of 2,100,000, with a hemoglobin of 46 per cent, and a white-cell count of 3100, with 36 per cent lymphocytes, 6 per cent monocytes, 3 per cent basophils and 55 per cent neutrophils.

On September 20 the red-cell count was 3,750,000, with hemoglobin of 78 per cent, and the white-cell count 6300, with 45 per cent neutrophils, 49 per cent lymphocytes, 4 per cent monocytes, 2 per cent eosinophils and 0.8 per cent reticulocytes. Urinalysis was negative. The total protein was 8 gm per 100 cc, with an albumin-globulin ratio of 1:4:1.

Stilbamidine therapy was instituted, consisting of 150 mg per day intravenously for the first 2 weeks and 300 mg daily or the last week, a total of 4,325 gm being given in the 21-day period. The temperature reached normal levels on the 12th day of therapy and has continued so to date. The edge of the spleen was palpated five fingerbreadths below the left costal margin during the first 2 weeks of therapy and gradually receded. On the 21st day of therapy, the spleen extended only one and a half fingerbreadths below the costal margin on inspiration, and the edge was barely palpable at rest.

The temperature curves during the hospital admissions are demonstrated in Fig. 2-5.

After his discharge from Walter Reed General Hospital on September 20, the patient continued to feel well. He regained his strength and carried on his normal activities.

On October 16 the liver edge was not felt and the tip of

## SUMMARY

A case of kala-azar is reported. Difficulties in diagnosis were encountered, emphasizing the varied nature of the disease. The patient relapsed after two courses of neostibosan. Complete cure was obtained with 4,325 gm of stilbamidine. It is

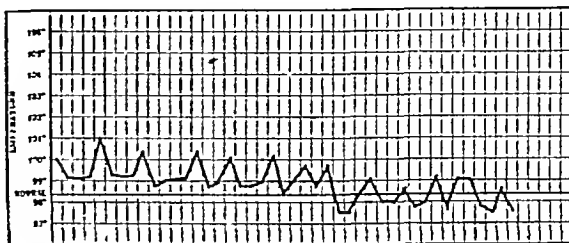


FIGURE 5 Temperature from August 31 to September 5

suggested that kala-azar be included in the differential diagnosis of any obscure febrile illness. Stilbamidine may be considered efficacious in relapsing visceral leishmaniasis until less toxic drugs have been proved to be of value.

## REFERENCES

1. Ecker H D and Lubitz J M. Kala azar in United States: review of literature and report of two cases: stilbamidine treatment. *Ann. Int. Med.* 26:720-735 1947.
2. Armstrong T G. Asymptomatic kala azar in soldiers from over seas. *Brit. M. J.* 2:918 1945.
3. Packham A. Leishmaniasis: cultivation of leishmania tropica from two American soldiers who had returned to United States from Near East. *J. A. M. A.* 129:544-547 1945.
4. Feldman A. Kala azar with onset of symptoms in Great Britain. *Brit. M. J.* 2:816 1946.
5. Burchenal J H and Woods R P. Visceral leishmaniasis: report of three cases of its occurrence in members of armed forces of United States. *War Med.* 7:173-177 1945.
6. Waud S P and Kruger S. Visceral leishmaniasis: report of case. *New Eng. J. Med.* 236:63 1947.
7. Marple C D. Visceral leishmaniasis (kala azar): report of case. *Ann. Int. Med.* 26:787-795 1947.
8. Hargreaves W H. Recent experiences in treatment of kala azar. *Mil. Surgeon* 100:212-214 1947.
9. May and Baker. Cited by Robertson D F. Personal communication.
10. Burchenal J H., Bowers R. and Haedick T A. Visceral leishmaniasis complicated by severe anemia—improvement following splenectomy. *Am. J. Trop. Med.* 27:699-709 1947.
11. Napier L E. and Sen Gupta P C. Peculiar neurological sequel to administration of 4,4'-diamidino-diphenylethylene (M & B 744). *Indian M. Gaz.* 77:71-74 1942.
12. Oastler E G. and Fidler H K. Cerebral lesions in healthy dogs by intravenous injection of 4,4'-diamidino stilbene. *Tr. Roy. Soc. Trop. Med. & Hyg.* 39:533-538 1946.

## ADDITIONAL REFERENCE

- Scovel F G. Kala azar: review of its incidence and epidemiology in China and clinical observation on 385 cases. *Ann. Int. Med.* 21:607-627 1944.

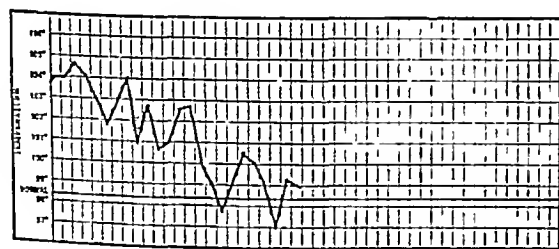


FIGURE 4 Temperature from May 9 to May 12

his spleen was just barely palpable. On January 15 1947, he noticed a numbness of his upper lip, both cheeks, ears and temples. There was definite anesthesia to light touch, but no change in pain or temperature sensation. Motor components were unchanged. This was thought to be dissociated anesthesia of the fifth cranial nerve.

On February 24 the hemoglobin was 91 per cent, the red-cell count 4,470,000, and the white-cell count 6200 and the patient reported improvement in the neurologic sensations.

On June 15 there was continued improvement in the neurologic symptoms. There had been no recurrence of fever or malaise, although the tip of the spleen was still palpable.

## CESAREAN SECTION AT THE BOSTON CITY HOSPITAL, 1936-1946\*

DANIEL J MCSWEENEY, MD,† AND ARTHUR J HASSETT, MD‡

## BOSTON

AT THE Boston City Hospital in the ten-year period from 1936 to 1946 there were 961 cesarean sections—3.3 per cent of 28,341 deliveries, or 1 cesarean section in every 29 cases. This incidence is about the same as that reported by Duncan and Doyle<sup>1</sup> for the previous ten years, in which there were 703 sections in 22,880 deliveries, an incidence of 3.07 per cent. The Boston Lying-in Hospital<sup>2</sup> reported an incidence of 3.4 per cent on its ward service, and the State of Massachusetts 3.3 per cent.<sup>3</sup> These figures suggest a general attitude of conservatism throughout Massachusetts in the performance of cesarean section, especially in the larger public ward service in the city of Boston.

From 1936 to 1939 there was a steady increase in the percentage of cesarean sections (Table 1),

TABLE 1 Yearly Incidence of Cesarean Section

YEAR	NO OF DELIVERIES	NO OF CESAREAN SECTIONS	INCIDENCE %
1936	3180	84	3.5
1937	3295	135	4.0
1938	3320	142	4.2
1939	3262	88	2.7
1940	3225	83	2.5
1941	2969	91	3.0
1942	2918	81	2.7
1943	2447	96	3.9
1944	1964	82	4.1
1945	1761	79	4.5

which gave way to an abrupt decline in 1939, when x-ray pelvimetry was adopted as an additional check on a patient's ability to deliver through the natural channels. Since 1943 surgeons have been more radical in the choice of abdominal delivery under the protecting influence of the blood bank, the sulfonamides and penicillin. The present tendency seems everywhere to be a broadening of the indications for the cesarean operation.

## AGE

Patients thirty-five years of age and over, called injudiciously "the elderly group," comprised 70 per cent of the series. These patients suffer more of the complications requiring cesarean section, and protection of the baby of the elderly primigravida provokes more serious consideration than

that of the younger gravida with a longer span of reproductive years ahead of her. In addition, prolonged labor and difficult forceps deliveries seem to cause in the former group more chronic debilitating conditions, such as prolapse, cystocele and relaxations of the pelvic floor.

## PARITY

Twenty-eight per cent of the sections were done on primigravidas. In the remaining 72 per cent constituting the multiparous cases, 606, or 87 per cent of 689 cases, were repeat sections. Only 83 cases (8 per cent of the total series) of primary cesarean section were done on multiparas.

The extraordinary number of repetitions of abdominal hysterotomy (Table 2) is due to the fact that no sterilizations are done at the Boston City Hospital, nor is a Porro cesarean hysterectomy done unless there is definite uterine disease to warrant its adoption. It is interesting that there were only 6 ruptured uteri in the decade of this study, 2 traumatic and 4 occurring in patients with scars from previous cesarean sections, all of whom had had only one previous section. There were no ruptured uterine scars in the 602 other

TABLE 2 Primary and Repeat Cesarean Sections

TYPE OF SECTION	NO. OF CASES
First	355
Second	349
Third	181
Fourth	52
Fifth	16
Sixth	7
Seventh	1

repeat sections, in 257 of which the patients were experiencing abdominal delivery for the third time or more frequently.

## INDICATIONS

The indications for cesarean section are presented in Table 3. If a patient has had a section on her first delivery she is invariably treated in like manner in subsequent pregnancies. On the other hand, if she has had a vaginal delivery without difficulty prior to her first section and there was no sepsis after the cesarean section, she is given a test of labor under careful observation. If the cervix yields readily and there is no evidence of dystocia, delivery is effected through the natural route as soon as full dilatation is attained. If a patient has

\*From the Department of Obstetrics, Boston City Hospital and Boston University School of Medicine.

†Professor of clinical obstetrics, Boston University School of Medicine; assistant visiting obstetrician, Boston City Hospital.

‡Formerly resident in obstetrics and gynecology, Boston City Hospital and assistant in obstetrics, Boston University School of Medicine.

and more than one cesarean section she is not allowed to go into labor, but a repeat section is done within the last four weeks of pregnancy as soon as the estimated size of the fetus offers fair assurance that the baby will weigh approximately 5 pounds or over.

The abdominal deliveries for disproportion since 1939 were done only after x-ray pelvimetry demonstrated inadequacies in the size and shape of the pelvis and then only after a fair test of labor. In his clinic the incidence of disproportion requiring cesarean section is about 1 in 100 cases.<sup>4</sup>

Uterine inertia, which seems to be interrelated with cervical dystocia, accounted for 36 of the operations. In these most disconcerting cases there is no discrepancy between the fetal head size and that of the pelvis and yet the uterine contractions and the rigidity of the cervix fail to allow natural termination of labor. Contraction-ring dystocia may rightfully be included in cervical dystocia, making a total of 40 cases, or 4 per cent of the cesarean sections being done for abnormalities in the propulsive factors of labor. This, we believe, is a comparatively low incidence.

Primiparous breech delivery was the causative factor in only 1.5 per cent of the cases. Of 1200 breech presentations only 17 cases, all in primiparas, required cesarean section. X-ray pelvimetry is done routinely in all cases of primiparous breech delivery, and an adequate test of labor allowed before the decision is made to perform an abdominal delivery.

Previous gynecologic plastic operations accounted for but 2 cases of the series. The rarity of this indication is due to the conservative policy of performing extensive vaginal repairs until the patient has passed the child-bearing age.

Placenta previa, we believe, is best treated by cesarean section, except in cases of low implantation with slight bleeding and a cervix effaced and dilatable, assuring a speedy onset and rapid termination of labor after artificial rupture of the membranes. Patients with placenta previa, if the diagnosis is made with sufficient confidence from soft-tissue x-ray films and cystograms, may undergo cesarean section without corroborative vaginal examination. If the x-ray film does not offer enough proof of the abnormally situated placenta a sterile vaginal examination is done as near term as possible with the operating room prepared for abdominal delivery.

Premature separation of the placenta is usually managed with cesarean section after the patient has recovered from the initial shock. In an occasional case with a soft, dilatable cervix rupture of the membranes and a tight abdominal binder are employed.

Fibroids were a rare indication for cesarean section, accounting for only 4 cases in this study,

and these presented obstructing tumors to delivery from below. Myomectomy was rarely done with the section, and there were no Porro cesarean hysterectomies with fibroids as an indication.

Sixteen cesarean sections were done for severe toxemia and eclampsia, a low incidence that is due partly to the infrequency of toxemias in the past decade and also to the conservative management of these cases. There were 9 cases of severe pre-eclampsia and 7 of eclampsia in this group with no deaths. One patient with severe toxemia with abruptio placentae, however, died of uremia and cortical necrosis of the kidneys. In the patient with severe toxemia who has reached a quiescent

TABLE 3 Indications for Cesarean Section

INDICATION	NO OF CASES
Repeat	606
Disproportion	141
Uterine inertia	36
Contraction ring	4
Primiparous breech delivery	17
Gynecologic repair	2
Placenta previa	68
Marginal	13
Partial	25
Complete	32
Premature separation of placenta	57
Fibroid uterus	4
Severe toxemia	9
Eclampsia	7
Ruptured uterus	6
Rheumatic heart disease	4

stage and in whom delivery must be effected as expeditiously as possible, if the cervix is not ripe for induction of labor, elective cesarean section is done preferably under local anesthesia with pentothal sodium intravenously, or with pentothal alone.

There were 6 cases of ruptured uterus, 2 traumatic from attempted delivery outside the hospital and 4 that followed rupture of scars of previous cesarean sections. The treatment was always hysterectomy.

Four patients with rheumatic heart disease were decompensated at the time of operation and were managed by cesarean section with considerable misgiving and with a fatal outcome in 3 cases. Medical consultation had offered an unfavorable prognosis whatever course was selected and suggested possible amelioration of symptoms if the fetus were removed through the abdominal route with the least possible trauma under local anesthesia. The severely decompensated cardiac patient in the last trimester will always present a difficult problem with a poor prognosis no matter how the pregnancy is terminated.

#### OPERATORS

Four hundred and forty cases were done by the residents and interns, and 521 by the visiting staff. Paradoxically, there were only 3 deaths among

the cases done by the residents, a mortality of 0.7 per cent, whereas 20 patients who were operated upon by the visiting staff died, a mortality of 4 per cent. The discrepancy in mortality rates is evidence that the more experienced group assumed the responsibility of the poorer risks. However, this fact should not detract appreciably from the excellent record of the resident staff.

### MORBIDITY

The incidence of morbidity is presented in Table 4. A temperature of 100.4°F or higher on any two days of the puerperium, exclusive of the first twenty-four hours, was considered evidence of infection. The morbidity in the entire series was 26.6 per cent. Since the introduction of the sulfonamide drugs and penicillin this has been reduced to 10 per cent. The rate for elective cesarean section was 15 per cent in contrast to 37 per cent for the emergency operation. The morbidity rate in the few cases in which the Waters extraperitoneal

TABLE 4 Morbidity

DURATION OF FEVER	NO. OF CASES	INCIDENCE
days		%
0	706	73.5
1	98	10.2
2	70	7.3
3	25	2.6
4	62	6.4
5 or more		

operation was done was 40 per cent. The patients who had suffered considerable blood loss were more inclined to show evidence of infection postoperatively, averaging 45 per cent. Ruptured membranes over twelve hours or labor over twenty-four hours caused temperature elevations in 40 per cent of the cases. Prophylactic administration of penicillin and the sulfonamides in cases potentially infected in which cesarean section is anticipated, together with the liberal use of transfusion to compensate for blood loss, is lowering these figures to a great extent.

### TYPE OF OPERATION

Most of the cesarean sections were done by the low cervical technic, which showed an increase from 79 per cent reported by Duncan and Doyle<sup>1</sup> to 91 per cent in our series (Table 5). The transverse incision was preferred because it was confined more readily to the lower uterine segment and provided less operative difficulty in repeat sections. The classic incision, which waned in popularity from a 20 per cent incidence in the previous decade to 6 per cent, is now performed only when the lower-segment operation is not

feasible because of varices, fibroids or inextensible adhesions preventing access to the lower segment.

The Waters extraperitoneal operation was done in 10 frankly infected cases, with no deaths. If patients who may require cesarean section are given prophylactic penicillin and sulfonamide therapy while undergoing a test of labor, the indications for the Waters technic are considerably decreased.

The Porro cesarean hysterectomy was done in 20 cases. Six cases of ruptured uterus were treated

TABLE 5 Types of Operation

OPERATION	NO. OF CASES	INCIDENCE
Low cervical	874	91
Transverse (Kerr)	800	82
Longitudinal (Kroenig)	74	8
Classic	57	6
Extraperitoneal (Waters)	10	1
Porro	20	2

in this manner. The other 14 were cases of uncontrollable bleeding, which included 6 cases of placenta previa, 5 of couvelaire uterus following abruptio placentae, 2 of hemorrhage from post-partum uterine atony, and 1 of placenta accreta with the placenta adherent to a previous cesarean scar. There were no deaths from the Porro operation.

### ANESTHESIA

The types of anesthesia are presented in Table 6. Prior to 1941 the anesthetic of choice was nitrous

TABLE 6 Types of Anesthesia

ANESTHESIA	NO. OF CASES
Nitrous oxide, oxygen and ether	537
Open ether	66
Spinal	323
Local	6
Pentothal	4

oxide, oxygen and ether. Since 1941 spinal anesthesia has been used almost routinely except in bleeding cases. Sodium pentothal was administered intravenously in 4 cases of severe toxemia. Local anesthesia was employed in only 6 cases, but its use should be adopted more generally since it is the safest of all anesthetics. Anesthesia for cesarean section is now administered only by the qualified men of the anesthesia service.

### FETAL MORTALITY

There were 72 fetal deaths making a gross fetal mortality of 7.5 per cent (Table 7). Discounting the cases of stillbirth due to ruptured uterus and hemor-

age, the rate was 3 per cent. Of the neonatal deaths the majority were due to prematurity, especially in the patients with placenta previa. In the cases in which the cesarean section was repeated

TABLE 7 *Fetal Mortality*

CAUSE	No OF DEATHS
Stillbirth	44
Ruptured uterus	6
Abruptio placentae	20
Placenta previa	18
Neonatal death	25
Prematurity	12
Atelectasis	10
Cerebral injury	4
Erythroblastosis	1
Congenital abnormality	1

there were 9 neonatal deaths, a mortality of 15 per cent.

### MATERNAL MORTALITY

The causes of death are presented in Table 8. There were 23 maternal deaths, a mortality of 2.4 per cent, this is an improvement over the previous decade, in which the rate was 4.3 per cent. Of these 23 cases, 7 had been badly managed by private physicians, and the patients were in poor condition. These cases included 3 of separated placenta with the patient in shock and badly exsanguinated, 2 of placenta previa in which the patients had been allowed to bleed for a long time before the decision was made to send the patient to the hospital and 2 of cephalopelvic disproportion in which the patients had been in labor over forty-eight hours and in which several attempts at manual dilatation of the cervix and forceps delivery had been made unsuc-

TABLE 8 *Maternal Mortality*

CAUSE	No OF CASES	PERCENTAGE OF TOTAL
Hemorrhage	8	4.8
Peritonitis	4	17.4
Embolism	3	13.0
Anesthesia	3	13.0
Cardiac decompensation	3	13.0
Pneumonia	1	4.4
Uremia	1	4.4
Total	23	

cessfully. The mortality for the cases followed through the entire pregnancy was 1.6 per cent.

The relation of the deaths to the indications for cesarean section is presented in Table 9. There were 5 deaths among the patients with repeat cesarean section. Two of these were from spinal anesthesia, and 1 from aspiration of vomitus during inhalation anesthesia, all of which occurred before the present well trained anesthesia service assumed the respon-

sibility of this important phase of obstetrics. One patient died of secondary hemorrhage twelve hours after operation. The fifth death was from embolus (proved at autopsy) one hour after delivery (the only unavoidable death in the group).

Five deaths occurred among the patients with disproportion. Three died from sepsis, and 2 of these cases had been mismanaged outside the hospital. All these cases occurred before the days of the sulfonamides and penicillin. One patient, who died from hemorrhage on the twenty-third post-partum day, had had several episodes of moderate bleeding before the fatal hemorrhage and should have had a hysterectomy early in the post-partum period. There was 1 death from embolism in this group.

In the cases of placenta previa there were 4 deaths. One was from sepsis, 2 from hemorrhage, and 1 from lobar pneumonia before the days of the antibiotics.

There were six deaths from separated placenta. Four patients died from shock and hemorrhage, 1 from uremia and cortical necrosis on the third post-

TABLE 9 *Deaths in Relation to Indications for Cesarean Section*

INDICATION	TOTAL No OF CASES	No OF DEATHS	MORTALITY %
Repeat cesarean section	606	5	0.8
Disproportion	141	3	2.1
Placenta previa	68	4	5.9
Separated placenta	57	6	10.5
Cardiac decompensation	4	3	75.0

operative day, and 1 from embolism on the fourteenth day.

Of the 4 patients with cardiac disease who underwent cesarean section while decompensated, 3 died. Two died of typical cases of cardiac decompensation (both elderly primiparas, aged forty-two and forty respectively), 1 in eight days and the other in six days. The third patient died in eleven days from an embolism.

### CONCLUSIONS

On the basis of these statistics certain axiomatic facts pertaining to cesarean section may be deduced.

Hemorrhage and sepsis are the most common causes of mortality from cesarean section.

Whole blood given early, rapidly and copiously is the only way to combat hemorrhage. Too often, transfusions are given too late, too slowly and in too small amounts.

Cesarean section must not be done in the presence of shock. Shock must first be treated as expeditiously as possible.

One must be sure there is no chance for secondary hemorrhage either from uterine atony or from improper hemostasis before the abdomen is closed.

Cesarean section has a distinct place in the treatment of toxemia and does not add to the risk especially if done under local or sodium pentothal anesthesia

There is no limit to the number of cesarean sections that a patient may undergo, provided sufficient attention is given to the uterine scar both before and at operation

The danger in cesarean sections after rupture of the membranes and prolonged labor is sepsis. Therefore, every patient in whom cesarean section is probable, when given a test of labor should receive sulfonamides and penicillin prophylactically after the first twelve hours. In the frankly infected cases the extraperitoneal operation should be done

Cesarean section in cardiac cases offers no advantage over delivery through the pelvis and should not be done unless there is some other indication.

Anesthesia for cesarean section must be administered by a trained anesthetist, especially if one decides to use spinal anesthesia

With proper attention to these suggestions the mortality for cesarean section should be kept below 1 per cent

#### REFERENCES

1. Duncan, C. J., and Doyle, J. B. Cesarean section: ten year study of 703 cases at Boston City Hospital. *New Eng J Med* 216:14, 1937
2. Irving, F. C. Ten years of cesarean section at Boston Lying-in Hospital. *Am. J. Obst. & Gynec.* 50:660-680, 1945
3. DeNormandie, R. L. Five year study of cesarean section in Massachusetts. *New Eng J Med* 227:533-538, 1942
4. McSweeney, D. J. and Maloney, A. M. Combined x-ray and external pelvimetry. *Am. J. Obst. & Gynec.* 46:102-109, 1943

## HOSPITAL ADMINISTRATION AS A CAREER

E. M. BLUESTONE, M.D.\*

NEW YORK CITY

THE doctor's prescription has been one of the most important characteristics of the medical profession throughout the ages. It is as much the symbol of the medical profession as the mortar and pestle of the profession of pharmacy. Men doubtless prescribed in the dark before they elaborated the wherewithal to diagnose. The earlier the prescription, the greater appears to have been the element of chance with which our professional ancestors approached their patients. It is still the rod and the staff that comfort the patient, if not the practitioner. Even the placebo carries a world of meaning. Nothing justifies a fee like a prescription, and that is why the practitioner in search of the Holy Grail avoids medicine that is odorless, colorless and tasteless. One need only ponder over the slowness with which the pharmacology laboratory is arriving in the hospitals of today to understand the tenacity of sentiment versus science in prescription writing. The pharmacy is still patronized more for the products of the nostrum vendor and the quack than for the tested remedies of the man of science. The incantations of primitive man have their unhappy survival in the hit-or-miss prescriptions that belie our scientific pretensions.

Those who are still in the academic stages, and those who are serving clinical apprenticeships, know much better about the needs of the patient than their ancestors did. Modern practitioners of medicine are not so helpless and need not tolerate the shotgun methods of yesterday. If they do, it must be for a compelling reason, and I suggest that the dilemma be thoughtfully weighed.

Though the principles and practice of social medicine are not yet taught in medical colleges and hospitals with the pedagogic energy that is expended on prescription writing, one cannot help becoming aware of its arrival, its staying power and its influence on this dilemma. Our descendants will be more keenly aware of its possibilities for good than we can be at present. Since we are confronted with this humanized concept of medical practice, we cannot help taking notice of it and should want to know more about it. For those who have aptitude for the practice of social medicine and are so constituted that they can find joy in it, new and bright horizons will appear. The doctor, in the role of social agent, has limitless possibilities. If, working in such an enlightened kind of medical practice, he finds a substitute to replace the fee-for-prescription method of compensation that dominates the individual practice of medicine (which, incidentally, must struggle with such a handicap to be scientific) he opens the doors of a room that is dimly lit and lets the sunshine in so that others, too, can benefit.

In recent decades of world upheaval, we have been taught many severe lessons that have brought home to us the broad concept of social medicine, in which the prescription is only one of many symbols. The practitioner is already beginning to merge his personality into this new concept, and he is doing it as an instrument of a sympathetic society. Before this development can proceed, however, someone must assume leadership and help to plan, build, organize and administer, to the end that we shall have worthy officership in this new army of practitioners. These officers should be located at general

\*Director, Montefiore Hospital

headquarters, as well as in field headquarters, and the hospital qualifies admirably for either purpose. According to the new trends, the hospital is beginning to emerge as the hub of medical activity radiating from its central diagnostic and therapeutic facilities, and serving the community as an integral part of it, are the outpatient department, the doctors' office building (which will bring the doctor closer to his workshop), the department for continued care (which will discharge a debt that has been owing for some time to the long-term patient), the department of psychiatry, the department of tuberculosis (if this illness is not brought under control sooner — and even if it is), the group-practice unit (for an insured group of patients), the health center, the convalescent unit and the preventorium. Hospital care in the home will also radiate from such a center and serve patients extramurally on an extension basis so that they will be cared for at all times and in all places, comprehensively. The practitioner never had a better friend than this kind of center promises to be, nor did the sick. He must, therefore, familiarize himself with its possibilities for good in his professional life as a man of science, unless he wants to remain a prescription writer who continues to practice uncritically, forever, what he was taught to prescribe in medical school. Each one of the activities revolving around the hospital calls for executive talents of a high order, and each one is beckoning to the young house-staff graduate who has the imagination, the vision and the other qualities of leadership to take advantage of such opportunities.

Hospital administration as a career is not limited to medical men, but medical men possess advantages, whereas laymen must overcome handicaps in this kind of executive work, which calls for considerable medical knowledge as well as social insight. It has been said that the hospital executive must also be a good "businessman" and that the layman has the edge on the physician in this respect, but this requirement is more apparent than real and is not based on actual experience in the hospitals of this country. This is not to deny that good business judgment is helpful to the medical executive. In the long run, however, medical knowledge, medical objectives and medical opinion must be sought and considered.

There was never a time in medical history when the need for qualified medical executives in hospitals and elsewhere was greater than it is today. The opportunities for qualified men are endless, with new areas for creative work opening up daily, and the conditions of service are favorable. The medical executive is able to live a full and useful life, with credit to himself and his family. Riches are not to be sought in the professions in any case. Medical executives live in comfortable material circumstances, unworried by profit motives, and are assured a continuous income, which is seldom inade-

quate. The reduction of the overhead costs, which must be balanced against income, is only one comparative aspect of the matter.

It is said, of course, that the medical executive must surrender some of his independence when he becomes subservient to a board of trustees, — of whom, by the way, he is always a few jumps ahead in the program if he is worth his salt, — but independence to do what? To be legally free, as some are, to practice alone while the four walls, like dead men, tell no tales? To charge whatever the traffic will bear, as some do, while rebelling inwardly at the necessity for such compromises with the high code of medical ethics taught in medical schools? The practitioner will become the man of science that he deserves to be, and ought to be, when he or his colleagues will stand up and, through the kind of leadership here outlined, challenge the prevailing method of distributing medical care.

No doubt the practitioner, be he physician, surgeon or specialist, is attracted by the more dramatic forms of medical practice. As a medical executive, I envy the surgeon his joy when a patient on whom he has performed a successful laparotomy is discharged cured, after a short stay in the hospital, though an occasional patient may be lost. His results are more tangible in terms of space and time. But the cures of the medical executive reach out into a wide area of space and cover a long period. Though the results of his planning are not so immediately visible, or heartwarming, to the medical executive they reach far more people and their effects often make medical history. Without the planner, the practitioner toils laboriously in vain.

Medical executive work, by its very nature, brings the rewards of good companionship. Work on the frontier is always exhilarating to the pioneer, and he is forever rubbing elbows with others whose outlook on medical life is similar to his own. The related specialties are close. Social service becomes a prize prescription, with a wealth of vital ingredients — none of which, by the way, act mysteriously. Social medicine, which is the practice of medicine in relation to all the social forces that influence our lives, is a more intelligible and more life-giving concept than the limited form of medical practice that preceded and survived the advent of the social sciences. It should therefore be cultivated for its worth and should attract qualified leadership.

The opportunities for full-time executive medical service are many, and these are knocking at the doors of young physicians who are prepared to put in an additional apprenticeship in administrative medicine. Schools for hospital administration, with mixed lay and medical student bodies, have come into vogue in recent years and provide an academic year of university training on a graduate level, followed by an administrative internship of a year leading to a master's degree. The alternative to this

kind of formal preparation is an apprenticeship to a good teacher, under whom the student qualifies in the school of experience. A combination of both is undoubtedly the best kind of preparation. In any case, the student should allow five years for seasoning from the time of his graduation from the house staff of a hospital before seeking an independent executive position where much will depend on his maturity of judgment. Apprenticeship of this kind, unlike the advanced residencies in clinical medicine, pays a good living wage, and the rest can safely be

charged up to investment by an ambitious and self-confident student. Dividends start flowing early because the opportunities are so great.

For the future medical executive there opens up a world of opportunity and one that remains unmatched in the learned professions. For those whose aptitudes and preferences are in clinical medicine, there are additional worlds to conquer, but these worlds will be conquered faster and more completely through a proper distribution of personnel where each can do the most good in his own way.

## MEDICAL PROGRESS

### CHEMOTHERAPY OF NEOPLASTIC DISEASE

#### II Trends in Experimental Cancer Therapy

DAVID A. KARNOFSKY, M.D.\*

NEW YORK CITY

The cancer chemotherapist, in the absence of a fundamental philosophy or a satisfactory approach to his problem, is an eclectic, borrowing ideas and discoveries from the more advanced or at least the more fruitful scientific disciplines. The range of his interests and the nature of his approach are shown in the number of chemicals and groups of substances under study. These agents are, for the most part, chiefly of interest in a historical and immediate sense for man, if not all, will ultimately be discarded. Until a fundamental discovery appears, each year will see new agents greeted with enthusiasm, and each decade will see some of these compounds through a cycle of interest and sometimes enthusiasm — created in various ways — and then active rejection or passive disuse. These cycles, of course, leave a residuum of basic and useful information that will make subsequent work more efficient and critical and from which, some day, important contributions may develop. In the following paragraphs the major current trends in cancer chemotherapy are reviewed, with emphasis on substances under recent clinical trial.

#### BIOLOGIC PRODUCTS

##### *Bacteria, Molds and Protozoa*

**Coley's mixed toxins.** In 1892, acting on the reported clinical observations that attacks of erysipelas in patients with inoperable cancer were sometimes associated with permanent or temporary tumor regressions, Coley began to use killed cultures of virulent streptococci isolated from patients with erysipelas in the treatment of cancer. Subsequently, *Bacillus prodigiosus* (*Serratia marcescens*) was added

to the cultures, since this organism was believed to increase the virulence of the streptococci. Vaccines of this general type were used for a number of years in many parts of the world. In spite of the occasional favorable reports, the therapeutic activity of the vaccine appears to have been inconstant and unpredictable, and its use was gradually abandoned. Apparently, an important factor in preventing an acceptable or definitive evaluation of Coley's toxins lay in the variability of the preparations used and the different dosages and technics of administration. In an effort to revive interest in this form of treatment, recent historical reviews of Coley's toxins have appeared.<sup>37, 38</sup> These reviews do not enhance the status of the agent, or present any compelling reason for its further clinical use. As an approach to cancer chemotherapy, Coley's work has anticipated and encouraged the modern investigations on purified bacterial toxins.

**Shear's polysaccharide.** In 1931 Gratia and Linz<sup>39</sup> reported that bacterial filtrates produced hemorrhages in a transplanted tumor in the guinea pig. Zahl and his group<sup>40-42</sup> tested a large number of bacterial filtrates and suspensions against Sarcoma 180 in mice, and found that the hemorrhage-producing substances occurred chiefly in gram-negative organisms, and were probably endotoxin antigens. Under the direction of Shear<sup>43</sup> an extensive cooperative study has been in progress on the isolation, characterization and mechanism of action of the hemorrhage-producing substance found in *B. prodigiosus* filtrates. The active material is homogeneous by electrophoresis and ultracentrifugation.<sup>43, 44</sup> Chemically, it appears to be composed chiefly of polysaccharides with small amounts of phospholipid and nitrogen in several unidentified

\*Associate Sloan Kettering Institute for Cancer Research fellow in medicine Memorial Hospital Center for Cancer and Allied Diseases fellow Jane Coffin Childs Memorial Fund for Medical Research

orms<sup>45</sup> The material is not inactivated by trypsin it is extremely toxic to mice, a dose of 0.01 mg (about 0.5 mg per kilogram of body weight) in mice weighing 20 gm will produce a significant mortality. It is antigenic and after repeated injections, larger doses are needed to produce a toxic effect. In mice a toxic dose of the polysaccharide will cause a fall in body temperature<sup>46</sup>, in rabbits and mice it is a pyrogenic agent.<sup>47</sup>

The purified agent on parenteral administration, at doses not injurious to the normal tissues, will induce hemorrhage within a few hours, followed by necrosis and partial regression of transplanted and spontaneous mouse tumors.<sup>48</sup> Mitotic activity in the tumor disappears one and a half hours after the injection of a maximum tolerated dose, the nuclei swell and then become pyknotic.<sup>49</sup> There is a fall in the blood flow in the tumor capillaries, numerous petechiae appear, and the blood flow finally ceases.<sup>50</sup> Several days later new capillaries begin to form at the periphery of the tumor with multiplication of the surviving tumor cells. The polysaccharide does not show any selective toxicity to cells in tissue culture.<sup>51</sup> The general interpretation of effect is that the polysaccharide acts by producing a "shock-like" state, the blood supply to the vulnerable capillaries in the tumor is decreased, and edema, hemorrhage and necrosis may then develop in the tumor. There is no satisfactory evidence of a direct toxic effect on the tumor cells.<sup>50</sup>

The purified polysaccharide was first used clinically by Brues and Shear<sup>52</sup> on several different types of tumor in 4 seriously ill patients. The agent, in very small doses, produced a high fever, leukocytosis and a fall of blood pressure, frequently to shock levels. Hemorrhage into the tumor and occasionally a decrease in tumor size were observed. Holloman<sup>53</sup> and Oakey<sup>54</sup> have reported their experiences on a total of 17 cases with a variety of tumors. The treatment appears to be hazardous, but the tumors sometimes regress and occasional temporary clinical improvement develops. Shear's group states, however, that the purified polysaccharide is not considered suitable for general clinical use.<sup>18</sup>

**Crude penicillin** Cornman<sup>55</sup> observed that crude penicillin was injurious in tissue cultures to several types of rat and mouse sarcomas at concentrations that did not damage normal fibroblasts. This selective effect was not found with purified penicillin.<sup>56, 57</sup> The penicillin impurity exerting this selective effect in tissue culture has not been identified.

Studies of the effects of a variety of mold filtrates and extracts on the neoplastic cell are now in progress.<sup>58, 59</sup> Cohen, Borsook and Dubnoff<sup>61</sup> tested a variety of micro-organisms by an *in vitro* technic for disclosing carcinoclastic microbial products, and they report that cultures of *Sporosarcina ureae* contain a substance injurious to tumor cells. Kidd<sup>60</sup> has reported that culture filtrates of *Aspergillus fumigatus*, presumably containing gliotoxin, were injuri-

ous to tumor cells *in vitro*, but this extract has not proved effective thus far against tumors *in vivo*.

**K-R** An endotoxin prepared from killed *Trypanosoma cruzi* (the causative agent of Chagas's disease), developed by Roskin<sup>61</sup> and Klyueva<sup>62</sup> and appropriately named K-R, has been reported to be effective in treating cancer in mice and man. In tumor-bearing mice infected with *T. cruzi*, Roskin observed a concentration of the organisms in the tumor, associated with destructive and regressive changes. Infections with *Borrelia duttoni* (*Spirochaeta duttoni*) (relapsing fever) and *Trypanosoma equiperdum* (dourine) were without effect on the tumors. Roskin, with the assistance of Klyueva, then prepared an endotoxin from *T. cruzi* that was also found to damage neoplastic cells. Regressions in Sarcoma 180 and Ehrlich's carcinoma of mice and in the Flexner-Jobling carcinoma of rats were produced without injury to normal tissue. If tumor cells were soaked in a K-R solution prior to implantation in mice, they failed to "take." The active material was water soluble, retained its activity after heating at 50°C for twenty minutes, but it lost its potency within ten to twelve days when kept at 1°C in the liquid state.

In 1941 K-R was first used in the treatment of patients with cancer. The subcutaneous, intramuscular or intratumoral injection of K-R caused cancers to disintegrate. Five out of 10 carcinomas of the larynx, 3 carcinomas of the cervix and 3 out of 5 carcinomas of the breast regressed remarkably under treatment. The beneficial effects varied directly with the dosage, large doses, however, caused a high temperature, and treatment was temporarily stopped. One unit was standardized as 1,000,000 *T. cruzi* organisms, and a course totaling 755 units has been given to a single patient.

The Russian reports of the remarkable results achieved with K-R therapy prompted confirmatory studies in this country. Hauschka<sup>63-65</sup> has carried out the most extensive work, using eight different strains of *T. cruzi*, including the one used by Roskin, against five types of tumor in mice. Mice infected with *T. cruzi* showed consistent retardation of tumor growth and occasional tumor regressions, but this was related to the virulence of the strain and the lives of the mice were not prolonged. The parasites did not concentrate in the tumors, as stated by Roskin, in fact, the cancer cells proper were only rarely parasitized, whereas the visceral organs and skeletal muscles were heavily infected. One virulent strain produced suppression of tumor growth coincident with weight loss and death eight to thirteen days after inoculation, but if the infection was checked with the quinoline derivative, Bayer 7602, tumor growth was resumed. Killed cultures and lysates of *T. cruzi* were without effect on tumor growth in mice,<sup>64, 65</sup> and Cohen, Borsook and Dubnoff<sup>61</sup> were unable to demonstrate any effect of *T. cruzi* on mammary carcinoma and Brown-Pearce

kind of formal preparation is an apprenticeship to a good teacher, under whom the student qualifies in the school of experience. A combination of both is undoubtedly the best kind of preparation. In any case, the student should allow five years for seasoning from the time of his graduation from the house staff of a hospital before seeking an independent executive position where much will depend on his maturity of judgment. Apprenticeship of this kind, unlike the advanced residencies in clinical medicine, pays a good living wage, and the rest can safely be

charged up to investment by an ambitious and confident student. Dividends start flowing early because the opportunities are so great.

For the future medical executive there opens up a world of opportunity and one that remains unmatched in the learned professions. For those whose aptitudes and preferences are in clinical medicine, there are additional worlds to conquer, but these worlds will be conquered faster and more completely through a proper distribution of personnel where each can do the most good in his own way.

## MEDICAL PROGRESS

### CHEMOTHERAPY OF NEOPLASTIC DISEASE

#### II Trends in Experimental Cancer Therapy

DAVID A. KARNOFSKY, M.D.\*

NEW YORK CITY

The cancer chemotherapist, in the absence of a fundamental philosophy or a satisfactory approach to his problem, is an eclectic, borrowing ideas and discoveries from the more advanced or at least the more fruitful scientific disciplines. The range of his interests and the nature of his approach are shown in the number of chemicals and groups of substances under study. These agents are, for the most part, chiefly of interest in a historical and immediate sense for many, if not all, will ultimately be discarded. Until a fundamental discovery appears, each year will see new agents greeted with enthusiasm, and each decade will see some of these compounds through a cycle of interest and sometimes enthusiasm — created in various ways — and then active rejection or passive disuse. These cycles, of course, leave a residuum of basic and useful information that will make subsequent work more efficient and critical and from which, some day, important contributions may develop. In the following paragraphs the major current trends in cancer chemotherapy are reviewed, with emphasis on substances under recent clinical trial.

#### BIOLOGIC PRODUCTS

##### *Bacteria, Molds and Protozoa*

**Coley's mixed toxins.** In 1892, acting on the reported clinical observations that attacks of erysipelas in patients with inoperable cancer were sometimes associated with permanent or temporary tumor regressions, Coley began to use killed cultures of virulent streptococci isolated from patients with erysipelas in the treatment of cancer. Subsequently, *Bacillus prodigiosus* (*Serratia marcescens*) was added

to the cultures, since this organism was believed to increase the virulence of the streptococci. Vaccines of this general type were used for a number of years in many parts of the world. In spite of the occasional favorable reports, the therapeutic activity of the vaccine appears to have been inconstant and unpredictable, and its use was gradually abandoned. Apparently, an important factor in preventing an acceptable or definitive evaluation of Coley's toxins lay in the variability of the preparations used and the different dosages and technics of administration. In an effort to revive interest in this form of treatment, recent historical reviews of Coley's toxins have appeared.<sup>37, 38</sup> These reviews do not enhance the status of the agent, or present any compelling reason for its further clinical use. As an approach to cancer chemotherapy, Coley's work has anticipated and encouraged the modern investigations on purified bacterial toxins.

**Shear's polysaccharide.** In 1931 Gratia and Linz<sup>39</sup> reported that bacterial filtrates produced hemorrhages in a transplanted tumor in the guinea pig. Zahl and his group<sup>40-42</sup> tested a large number of bacterial filtrates and suspensions against Sarcoma 180 in mice, and found that the hemorrhage-producing substances occurred chiefly in gram-negative organisms, and were probably endotoxin antigens. Under the direction of Shear<sup>18</sup> an extensive cooperative study has been in progress on the isolation, characterization and mechanism of action of the hemorrhage-producing substance found in *B. prodigiosus* filtrates. The active material is homogeneous by electrophoresis and ultracentrifugation.<sup>43, 44</sup> Chemically, it appears to be composed chiefly of polysaccharides with small amounts of phospholipid and nitrogen in several unidentified

\*Associate Sloan-Kettering Institute for Cancer Research, fellow in medicine, Memorial Hospital Center for Cancer and Allied Diseases, fellow, Jane Coffin Childs Memorial Fund for Medical Research.

orms<sup>45</sup> The material is not inactivated by trypsin it is extremely toxic to mice, a dose of 0.01 mg (about 0.5 mg per kilogram of body weight) in mice weighing 20 gm will produce a significant mortality. It is antigenic and after repeated injections, larger doses are needed to produce a toxic effect. In mice a toxic dose of the polysaccharide will cause a fall in body temperature<sup>46</sup>, in rabbits and mice it is a pyrogenic agent.<sup>47</sup>

The purified agent on parenteral administration, at doses not injurious to the normal tissues, will induce hemorrhage within a few hours, followed by necrosis and partial regression of transplanted and spontaneous mouse tumors<sup>48</sup>. Mitotic activity in the tumor disappears one and a half hours after the injection of a maximum tolerated dose, the nuclei swell and then become pyknotic<sup>49</sup>. There is a fall in the blood flow in the tumor capillaries, numerous petechiae appear, and the blood flow finally ceases<sup>50</sup>. Several days later new capillaries begin to form at the periphery of the tumor with multiplication of the surviving tumor cells. The polysaccharide does not show any selective toxicity to cells in tissue culture<sup>51</sup>. The general interpretation of effect is that the polysaccharide acts by producing a "shock-like" state, the blood supply to the vulnerable capillaries in the tumor is decreased, and edema hemorrhage and necrosis may then develop in the tumor. There is no satisfactory evidence of a direct toxic effect on the tumor cells<sup>50</sup>.

The purified polysaccharide was first used clinically by Brues and Shear<sup>52</sup> on several different types of tumor in 4 seriously ill patients. The agent, in very small doses, produced a high fever, leukocytosis and a fall of blood pressure, frequently to shock levels. Hemorrhage into the tumor and occasionally a decrease in tumor size were observed. Holloman<sup>53</sup> and Oakes<sup>54</sup> have reported their experiences on a total of 17 cases with a variety of tumors. The treatment appears to be hazardous, but the tumors sometimes regress and occasional temporary clinical improvement develops. Shear's group states, however, that the purified polysaccharide is not considered suitable for general clinical use<sup>16</sup>.

**Crude penicillin** Cornman<sup>55</sup> observed that crude penicillin was injurious in tissue cultures to several types of rat and mouse sarcomas at concentrations that did not damage normal fibroblasts. This selective effect was not found with purified penicillin<sup>56, 57</sup>. The penicillin impurity exerting this selective effect in tissue culture has not been identified.

Studies of the effects of a variety of mold filtrates and extracts on the neoplastic cell are now in progress<sup>58, 59</sup>. Cohen, Borsook and Dubnoff<sup>60</sup> tested a variety of micro-organisms by an in vitro technic for disclosing carcinoclastic microbial products and they report that cultures of *Sporosarcina ureae* contain a substance injurious to tumor cells. Kidd<sup>60</sup> has reported that culture filtrates of *Aspergillus fumigatus*, presumably containing gliotoxin were injuri-

ous to tumor cells in vitro, but this extract has not proved effective thus far against tumors in vivo.

**K-R** An endotoxin prepared from killed *Trypanosoma cruzi* (the causative agent of Chagas's disease), developed by Roskin<sup>61</sup> and Klyueva<sup>62</sup> and appropriately named K-R has been reported to be effective in treating cancer in mice and man. In tumor-bearing mice infected with *T. cruzi*, Roskin observed a concentration of the organisms in the tumor, associated with destructive and regressive changes. Infections with *Borrelia duttoni* (*Spirochaeta duttoni*) (relapsing fever) and *Trypanosoma equiperdum* (dourine) were without effect on the tumors. Roskin, with the assistance of Klyueva, then prepared an endotoxin from *T. cruzi* that was also found to damage neoplastic cells. Regressions in Sarcoma 180 and Ehrlich's carcinoma of mice and in the Flexner-Jobling carcinoma of rats were produced without injury to normal tissue. If tumor cells were soaked in a K-R solution prior to implantation in mice, they failed to "take". The active material was water soluble, retained its activity after heating at 50°C for twenty minutes, but it lost its potency within ten to twelve days when kept at 1°C in the liquid state.

In 1941 K-R was first used in the treatment of patients with cancer. The subcutaneous, intramuscular or intratumoral injection of K-R caused cancers to disintegrate. Five out of 10 carcinomas of the larynx, 3 carcinomas of the cervix and 3 out of 5 carcinomas of the breast regressed remarkably under treatment. The beneficial effects varied directly with the dosage, large doses, however, caused a high temperature and treatment was temporarily stopped. One unit was standardized as 1,000,000 *T. cruzi* organisms, and a course totaling 755 units has been given to a single patient.

The Russian reports of the remarkable results achieved with K-R therapy prompted confirmatory studies in this country. Hauschka<sup>63-65</sup> has carried out the most extensive work, using eight different strains of *T. cruzi*, including the one used by Roskin, against five types of tumor in mice. Mice infected with *T. cruzi* showed consistent retardation of tumor growth and occasional tumor regressions, but this was related to the virulence of the strain and the lives of the mice were not prolonged. The parasites did not concentrate in the tumors, as stated by Roskin, in fact the cancer cells proper were only rarely parasitized, whereas the visceral organs and skeletal muscles were heavily infected. One virulent strain produced suppression of tumor growth coincident with weight loss and death eight to thirteen days after inoculation, but if the infection was checked with the quinoline derivative, Bayer 7602, tumor growth was resumed. Killed cultures and lysates of *T. cruzi* were without effect on tumor growth in mice<sup>64, 65</sup> and Cohen, Borsook and Dubnoff<sup>61</sup> were unable to demonstrate any effect of *T. cruzi* on mammary carcinoma and Brown-Pearce

carcinoma by tests in vitro Malisoff,<sup>66</sup> however, reported that by means of K-R preparation he produced complete regression of 55 per cent of tumors (Sarcoma 180 and a spontaneous mammary carcinoma) in mice, but his work has been severely criticized.<sup>66</sup> In view of the general failure to confirm the laboratory aspects of Roskin and Klyueva's work, clinical trials with K-R are not indicated.

### *Urine and Tissue Preparations*

*H 11* H 11 is an extract of normal human urine reported to contain growth-inhibiting substances.<sup>67</sup> One group of workers has found that it slowly but ultimately inhibited the growth of the Twort carcinoma in mice,<sup>67</sup> but others were unable to demonstrate any therapeutic effect on mouse tumors.<sup>68, 69</sup> Since 1941, H 11 has been used in England for the treatment of inoperable carcinoma, but the remarkable therapeutic effects attributed to it have not been confirmed.<sup>70</sup>

*Myelokentric acid* Miller, Wearn and Heinle,<sup>71</sup> in 1939, described substances obtained from the urine of leukemic patients that induced stimulation of the myeloid and lymphoid systems in laboratory animals. Subsequent study by Heinle et al.<sup>72</sup> led to the conclusion that a substance can be extracted from the urine of patients with chronic myelogenous leukemia that will induce myeloid metaplasia in guinea pigs. The substance responsible for this effect appeared to be protein in nature.

On the other hand, a more complicated situation is suggested by Turner and Miller.<sup>73</sup> In the urine of patients with chronic myelogenous leukemia, a substance that produced myeloid metaplasia was obtained, whereas, in chronic lymphatic leukemia, the urine extract induced lymphoid metaplasia. These substances were named myelokentric and lymphokentric acid, respectively. In Hodgkin's disease and monocytic leukemia an intermediate effect in guinea pigs was obtained, and in these diseases the urine was found to contain a mixture of myelokentric and lymphokentric acids. Liver extracts contained both fractions. Extracts of myeloid leukemic tissue produced myeloid metaplasia, and lymphoid leukemic tissue, lymphoid metaplasia, tissue extracts from patients with Hodgkin's disease tissue caused a mixed reaction in the guinea pig.<sup>74</sup>

Miller, Herbut and Jones<sup>75</sup> have treated 8 patients with lymphoblastic leukemia with crude myelokentric acid. They observed 13 partial remissions in these patients, and at autopsy the disease appeared altered by the treatment. They do not recommend this treatment because the preparation is crude, it is very difficult to obtain, and there is no standard dosage.

*Splenic extracts* For many years, splenic extracts and preparations containing spleen, such as "splendotheran" and "aristotrop,"<sup>71</sup> have been proposed for the treatment of cancer, and all have fallen

into disrepute. Recently, however, it was reported that a splenic extract induced tumor regressions in mice and definite improvement and tumor regression in 3 patients with carcinoma.<sup>76</sup>

*A C S* Human spleen has been used as an antigen in rabbits to produce an antiserum, the "antitumoral cytotoxic serum" or A C S. This substance has been proposed by Bogomolets<sup>77</sup> as a formidable adjunct in the treatment of many diseases, including cancer. In inoperable cancer, he has reported that its use may reduce pain, improve the general condition of the patient, cause metastases to regress and sometimes prolong life. A C S made from mouse spleen will inhibit tumor transplants in mice, and rat A C S will inhibit the growth of the Walker rat Sarcoma 319 in vitro.<sup>78</sup>

Two clinical reports on A C S have appeared in this country.<sup>79, 80</sup> In a preliminary report on 106 cases, Davis<sup>79</sup> observed occasional relief of pain, gain in weight, increase in appetite and a sense of well-being. One patient with myeloid leukemia showed a fall in white-cell count with each course of treatment. A C S, however, could not be shown to prolong life. The usual course of treatment was 0.5 cc of the serum on the first, 1 cc on the fourth and 1.5 cc on the seventh day, courses were generally repeated every six weeks. Skapier<sup>80</sup> used the same dosage schedule in patients with Hodgkin's disease, and he observed a decrease in the sedimentation rate in 10 and a gain in weight in 12 out of 22 patients. There was no significant regression in enlarged lymph nodes. A C S does not appear to have any specific action in neoplastic disease, but Bogomolets's approach is of considerable interest.

Boylard<sup>81</sup> fed tumor-bearing mice various muscle extracts. The most effective inhibition of tumor growth was produced by extracts containing ethanolamine or cadaverine hydrochloride. Mouse carcinoma 2146 mixed with histone or protamine prior to inoculation showed a definite but transient decrease in growth rate, whereas human plasma or egg albumen did not have this effect.<sup>82</sup> The pentose nucleotides were injected into mice implanted with methylcholanthrene sarcomas, adenylic and guanylic acids inhibited tumor growth but also caused amyloidosis, cytidylic acid had little effect, and uridylic acid stimulated tumor growth.<sup>83</sup> Several dipeptides and d,l-dipeptides and polypeptides were found to have no effect on the growth of mouse and rat tumors.<sup>84</sup>

### *Vitamins*

The accessory food substances have been examined for their role in cancer growth, either by giving an excess of the vitamin or by producing a specific vitamin deficiency. A deficiency may be produced by dietary restrictions or the administration of specific antimetabolites.

*Biotin* As a result of the demonstration that biotin was essential for animal growth and that avi-

in, a protein contained in egg white, antagonized avidin, Laurence<sup>85</sup> suggested that avidin might be useful in the treatment of cancer. Mice on a biotin-deficient diet and mice fed large amounts of avidin showed no decrease in the rate of tumor growth.<sup>86, 87</sup> The feeding of large amounts of egg white to a total of 12 patients with cancer produced no clinical evidence of a biotin deficiency and no alteration in the course of the disease.<sup>88, 89</sup>

**Paraminobenzoic acid (PABA)** The influence of paraminobenzoic acid on chronic leukemia was examined by Zarafonitis et al.<sup>90</sup> It was given orally to 10 patients with chronic leukemia in doses of 2 to 4 gm every two hours, so that a blood level of 10 to 30 mg per 100 cc, and frequently higher, was maintained. This dose produced a fall in white-cell count, usually after two or three weeks of treatment. When treatment was discontinued the white-cell count promptly rose. While the drug was being given, some of the patients showed a partial clinical remission, which was slight and transient. The effects were more striking in chronic myelogenous than in chronic lymphatic leukemia. There is no suggestion that PABA has a significant therapeutic effect in leukemia. Bichel,<sup>91</sup> on the other hand, has reported that PABA will raise the white-cell count in leukemia.

**Pyridoxine** The growth of the Flexner-Jobling carcinoma in rats and 2 different transplantable tumors in mice was decreased on a pyridoxine-deficient diet.<sup>92</sup> A potent pyridoxine antagonist, desoxypyridoxine, when given to mice on a pyridoxine deficient diet, inhibited the growth of a transplanted lymphosarcoma.<sup>93</sup>

**Teropterin** Lewisohn and his group<sup>94-96</sup> reported that spleen extract, extracts of the spleens from mice cured of Sarcoma 180 ("healed-spleen extract"), yeast extract, pearled barley extract, inositol and *Lactobacillus casei* factor (pteroyl-triglutamic acid, or teropterin), cured an appreciable percentage of mice inoculated with Sarcoma 180. The "healed-spleen extract" and pteroyltriglutamic acid also induced regressions in spontaneous mammary tumors in mice. Pteroylglutamic acid did not cause tumor regression.<sup>97</sup> Several other laboratories were unable to confirm these results,<sup>98, 99</sup> and there is no substantial laboratory evidence that pteroyltriglutamic acid has any influence on tumor growth.

In the past five years spectacular advances have been made in the chemistry and pharmacology of the folic acid compounds, pteroylglutamic acid and its conjugates.<sup>100</sup> Pteroylglutamic acid and pteroyltriglutamic acid (teropterin) produce hematologic remissions in pernicious anemia, nutritional macrocytic anemia and sprue.<sup>101</sup> In laboratory animals no significant qualitative differences in the pharmacologic actions of the pteroylmonoglutamic and triglutamic acid forms have been described.

On the basis of Lewisohn's work, Farber et al.<sup>102</sup> studied the effects of pteroyldiglutamic and triglu-

tamic acid on a series of 90 patients with a variety of neoplastic diseases. They found that these agents given intravenously or intramuscularly had no immediate or delayed toxicity or unpleasant side-effects. On the basis of their clinical experience, they recommended a daily dose of 20 mg. Patients were reported to feel better, showed an increase in energy, appetite and sense of well-being, and a diminution in apprehension and pain. Furthermore, in some of the treated cases, the tumors showed histologic changes that could be attributed to therapy. Lehy et al.<sup>103</sup> claimed that teropterin reduced the narcotic requirements of patients with inoperable cancer. Teropterin is now being sold as a palliative agent in cancer. It is therefore important to note that the therapeutic effects ascribed to teropterin are couched in such tenuous and devious terms that they defy critical analysis. In the absence of reproducible and consistent objective evidence of effect on neoplastic disease, teropterin cannot be regarded seriously as a chemotherapeutic agent against cancer.

Several folic acid antagonists have been prepared.<sup>104</sup> Meyer,<sup>105</sup> in a preliminary report, studied the effect of two of these compounds on acute leukemia. He observed a transient remission in 3 out of 5 cases. More recently, an extremely toxic folic acid derivative, 4 amino-pterovylglutamic acid (aminopterin), has been under study. This material does not behave in animals like a typical folic acid antagonist, and it appears to have toxic properties of its own. It has recently been reported to induce temporary remissions in acute leukemia in children.<sup>106</sup>

### Hormones

Studies of the therapeutic effects of the sex hormones on tumors arising in sex-linked organs have been conducted almost entirely in man. It is extremely difficult to obtain transplantable animal tumors that are sensitive to the influence of sex hormones, androgens<sup>107</sup> and estrogens<sup>108</sup> have little influence on the growth of the commonly used mouse tumors. In man, the therapeutic effect of the several types of estrogenic hormones on carcinoma of the prostate is attributed to estrogenic activity per se. It is of interest that alpha-bromo-alpha, beta, beta-triphenylethylene, a relatively weak estrogen as compared with stilbestrol, is stated to be unusually effective in the treatment of prostatic carcinoma.<sup>109</sup>

The adrenocortical hormones, which are involved in the metabolism of lymphatic tissue, have been shown to affect tumors of hematopoietic origin in mice. Heilman and Kendall<sup>110</sup> reported that 11-dehydro-17-hydroxycorticosterone (compound E), when given orally or parenterally, will produce a temporary regression of a transplantable lymphosarcoma in mice. This effect was more consistent in female mice or castrated male mice. Murphy and

Sturm<sup>111</sup> have found that treatment with the adrenocortical hormones or the pituitary adrenotropic hormone decreased the susceptibility of rats to a transplantable lymphatic leukemia. Law and Speirs<sup>112</sup> have described profound palliative effects, marked tumor regression and possibly some prolongation of life in mice with spontaneous lymphoid leukemia treated with adrenocortical extracts.

### CELL POISONS

There are a number of cellular poisons that, in the normal animal, are injurious to the more actively growing tissues (chiefly those of the blood-forming organs and the gastrointestinal tract). None of these agents have been shown to have a highly selective effect on cancer cells, per se, but certain tumors are temporarily more sensitive to these agents than the most susceptible of the normal tissues. Many of these agents, therefore, have been tested, and some are used extensively in the palliative treatment of cancer.

#### Nitrogen Mustards

The nitrogen mustards have the fundamental structure  $\text{ClC}_2\text{H}_4\text{N}^+\text{R}$ . The *bis* (beta-chloro-

ethyl) group is essential for the toxic characteristics of these agents (although certain minor modifications do not change its activity qualitatively), whereas the R group may be varied considerably without alteration of the essential characteristic pharmacologic actions of the molecule. Under physiologic conditions, active members of this group undergo rapid intermolecular rearrangement with the loss of a Cl to form an imine linkage. This is illustrated by the most common nitrogen mustard studied, methyl *bis* (beta-chloroethyl) amine hydrochloride  $\text{Cl}^-\text{C}(\text{CH}_2\text{CH}_2\text{Cl})_2\text{N}^+\text{CH}_3$ . The imine linkage

is the reactive part of the molecule, reacting with a great number of biologic substances. The pharmacologic action of the nitrogen mustards has been reviewed,<sup>113-118</sup> and their toxic actions from a physiologic<sup>116, 117</sup> and a pathologic point of view have been described.<sup>118, 119</sup> These compounds have been shown to produce cytologic damage,<sup>120-122</sup> mutations in *Drosophila*<sup>123</sup> and *Neurospora*<sup>124</sup> and selective effects on differentiating embryonic cells.<sup>125</sup> Their radiomimetic effects have been emphasized.<sup>114, 119</sup> Alterations in their chemical structure have produced marked changes in their pharmacologic activity.<sup>114, 115, 126, 127</sup>

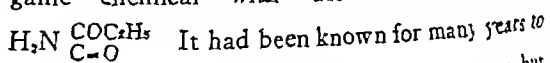
The nitrogen mustards (and the closely allied sulfur mustards) exert an inhibitory effect on the growth of certain mouse tumors,<sup>128, 129</sup> prolong the life of mice with transmitted leukemia,<sup>26</sup> selectively inhibit the growth of the mouse Sarcoma 180 on the chorioallantoic membrane of the chick embryo<sup>28</sup> and exert a therapeutic effect on fowl leukosis.<sup>31</sup>

Burchenal and his associates<sup>28</sup> have examined the activity of a large number of nitrogen mustard analogues in prolonging the life of mice with transmitted mouse leukemia. They found that, in general, the quaternary ammonium compounds and the mono-(beta-chloroethyl) group compounds were inactive, whereas the bis (beta-chloroethyl) groups and bis (beta-bromoethyl) groups and diamine mustards with 4 beta-chloroethyl groups were active in prolonging life. There seemed to be a direct correlation of the radiomimetic toxic effect of a nitrogen mustard and therapeutic activity.

The clinical use of methyl-*bis* (beta-chloroethyl) amine hydrochloride (HN2) is discussed in the next section. Two nitrogen mustard derivatives, 1,3 propane diamine (NNN' N' tetrakis [2-chloroethyl]) (SK136) and 1,3 chloropropyl diamine (NNV' N' tetrakis [2-chloroethyl]) (SK137), which showed therapeutic activity against mouse leukemia, have been tested clinically.<sup>140</sup> Although these agents do not seem to produce as much nausea and vomiting as HN2, they cause dizziness and, occasionally, toxic psychoses, and therapeutically, they do not appear to be more effective than HN2.

#### Urethane

Ethyl carbamate is a relatively simple organic chemical with the following formula:



It had been known for many years to exert a suppressive effect on growth processes, but interest in this agent in relation to neoplastic disease is only of recent origin. In 1939 Lefevre<sup>141</sup> described abnormal development and retarded growth in seedlings exposed to ethylphenyl carbamate. Templeman and Sexton<sup>142</sup> undertook a systematic survey of the aryl carbamates and related substances as plant-growth inhibitors. They found isopropyl phenylcarbamate to be most effective, urethane and methyl carbamate were inactive. Haddow and Sexton,<sup>143</sup> therefore, examined the effects of carbamates on tumor growth in animals. Phenyl urethane and urethane proved to be equally effective in inhibiting the growth of spontaneous mammary tumors in mice and the transplanted Walker carcinoma 256 in rats and, among the members of the carbamate series tested, these substances were unique in having this effect. Subsequently, numerous confirmatory reports appeared, demonstrating the suppressive action of urethane on rat Sarcoma 39,<sup>134</sup> transplanted lymphatic leukemia in rats<sup>144</sup> and transplanted<sup>126, 128-129</sup> and spontaneous<sup>140</sup> leukemia in mice. The clinical application of urethane is discussed below.

In addition to the suppressing effect of the drug on tumor growth, the demonstration that urethane was carcinogenic also aroused interest. In 1943 Nettleship and Henshaw<sup>145</sup> reported that urethane administration induced pulmonary adenomas in mice, and a similar action has been recorded in

<sup>142</sup> An extensive literature now exists on the carcinogenicity of urethane. Larsen<sup>143</sup> has shown a remarkable specificity of the carcinogenic activity of ethyl carbamate, methyl carbamate is ineffective, and isopropyl carbamate has one-eighth and n-propyl urethane one-eightieth the carcinogenic activity of urethane.

Dustin<sup>144</sup> found that the parenteral administration of urethane to mice reduced mitotic activity and produced cellular degeneration in the intestinal mucosa. There was a decrease in the reticulocyte count in the peripheral blood of rabbits and a slight shrinkage in the size of lymph nodes, but injury to the bone marrow was not apparent.<sup>145</sup> Some hematopoietic injury can be produced in man with urethane,<sup>146</sup> and this may be due to the greater sensitivity of the human bone marrow as compared with that of lower animals. Urethane appears, therefore, to act as a mild cell poison *in vivo*. Vascular and parenchymal liver injury<sup>147</sup> and liver tumors<sup>148</sup> have been reported in rats treated with urethane.

#### Colchicine

Colchicine, an alkaloid obtained from the autumn crocus, is a mitotic poison, arresting cell division in the metaphase. It has been shown to induce temporary regressions of lymphoid tumors<sup>149</sup> and to prolong life in leukemic mice.<sup>150</sup> Ludford,<sup>149</sup> in a review of colchicine in the experimental chemotherapy of cancer, concludes that "regression of tumor growth subsequent to colchicine treatment is primarily the result of hemorrhages following the disruption of newly formed capillaries." The effect of colchicine on animal tumors is not significantly enhanced when the drug is given in combination with x-ray therapy,<sup>150, 151</sup> bacterial toxins<sup>152</sup> or 2-methyl-naphthoquinone<sup>153</sup> a substance with high vitamin K activity. A large number of colchicine derivatives have been tested against tumors, but none have shown any greater selective action than colchicine on neoplastic cells.<sup>149</sup>

Colchicine will induce an increase in mitotic figures in human tumors within twelve hours.<sup>154, 155</sup> Of 4 patients with advanced carcinoma treated with colchicine 2 died within a few days, apparently of colchicine poisoning, with fever, diarrhea, pancytopenia and bleeding tendencies. The remaining 2 survived to show some tumor regression.<sup>156</sup> The dosage varied from 12 to 22 mg in four or five days. It was concluded that although cancer cells are susceptible to colchicine, the concomitant toxic effect makes its use very hazardous. Colchicine was not found to be very effective in human leukemia,<sup>157, 158</sup> but the clinical trials were inadequate.

#### Podophyllin

Podophyllin, an extract of the dried rhizomes and roots of the mandrake plant, has been used for many years as a cathartic. It is composed of resins and an active principle, podophyllotoxin. When applied

locally, podophyllin is effective in the treatment of condyloma acuminata, and a similar therapeutic effect has been obtained with colchicine.<sup>159</sup> Podophyllin also blocked mitosis in the root tips of *Allium cepa*.<sup>160</sup> Podophyllin and podophyllotoxin have produced hemorrhage in mouse tumors.<sup>161</sup> In tissue cultures, podophyllin and, to a lesser extent, podophyllotoxin have a selective damaging effect on mouse tumor cells.<sup>162</sup> Podophyllin appears to be similar to colchicine in many of its toxic effects.

#### CARCINOGENIC AGENTS

In 1935 Haddow<sup>162</sup> demonstrated that potent carcinogens, including 1,2,5,6-dibenzanthracene and 1,2-benzpyrene, inhibited the growth of the Jensen rat sarcoma, 9,10-dimethyl-1,2-benzanthracene inhibited the growth of Sarcoma 180<sup>163</sup> and prolonged the life and, in some cases, cured mice with transmitted leukemia.<sup>164-166</sup> This agent produced leukopenia, but leukemic mouse cells were more sensitive to its action than the normal white cells. Engelbreth-Holm and Stamer<sup>167</sup> treated 11 patients with 9,10-dimethyl-1,2-benzanthracene. The agent was suspended in a 2.5 per cent solution in distilled water, and was given intravenously in single doses, as large as 1 gm daily, a total course consisting of 1 to 11 gm. The injection was well tolerated, but it produced fever, with some nausea. A brief clinical remission occurred in 1 of 5 patients with acute leukemia, a more prolonged remission developed in 2 patients with chronic myelogenous leukemia and 2 patients with chronic lymphatic leukemia showed definite improvement. The treatment was without effect in 2 patients with multiple myeloma.

Seligman et al.<sup>168</sup> have synthesized a number of noncarcinogenic hydrocarbons related structurally to the carcinogens. These agents were tested for chemotherapeutic activity in transmitted myeloid leukemia, mammary adenocarcinoma and fibrosarcoma in mice. None of these compounds or their carcinogenic analogues, prolonged the life of leukemic mice, but some compounds inhibited the growth of solid tumors.

The carcinogenic activity of another class of carcinogens, the aminostilbenes, was detected because it was first found to inhibit tumor growth.<sup>169</sup> Clinical trials have been started with 2'-methyl and 2'-chloro-4-dimethyl aminostilbene, but the difficulties of administration have, thus far, not been overcome.<sup>170</sup> Boyland<sup>170</sup> has commented on the fact that the carcinogenic agents are the ones that have proved to be most effective in the treatment of cancer, these include x-rays, Fowler's solution, urethane, estrogens and the nitrogen mustards (several mice treated chronically with this agent have developed tumors).<sup>171</sup>

Flory et al.<sup>24, 25</sup> tested a variety of substances against several strains of transmitted leukemia. *Potassium arsenite* and *benzene*<sup>172</sup> were effective in

prolonging the lives of leukemic mice, and one type of leukemia (L1394) was cured occasionally with benzene. Other organic arsenicals and benzene derivatives tested were less effective.

### RADIOACTIVE SUBSTANCES

X-rays or radioactive isotopes, which injure cells by their radiations, cannot be regarded as chemotherapeutic agents. Since one of the principles of isotope therapy, however, is the localization of the radioactive agents in certain tissues, the biochemical properties of the radioactive material are of great importance. The chemotherapist, therefore, has a fundamental role in this field. If he were to discover a substance that concentrated in certain types of tumors, it would be possible to make one or more of the atoms in this compound radioactive, and thereby specifically irradiate the neoplastic tissue. With this in mind, Bloch and Ray<sup>175</sup> have described methods for incorporating radioactive iodine in a variety of organic compounds.

Thus far, only radioactive elements have been tested as therapeutic agents in cancer. Radioactive phosphorus and iodine are in clinical use, and they are discussed below. Radioactive strontium concentrates selectively in areas of active bone formation, and it has been tried, with disappointing results, in the treatment of bone tumors.<sup>8</sup> Radioactive manganese ( $Mn^{52}$ ), with a half-life of six and a half days, is given as a colloidal sol and it is taken up by the reticuloendothelial system. It has been used in the treatment of diseases of the hematopoietic system and allied disorders.<sup>174</sup> Colloidal radioactive gold ( $Au^{198}$ ), with a half-life of two and three-quarter days, has been used more recently for this purpose.<sup>175</sup> Radioactive arsenic is an interesting isotope, but therapeutic trials with this agent have not yet been reported. Radioactive sodium ( $Na^{24}$ ), with a half-life of fourteen and four-fifths hours, is evenly distributed throughout the body, and it provides a method for controlled total body irradiation. It has produced effects similar to total body irradiation in mouse leukemia.<sup>176</sup> Hahn and Sheppard<sup>177</sup> have analyzed the properties of radioactive isotopes that would make them suitable for therapeutic use. It is inevitable that a large number of radioactive isotopes and compounds containing radioactive atoms will be characterized and evaluated in the treatment of cancer.

### MISCELLANEOUS COMPOUNDS

Literally thousands of miscellaneous substances have been tested or are now under test for selective effects on neoplastic cells. They are greatly diversified, and they cannot easily be brought together.

#### Dyes

Many dyes have been tested in the hope of finding one that concentrated selectively in tumors. Zahl and Waters<sup>178</sup> tested a series of colloidal dyes,

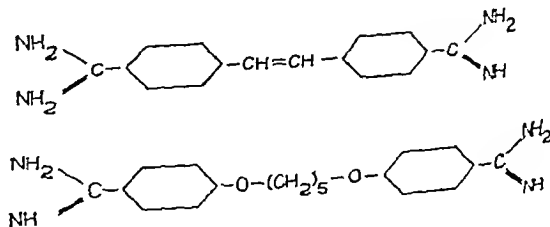
but could not demonstrate a selective uptake by tumor cells. The dye concentrated to some extent in the stroma surrounding the tumor, or at the interface of the viable and necrotic tissue. Boyland tested various derivatives of sulfonamides, and found that 4,4'-diaminodiphenyl sulfoxide, sodium sulfanilyl-sulfanilate<sup>21</sup> and 4,4'-diaminodiphenyl-ether<sup>179</sup> were most effective in temporarily inhibiting tumor growth in mice. The last compound, however, did not prove effective on clinical trial.<sup>21</sup> Lewis and Goland<sup>180,181</sup> tested a long list of acidic and other dyes by oral administration. Many of these stained tumors in mice and caused some retardation of growth, they did not prevent tumors from "taking" on transplantation or produce regressions in growing tumors.

#### Heptaldehyde

Strong<sup>182</sup> observed that heptyldehyde-sodium bisulfite, given in the proper dosage, caused regression and liquefaction in spontaneous mammary carcinoma in mice, although the regressions were rarely permanent. Boyland<sup>20,183</sup> tested a number of aldehydes, ketones and glucosides, and was able to report that, of these, citral and heptaldehyde inhibited the growth of spontaneous and transplanted tumors. Heptaldehyde sodium bisulfite methylsalicylate was selectively injurious in tissue culture to human and mouse mammary carcinomas and to rat lymphosarcoma.<sup>184</sup> Although heptaldehyde appeared to have an excellent record in the laboratory as an effective chemotherapeutic agent against neoplastic cells, it proved to be ineffective on clinical trial in 11 patients with metastatic mammary carcinoma<sup>185</sup> and in 3 patients with lymphoma.<sup>186</sup>

#### Stilbamidine

Stilbamidine (4,4'-diamidinostilbene) and a derivative, pentamidine (4,4'-(pentamethylenedioxy)dibenzamidine), are drugs that have proved effective in the treatment of kala-azar.<sup>178-189</sup> The formulas respectively, are as follows:



Because patients with kala-azar develop an elevated serum globulin, Snapper<sup>190,191</sup> used stilbamidine in multiple myeloma, a neoplastic disease in which a high serum globulin level is often present, with palliative results.

The mechanism of the action of stilbamidine in multiple myeloma is not definitely established, but several pertinent observations have been made. Popac<sup>192, 193</sup> has shown that stilbamidine reacts with nucleic acid to form a relatively inactive product, he suggests that stilbamidine acts by producing a dissociation of the protamine-ribonucleate complex, with the formation of protamine and a relatively insoluble stilbamidine-ribonucleate complex. Snapper et al<sup>194-196</sup> have described basophilic inclusion bodies that appeared in the myeloma cells after treatment with stilbamidine. These granules were shown to contain ribose nucleic acid. The inclusion bodies may develop one or two weeks after treatment has begun, persisting for many months. They occur most frequently in patients with disturbed protein metabolism — that is, in almost all patients with hyperglobulinemia and in most patients with normal serum globulin with Bence-Jones proteinuria, but in none of the patients with a normal serum globulin level without Bence-Jones proteinuria.<sup>196</sup>

Stilbamidine is made up as a di-isethionate salt, which is more stable and water soluble than the hydrochloride salt. The solution must be prepared immediately before use, and may be given intravenously or intramuscularly. If the intravenous injection is too rapid, flushing and a fall in blood pressure may occur. Aged solutions of stilbamidine have produced liver and kidney damage, but in a careful study of the toxicity of fresh stilbamidine, Arai and Snapper<sup>197</sup> were unable to show any untoward effects in the liver, kidneys and peripheral blood.

The unpleasant side action of stilbamidine therapy is the development of a facial neuropathy due to toxic degeneration of the principal sensory nucleus of the trigeminal nerve, usually appearing two to five months after treatment. It is characterized clinically by numbness, formication and itching, and a dissociation anesthesia evidenced by a loss of sensation to light touch. Ten out of 18 patients in the series of Arai and Snapper<sup>197</sup> developed this syndrome. The symptoms slowly subside, but the dissociated anesthesia may persist. Continuation of stilbamidine therapy does not seem to aggravate the symptoms.

The recommended dosage is a first injection of 50 mg, a second of 100 mg and 150 mg per dose thereafter. The injections are usually given every other day, but daily doses may be used. In most cases a total of 4 to 6 gm of stilbamidine has been given over a period of four or five months. Snapper<sup>191</sup> considers it essential that the patient be kept on a diet low in animal protein to obtain a therapeutic effect.

The effect of stilbamidine therapy in multiple myeloma is chiefly limited to the relief of severe bone pain. This relief is reported to be so striking that a bedridden patient may begin to walk again after four injections, and it is suggested that ambu-

lation be started cautiously since excessive activity may precipitate spontaneous fractures.<sup>191</sup> The bone pain may be alleviated indefinitely by therapy, and improvement has lasted for a year and longer.

Gibson and Pogge<sup>198</sup> have analyzed the results of a pooled survey of 186 cases of multiple myeloma treated with stilbamidine. Twenty-four and seven-tenths per cent experienced complete relief of pain, the predominating symptom, and 38.7 per cent obtained partial relief of pain. The remainder of the patients were either unaffected or made worse. In 76 of 99 cases studied by serial x-ray examination, there was no increase in the size of the lesions, although regressions were rare. Toxic effects on the blood or kidneys were not reported, but facial neuropathy has, thus far, developed in 30 patients. Stilbamidine had no influence on the course of lymphatic and myeloid leukemia, lymphosarcoma, Hodgkin's disease and carcinoma.<sup>190</sup>

The clinical data indicate that stilbamidine may be of value in the treatment of the severe and often disabling bone pain of multiple myeloma, but there is no satisfactory evidence that it allays the systemic effects, inhibits the extension or prolongs the course of the disease.

Rubenstein,<sup>199</sup> on a rationale similar to Snapper's, recently reported that an antimony-containing compound, neostibosan, produced relief of bone pain and basophilic granulations in the myeloma cells in multiple myeloma. He states that, "in general, our observations on antimony are strikingly similar to those of Snapper, using stilbamidine, a drug containing no antimony."

### *Enzyme Poisons*

Many enzyme poisons have been tested in an attempt to inhibit tumor growth. Since tumor cells are deficient in catalase, Boyland<sup>170</sup> tested a catalase inhibitor, *o*-nitroso-*B*-naphthol. This compound inhibited the growth of mouse tumors at tolerated doses. Brunschwig et al<sup>200</sup> found that sulfhydryl inhibitors, iodoacetate and maleate caused a retardation in tumor growth. Woodhouse<sup>201</sup> obtained tumor inhibition with malonic acid but not with succinic acid. Sodium fluoride, iodoacetic acid, malonic acid and sodium azide have been used clinically in the treatment of leukemia, lymphosarcoma and several types of carcinoma.<sup>202, 203</sup> Alterations in the neoplastic cells and temporary clinical remissions in acute leukemia have been attributed to treatment with one or more of these chemicals.

Kline et al<sup>204, 205</sup> have tested a number of pure chemicals and plant hormones *in vitro* and *in vivo*. The plant hormones had some inhibiting effects on the tumor cells *in vitro*, but were ineffective in inhibiting the growth of tumors in mice and rats. Belkin<sup>206</sup> found di-(hydroxymethyl) peroxide to be without effect in spontaneous transplanted and carcinogen-induced mouse tumors. Suramin (Ger-

manin), an anticoagulant, inhibited the growth of lymphosarcoma in mice, and caused lymphocytic fragmentation.<sup>207</sup> Chambers et al<sup>208</sup> demonstrated that tetraethyl and tetra methyl-o-phenylenediamine selectively damage neoplastic lymphocytes in tissue culture. Thiouracil<sup>209, 210</sup> was of no value in the treatment of leukemia. The injection of one of a variety of amino acids subcutaneously,<sup>211</sup> glycogen intravenously<sup>212</sup> or ethyl alcohol intraperitoneally<sup>213</sup> induced regressions in transplanted tumors in mice or rats.

Geshickter and Reid<sup>213</sup> have made oil-soluble organometallic compounds containing copper, cobalt, manganese, zinc, nickel and iron. Some of these compounds occasionally induced partial and temporary remissions in chronic and acute leukemia, and nickel monobutyl phthalate is reported to produce occasional favorable effects in some cases of carcinoma.

## REFERENCES

- Nauts H C, Swift, W E. and Coley, B L. Treatment of malignant tumors by bacterial toxins as developed by late William B. Coley, M.D. reviewed in light of modern research. *Cancer Research* 6: 205-216 1946
- Nauts H C and Coley B L. Review of treatment of malignant tumors by Coley bacterial toxins. In *Approaches to Tumor Chemotherapy*, 6. Pp 217-235
- Gratia A and Lantz, R. Le phénomène de Shwartzman dans le sarcome du Cochay. *Compt rend Soc de biol* 108: 427 1931
- Zahl P A, Hutner, S H, Spitz, S, Sugura K, and Cooper F S. Action of bacterial toxins on tumors. I. Relationship of tumor-hemorrhagic agent to endotoxin antigens of gram negative bacteria. *Am J Hyg* 36: 224-242 1942
- Hutner S H and Zahl, P A. Action of bacterial toxins on tumors. IV. Distribution of tumor-hemorrhagic agents among bacterial species. *Proc Soc Exper Biol & Med* 52: 364-368 1943
- Zahl P A, Starr M P and Hutner S H. Effect of bacterial toxins on tumors. VII. Tumor-hemorrhagic factor in bacteria. *Am J Hyg* 41: 41-56 1945
- Shear M J and Turner F C. Chemical treatment of tumors: nature of hemorrhage producing fraction from *Serratia marcescens* (Bacillus prodigiosus) culture filtrate. *J Nat Cancer Inst* 4: 81-97 1943
- Kahler H, Shear M J and Hartwell J L. Chemical treatment of tumors: ultracentrifugal and electrophoretic analysis of hemorrhage producing fraction from *Serratia marcescens* (Bacillus prodigiosus) culture filtrate. *J Nat Cancer Inst* 4: 123-129 1943
- Hartwell J L, Shear M J and Adams J R, Jr. Chemical treatment of tumors: nature of hemorrhage producing fraction from *Serratia marcescens* (Bacillus prodigiosus) culture filtrate. *J Nat Cancer Inst* 4: 107-122 1943
- Beck L V. Temperature changes produced in mice with *S. marcescens* polysaccharide. In *Approaches to Tumor Chemotherapy*, 5. Pp 265-270
- Westfall B B and Dunn T B. Blood uric acid and protease, body temperature and glomerular clearance of rabbits implanted with Brown Pearce carcinoma and treated with polysaccharide from *Serratia marcescens*. *J Nat Cancer Inst* 7: 115-121 1946
- Shear M J. Chemical treatment of tumors: reactions of mice with primary subcutaneous tumors to injection of hemorrhage producing bacterial polysaccharide. *J Nat Cancer Inst* 4: 461-476 1944
- Diller I C. Nuclear changes produced by *S. marcescens* (B. prodigiosus) polysaccharide. In *Approaches to Tumor Chemotherapy*, 5. Pp 260-264
- Algire G H, Legallis F Y, and Park H D. Vascular reactions of normal and malignant tissues in vivo. II. Vascular reaction of normal and neoplastic tissues of mice to bacterial polysaccharide from *Serratia marcescens* (Bacillus prodigiosus) culture filtrate. *J Nat Cancer Inst* 8: 53-62 1947
- McConnell J R. Preparation of polysaccharide solutions for clinical use and tissue culture experiments. In *Approaches to Tumor Chemotherapy*, 5. Pp 271
- Brues A M and Shear M J. Chemical treatment of tumors: reactions of four patients with advanced malignant tumors to injection of polysaccharide from *Serratia marcescens* culture filtrate. *J Nat Cancer Inst* 5: 195-203 1944
- Holloman A L. Reactions of patients and of tumors to injection of *S. marcescens* polysaccharide in eight cases of malignant disease. In *Approaches to Tumor Chemotherapy*, 5. Pp 273-276
- Oakey R. Reactions of patients to injection of *S. marcescens* polysaccharide in nine further cases of malignant disease. In *Approaches to Tumor Chemotherapy*, 5. Pp 277
- Cornman, I. Selective lethal effect of penicillin on sarcoma cells growing with normal tissue in roller tube cultures. *J. Gen. Path.* 28: 113-118 1944
- Lewis M R. Failure of purified penicillin to retard growth of rats of sarcoma in mice. *Science* 100: 314 1944.
- Gey G O, Gey M K, Inou, F and Vedder H. Effects of penicillin and purified penicillin on continuous cultures of human malignant cells. *Bull Johns Hopkins Hosp* 77: 116-131 1944
- Stool, C C, Singura K, and Rhoads C, P. Infective and biologic preparations on viability and growth of sarcoma, melanoma and carcinoma in mice. *Fourth International Cancer Research Congress*. St Louis September 1947. P 88
- Mahoney J F. Some significant aspects of venereal disease research. *J Ven Dis Inform* 28: 129-132 1947
- Kidd, J G. Effects of antibiotic from *Aspergillus fumigatus* on tumor cells in vitro and its possible identity with penicillin. *Science* 105: 511-513 1947
- Roskin G. Toxin therapy of experimental cancer in the case of protozoan infections upon transplanted cancer. *Can Res* 6: 363-365 1946
- Klyueva, N G. Paths of cancer biotherapy. *Ar. R. S. S. Med.* 4: 403-414 1947
- Hauschka T, Saxe J H, Jr, and Blair M. Treatment of mouse tumors. *J Nat Cancer Inst* 7: 189-194 1944
- Hauschka T. Protozoa and cancer. In *Approaches to Tumor Chemotherapy*, 6. Pp 250-257
- Hauschka T S, and Goodwin, M B. *Trypanosoma evansi* (KR) in treatment of malignant mouse tumors. *Science* 107: 602 1948
- Malisoff W M. Action of endotoxin of *Trypanosoma evansi* (KR) on malignant mouse tumors. *Science* 106: 591-594 1947
- Williams J L and Waters, C L. Tumour inhibitor with extract of urine. *Nature* London 159: 503, 1947
- Gye W E, Ludford, R J, and Barlow, H. Failure of H11 to retard growth of tumours in mice. *Brit M J* 2: 65-67 1943
- Woodhouse, D L. Effect of injections of H11 on growth of mouse tumours. *Brit M J* 2: 231 1943
- Kidd H A. Observations on use of H11 in carcinoma. *Brit M J* 2: 67-69 1943
- Miller F R, Wearn J T and Heinle, R W. Proliferation of myeloid and lymphoid cells induced by extracts of urine from leucemic patients. *Proc Soc Exper Biol & Med* 41: 479 1937
- Heinle, R W, Hirschmann H, and Wearn J T. Myeloid leucemia factor from human urine. In *Approaches to Tumor Chemotherapy*, 6. Pp 77-95
- Turner D L and Miller, F R. Chemistry of substances responsible for stimulation of lymphopoiesis and myelopoiesis. In *Approaches to Tumor Chemotherapy*, 6. Pp 64-76
- Erf I, A, Turner D L and Miller F R. Cellular changes induced by extracts of human organs. *Blood* 1: 379-386 1946
- Miller, F R, Herbst, P A and Jones H W. Treatment of lymphoblastic leukemia with crude myelokentine acid. *Blood* 2: 1533 1947
- Watson G F, Diller I C and Ludwick, N V. Spleen extract and tumor growth. *Science* 106: 348 1947
- Bogomolets, A A. Antitumoral cytotoxic serum as means of pathogenic therapy. *Am Rev Sot Med* 1: 101-112 1943
- Pomerat, C M. Reticulo-endothelial immune serum (REIS). III. Effect of strong concentrations on growth of Walker rat sarcoma 319 in vitro. *Cancer Research* 5: 724-728 1945
- Davis, W D Jr. Clinical observations in patients treated with antitumoral cytotoxic serum: preliminary report. *Am J Med* 3: 123 1947
- Skapier J. Therapeutic use of antitumoral cytotoxic serum (AC) in Hodgkin's disease. *Cancer Research* 7: 369-371 1947
- Boydland E. Experiments on chemotherapy of cancer. I. Effect of muscle extract and aliphatic bases. *Biochem J* 35: 128-132 1941
- Stedman E, Stedman E, and Pettigrew F W. Retardation of growth of mouse carcinoma 2146 by histone and protom. *Biochem J* 38: 31 1944
- Barker G R, Gulland, J M and Parsons L D. Tissue changes in experimental mice treated with pentose nucleosides. *Nature* 157: 482 1946
- Abderhalden R. Untersuchungen über den Einfluss von d u d d. I. Di- und Polypeptiden auf die Entwicklung von Impftumoren. *Ztschr f. Physik. Chem* 270: 9-13 1941
- Lawrence W L. Induced biotin deficiency as possible explanation of observed spontaneous regressions in malignancy. *Science* 94: 88 1941
- Kensler C J et al. Influence of egg white and avidin feeding on tumor growth. *Cancer Research* 3: 823 1943
- West P M and Woglom W H. Abnormalities in distribution of biotin in certain tumors and embryo tissues. *Cancer Research* 2: 324-331 1942
- Rhoads C P and Abels J C. Administration of egg white and avidin concentrates to patients with cancer. *J. Nat. Cancer Inst* 1261-1263 1943
- Kaplan I I. One year observations of treatment of cancer with avidin (egg white). *Am J Hyg* 50: 207-233 1944
- Zarafonitis C J D, Andrews G A, Meyers M C, and Beth F H. Para-aminobenzoic acid in leukemia. *Blood* (in press)
- Bichel J. Effect of p-aminobenzoic acid on leucocyte count in leukemia. *Nature* London 161: 353 1948
- Kline B E, Ruch H P, Baumann, C A and Lavik P S. Effect of pyridoxine on tumor growth. *Cancer Research* 3: 825-837 1943

- Stoerck, H. C. Regression of lymphosarcoma implants in pyridoxine-deficient mice. *J Biol Chem* 171 437 1947
- Lewisohn R. Effect of subcutaneous injections of concentrated spleen extract on mouse sarcoma 180. *Surg Gynec & Obst* 66 563 576 1938
- Leuchtenberger R., Leuchtenberger C., Laszlo D. and Lewisohn R. Influence of 'folic acid' on spontaneous breast cancers in mice. *Science* 101 46 1945
- Lewisohn R., Laszlo D., Leuchtenberger C. and Leuchtenberger R. Chemotherapeutic regressions of transplanted and spontaneous cancers in mice. In *Approaches to Tumor Chemotherapy*. Pp 139-207
- Lewisohn R., Leuchtenberger C., Leuchtenberger R., and Keresztesy J. Influence of liver L. casei factor on spontaneous breast cancer in mice. *Science* 104 436 1946
- Sugimura K. Effect of intravenous injection of yeast and barley extracts and L. casei factor upon spontaneous mammary adenocarcinoma in mice. In *Approaches to Tumor Chemotherapy*. Pp 208-215
- Zahl P. A. and Hutner S. H. Note growth inhibition of mouse sarcoma 180. In *Approaches to Tumor Chemotherapy*. Pp 214-216.
- Jukes T. H. and Stokstad E. L. R. Pteroylglutamic acid and related compounds. *Physiol. Rev* 28:51-106 1948
- Spies T., Lopez, G. G., Milanes F., and Aramhura T. Synthetic folic acid effectiveness of conjugated form in treatment of tropical sprue, Addisonian pernicious anemia and nutritional macrocytic anemia. *J. A. M. A.* 134 18-20 1947
- Farber S., et al. Action of pteroylglutamic conjugates on man. *Science* 106 619-621 1947
- Lehr S. P., Wright L. T., Weintraub S. and Arons I. Use of teropterin in neoplastic disease: preliminary clinical report. *Tr. New York Acad. Sc (Sp No Ser II)* 10 74-81 1948
- Smith J. M., Cosulich D. B., Hultquist, M. E. and Seeger D. R. Chemistry of certain pteroylglutamic acid antagonists. *Tr. New York Acad. Sc (Sp No Ser II)* 10 82 1948
- Meyer L. M. Use of folic acid derivatives in treatment of human leukemia. *Tr. New York Acad. Sc (Sp No Ser II)* 10 99 102 1948
- Farber S., Diamond, L. K., Mercer R. D., Sylvester R. F. Jr., and Wolf J. A. Temporary remissions in acute leukemia in children produced by folic acid antagonist, 4-aminopteroyl glutamic acid (aminopterin). *New Eng J Med* 238 787-793 1948
- Jones E. E. Effect of testosterone propionate on mammary tumors in mice of C3H strain. *Cancer Research* 1 787 789 1941
- Hackmann C. Über den Einfluss der Keimdrüsenwirkstoffe auf Entstehung und Wachstum maligner Tumoren. *Ztschr f. physiol. Chem* 274 31-38 1942
- Berger M., and Bañ-Hoàng Ph. Treatment of prostatic carcinoma with a bromo-a-B-B-triphenylethylene (559). *Lancet* 2 172 1947
- Heilman, F. R. and Kendall E. C. Influence of 11-dehydro-17-hydroxycorticosterone (compound E) on growth of malignant tumor in mouse. *Endocrinology* 34 416-420 1944
- Murphy J. B. and Sturm, E. Effect of adrenal cortical and pituitary adrenotropic hormones on transplanted leukemia in rats. *Science* 99 303 1944
- Law L. W. and Speirs R. Response of spontaneous lymphoid leukemias in mice to injection of adrenal cortical extracts. *Proc Soc Exper Biol & Med* 66:226-230 1947
- Rhoads C. P. Sword and ploughshare. *J Mt Sinai Hosp* 13 299-309 1947
- Gilman, A. and Philips F. S. Biological actions and therapeutic applications of B-chloroethyl amines and sulfides. *Science* 103 407-415 1946.
- Philips F. S., and Gilman A. Relation of chemical constitution and biological action of nitrogen mustards. In *Approaches to Tumor Chemotherapy*. Pp. 285-292.
- Houck, C. R., Crawford, B., Bannon J. H., and Smith H. W. Studies on mechanism of death in dogs after systemic intoxication by intravenous injection of methyl bis (B-chloroethyl) amine or tris (B-chloroethyl) amine. *J Pharmacol & Exper Therap* 90 277 292 1947
- Karnofsky D. A., Graef L. and Smith H. W. Studies on mechanism of action of nitrogen and sulfur mustards in vivo. *Am J Path.* 24 275-292 1948
- Kindred, J. E. Histologic changes occurring in hemopoietic organs of albino rats after single injections of 2-chloroethyl vesicants: quantitative study. *Arch Path.* 43 253-295 1947
- Graef L., Karnofsky D. A., Jager V. B., Krichesky B. and Smith H. W. Clinical and pathological effects of nitrogen and sulfur mustards in laboratory animals. *Am J Path.* 24 1-47 1948
- Friedenwald, J. S., Buschke W., Scholz, R. O. and Moses S. G. Some effects of sulfur and nitrogen mustards on cell nuclei in mammalian cornea. In *Approaches to Tumor Chemotherapy*. Pp 358-378.
- Staff of Wilmer Institute. Studies on physiology, biochemistry and cytopathology of cornea in relation to injury by mustard gas and allied toxic agents. *Bull Johns Hopkins Hosp* 82 81-352 1948
- Koller P. C. Behavior of tumor cell under influence of irradiation and chemicals. *Fourth International Cancer Research Congress* St. Louis September 1947 P 142.
- Auerbach C., Robison J. M., and Carr J. G. Chemical production of mutations. *Science* 105 243 247 1947
- Horowitz, M. H., Houlahan M. B., Hingate, M. G., and Wright, B. Mustard gas mutations in neurospora. *Science* 104:235 1946.
- Bodenstein, D. Effects of nitrogen mustard on embryonic amphibian development. I. Ectodermal effects. *J Exper Zool* 104 311 341 1947
- Anslow W. P., Jr. Karnofsky D. A., Jager, B. V., and Smith H. W. Toxicity and pharmacological action of nitrogen mustards and certain related compounds. *J Pharmacol. & Exper Therap* 91 224-235 1947
- Goldin A., Noe H. A., Landing B. H., Goldberg B. and Fugmann. Some relationships of structure to biological activity in nitrogen mustards and related compounds. *Fourth International Cancer Research Congress* St. Louis September 1947 P 54
- Boydland E., Koller P. C. and Warwick, O. H. Effects of chloroethylamines on tumors. *Fourth International Cancer Research Congress* St. Louis September 1947 P 89
- Bass A. D. and Freeman M. L. H. Response of certain mouse tumors to bis (B-chloroethyl) sulfide (mustard gas). *J Nat Cancer Inst.* 7 171-176 1946
- Burchenal J. H. Newer nitrogen mustards in treatment of leukemia. *Radiology* 50 494-499 1948
- Lefevre J. Similitude des actions cytologiques exercées par le phénylurethane et la colchicine sur des plantules végétales. *Compt. rend Acad d sc* 208:501-504 1959
- Templeman W. G. and Sexton W. A. Effect of some arylcarbamate esters and related compounds upon cereals and other plant species. *Nature* London 156 630 1945
- Haddow A. and Sexton W. A. Influence of carbamic esters (nrethane) on experimental animal tumours. *Nature* London 157 500-501 1946.
- Yu S. T. Effect of ethyl carbamate on rat sarcoma 39. *Fourth International Cancer Research Congress* St. Louis, September 1947 P 105
- Murphy J. B. and Sturm, E. Inhibitory effect of ethyl nrethane on development of lymphatic leukemia in rats. *Cancer Research* 7 417-420 1947
- Engstrom R. M., Kirschbaum, A. and Mixer H. W. Effect of urethane on mouse myelogenous leukemia. *Science* 105 255 1947
- Kirschbaum, A., and Lu C. S. Effect of urethane on maturation of leukocytes of mouse myelogenous leukemia. *Proc Soc Exper Biol & Med* 65 62 1947
- Law L. W. Effect of nrethane on transplantable acute lymphoid leukemia. *Proc Soc Exper Biol. & Med.* 66 158-161 1947
- Weir D. R. and Henkle, R. W. Effect of nrethane on transplanted leukemia of Ak mice. *Proc Soc Exper Biol & Med* 66 268-270 1947
- Law L. W. Urethane (ethyl carbamate) therapy in spontaneous leukemias in mice. *Proc Nat. Acad Sc* 33 204-210 1947
- Nettleship A. and Henshaw P. S. Induction of pulmonary tumors in mice with ethyl carbamate (urethane). *J Nat. Cancer Inst.* 4 309 319 1943
- Jaffe W. G. Carcinogenic action of ethyl urethane on rats. *Cancer Research* 7 107-113 1947
- Larsen C. D. Evaluation of carcinogenicity of series of esters of carbamic acid. *J Nat Cancer Inst* 8 59-101 1947
- Dustin P. Cytological action of ethylcarbamate (nrethane) and other carbamic esters in normal and leukaemic mice and in rabbits. *Brit J Cancer* 1 48-59 1947
- Moerschlin S. Zum Wirkungsmechanismus des Urethans bei Leukämien. *Helvet med acta* 14 279 294 1947
- Paterson E., Haddow A., ApThomas I. and Watkinson J. M. Leukaemia treated with urethane compared with deep x-ray therapy. *Lancet* 1 677-682 1946
- Doljanski L. and Rosin A. Studies on early changes in livers of rats treated with various toxic agents with special reference to vascular lesions. I. Histology of rat's liver in nrethane poisoning. *Am J Path.* 20 945-959 1944
- Litt F. J., Kirschbaum, A. and Strong L. C. Action of colchicine on transplanted malignant lymphoid neoplasm in mice of C3H strain. *Am. J. Cancer* 34 196-215 1938
- Landford R. J. Colchicine in experimental chemotherapy of cancer. *J. Nat. Cancer Inst* 6 89-101 1947
- Brues, A. M., Marble B. B. and Jackson, E. B. Effects of colchicine and radiation on growth of normal tissue and tumors. *Am J Cancer* 38 159-168 1940
- Hirshfield J. W., Tennant, R., and Oughterson A. W. Effect of colchicine and x-ray on transplantable mammary carcinoma in mice. *Yale J Biol. Med* 13:51-59 1940
- Andervont, H. B. Effect of colchicine and bacterial products on transplantable and spontaneous tumors in mice. *J Nat Cancer Inst* 1 361 366 1940
- Boydland E. and Boydland, M. E. Studies in tissue metabolism. 12. Action of colchicine on transplanted induced and spontaneous mouse tumors. *Biochem J* 34 280 284 1940
- Oughterson A. W., Tennant R. Jr., and Hirshfield J. W. Effect of colchicine on human tumors. *Proc Soc Exper Biol & Med.* 36 661-664 1977
- Levine M. and Silver G. B. Mitotic response to colchicine in human cancer. *Proc Soc Exper Biol. & Med* 65:54-60 1947
- Seed L., Slaughter D. P., and Limarzi L. R. Effect of colchicine on human carcinoma. *Surgery* 7 696-709 1940
- Paul J. T., Brown W. O., and Limarzi L. R. Effect of colchicine on chronic myeloid leukemia. *Am J Clin Path* 11 210 218 1941
- Kneeder W. H. Colchicine in acute myelogenous leukemia. *J. A. M. A.* 129 272 1945
- Sullivan M. and Blanchard D. Podophyllotoxin. *Bull. Johns Hopkins Hosp* 81 65-67 1947
- Sullivan B. J., and Wechsler H. I. Cytological effects of podophyllin. *Science* 105 435 1947
- Belkin M. Effect of podophyllin on transplanted mouse tumors. *Federation Proc* 6 308 1947

- 162 Haddow A Influence of certain polycyclic hydrocarbons on growth of Jensen rat sarcoma *Nature London* 136 868 1935
- 163 Stamer S Effects of 9 10-dimethyl-1 2 benzantracene on transplanted tumours *Acta path et microbiol Scandinav* 18:533-557 1941
- 164 *Idem* Effect of carcinogenic hydrocarbon on manifest malignant tumors in mice eradication of transplanted leukemia in mice and attempts at inhibition of other manifest malignant tumors in mice by treatment with 9 10-dimethyl-1 2 benzantracene *Acta path et microbiol Scandinav* (Supp 47) 1943
- 165 Stamer S and Engelbreth Holm J Influence of carcinogenic hydrocarbon upon transplanted leukemia *Acta path et microbiol Scandinav* 20 360 371 1943
- 166 Stamer S Further experimental studies on intravenous injection of 9 10-dimethyl-1 2 benzantracene in mice (tolerance excretion effect on normal blood cells) *Acta path et microbiol Scandinav* 22 65-72 1945
- 167 Engelbreth Holm J and Stamer S Treatment of leukemia with 9 10-dimethyl-1 2 benzantracene In *Approaches to Tumor Chemotherapy* Pp 418-430
- 168 Seligman A M Friedman O M Gofstein R M and Sweet B N Mouse tumor growth inhibition with compounds related to carcinogenic hydrocarbons *Fourth International Cancer Research Congress St Louis September, 1947* P 90
- 169 Haddow A, Harris R J C, and Kon G A R Inhibition of growth by amino-s-diarylethylenes *Biochem J* 39 2 1945
- 170 Boyland E Chemical carcinogenesis and experimental chemotherapy of cancer *Yale J Biol & Med* 20 321-341 1948
- 171 *Idem* Personal communication
- 172 Flory C M, Steinhardt, I D and Furth J Further observations on effect of benzene on strain of myeloid chloroleukemia in mice and on changes produced in leukemic cells by chemical *Blood* 1 367, 1946
- 173 Bloch H S and Ray F E Organic radioiodo compounds for cancer research *J Nat Cancer Inst* 7 61-66 1946
- 174 Hahn P F and Sheppard C W Selective radiation obtained by intravenous administration of colloidal radioactive isotopes in diseases of lymphoid system *South. M J* 39 558-562 1946
- 175 Sheppard C W Goodell J P B and Hahn, P F Colloidal gold containing radioactive isotope Au<sup>198</sup> in selective internal radiation therapy of diseases of lymphoid system *J Lab & Clin Med* 32 1437-1441 1947
- 176 Evans T C Effects of radioactive sodium on leukemia in mice *Cancer Research* 6 498 1946
- 177 Hahn P F and Sheppard C W Therapeutic use of radioactive elements in malignancy *Ann Int Med* 28 598-606 1948
- 178 Zahl, P A and Golland, P P Localization of colloidal dyes in animal tumors *Proc Soc Exper Biol & Med* 48 304-310 1941
- 179 Boyland E Experiments on chemotherapy of cancer effect of aromatic bases *Biochem J* 40 55-58 1946
- 180 Lewis M R and Golland, P P In vivo staining and retardation of tumors in mice *Anat. Rec* 99 359-378 1947
- 181 *Idem* In vivo staining and retardation of tumors in mice by acridine compounds *Am. J M Sc* 215 282-289 1948
- 182 Strong L C Effect of heptylaldehyde sodium bisulfite in spontaneous tumors of mammary gland in mice. *Cancer Research* 1 473-476 1941
- 183 Boyland E Experiments on chemotherapy of cancer IV Further experiments with aldehydes and their derivatives *Biochem J* 34 1196-1201 1940
- 184 Cameron G Kensler C J and Chambers R Action of heptanol sodium bisulfite methylsalicylate and of 2 4 6-trimethylpyridine on tissue cultures of human and mouse carcinoma and rat lymphosarcoma *Cancer Research* 4 495-501 1944
- 185 Abels J C et al Clinical effects of aldehyde bisulfites in patients with cancer I Administration of heptaldehyde bisulfite to patients with inoperable mammary carcinoma metastatic to bone *Cancer Research* 4 438-443 1944
- 186 Singher, H O Abels, J C Craver L F and Rhoads C P Clinical effects of aldehyde bisulfites in patients with cancer II Administration of heptaldehyde bisulfite to patients with lymphomas *Cancer Research* 4 444-446 1944
- 187 Adams A R D and Yorke W Studies in chemotherapy case of Indian kala azar treated with 4 4-diamidino stilbene *Ann Trop Med* 33 323-326 1939
- 188 Adler S, and Rachmilewitz, M. Note on treatment of leishmaniasis infantum with 4 4-diamidino stilbene. *Acta Trop Med* 33 327-330 1939
- 189 Burchenal J H Bowers, R. F., and Hedicke, T A. Visceral leishmaniasis complicated by severe anemia improved following splenectomy *Am J Trop Med.* 27:699 709 1941
- 190 Snapper I On influence of stilbamidine on multiple myeloma *J Mt Sinai Hosp* 13 119 127, 1946
- 191 *Idem* Stilbamidine and pentamidine in multiple myeloma. *J A M A* 133 157-161 1947
- 192 Kopac M J Cellular mechanisms in chemotherapy *Tr Am York Acad Sc* 8 5-10 1945
- 193 *Idem* Some cellular and surface chemical aspects of tumor chemotherapy In *Approaches to Tumor Chemotherapy* Pp 275
- 194 Snapper I and Schneid B On influence of stilbamidine on myeloma cells *Blood* 1:534-536 1946
- 195 Snapper I Mirsky A E, Rus H Schneid, B., and Reschal M Development of inclusion bodies containing ribose nucleic acid in myeloma cells after injections of stilbamidine determined by benzidine in myeloma tissue *Blood* 2:311 322, 1947
- 196 Snapper I and Schneid B Development of basophilic inclusion bodies in myeloma cells after stilbamidine treatment. *Acta Med* 27:541-547, 1947
- 197 Arai H and Snapper I Influence of stilbamidine upon liver function liver function and peripheral blood in multiple myeloma. *New York State J Med* 47 1867 1874 1947
- 198 Gibson A and Pogge R C Personal communication.
- 199 Rubenstein M A Chemotherapy of multiple myeloma and autophagy *Blood* 2 555 563 1947
- 200 Brunschwig A., Arnold J and Edgecomb J Simultaneous retardation of neoplastic growth by sulfhydryl compounds. *Cancer Research* 6:560-562, 1946
- 201 Woodhouse D L Chemotherapeutic investigations in cancer with reference to influence of certain organic dibasic acids diamine compounds and nitro compounds on tumors in mice *Cancer Research* 7 398-401 1947
- 202 Kleiner I S Block, M M and Bolker H. Energy mechanism in malignant tumors in relation to chemotherapy *Fourth International Cancer Research Congress St Louis September 1947* P 107
- 203 Bolker H, Block, M M and Kleiner S Some cellular and tissue effects of specific enzyme inhibitors on human malignant neoplasms *Fourth International Cancer Research Congress St Louis September 1947* P 107
- 204 Kline B E, Wasley W L and Rusch, H. P Tumor inhibitor studies. I Effect of pure chemical compounds on tumor tissue *Cancer Research* 2 645-648, 1942
- 205 Kline B E and Rusch H P Tumor inhibitor studies. II Effect of plant hormones on tumor growth. *Cancer Research* 3 707-710, 1943
- 206 Belkin, M Lack of influence of di-(hydroxymethyl) peroxide on incidence and growth of transplanted, induced and spontaneous mouse tumors *Cancer Research* 2 264-279 1942
- 207 Williams W L Effects of suramin (germanin) azo dyes, and vasodilators on mice with transplanted lymphosarcomas *Cancer Research* 6 344-353 1946
- 208 Chambers R, Cameron G., and Kopac M J Neoplasm studies. XI Effects in tissue cultures of N,N,N',N'-tetramethyl-o-phenylenediamine and other compounds on malignant lymph node. *Cancer Research* 3 293 295 1943
- 209 Limarzi L R, Kulasavage R. J and Pirani, C. L Effect of thiouracil on leukemia *Blood* 1 426-445 1946
- 210 Hansen Pruss O C Thiouracil in treatment of leukemia *Proc Soc Exper Biol & Med* 64 496-500 1947
- 211 Beard H H and Givens E Further observations upon effect of subcutaneous injection of amino acids and creatine upon appearance growth and regression of Emge sarcoms in rats *Exper Med & Surg* 2 125-128 1944
- 212 Ball H A Effect of intravenous glycogen administration on rate of growth of Walker carcinosarcoma 256 and sarcoma 180 *Cancer Research* 2 823-827 1942
- 213 Geshickter C F and Reid E. E. Administration of oil-soluble organo-metallic compounds in malignancy In *Approaches to Tumor Chemotherapy* Pp 431-442

## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

TRACY B MALLORY, M D, *Editor*

BENJAMIN CASTLEMAN, M D, *Associate Editor*

EDITH E PARRIS, *Assistant Editor*

### CASE 34331

#### PRESENTATION OF CASE

A twenty-five-year-old man entered the hospital because of blurring of vision.

During the year before admission the patient was occasionally bothered by shortness of breath on exertion, and three months before admission he noted the onset of moderately severe frontal headaches. One month before admission blurring of vision appeared, which rapidly progressed until it was unsafe for the patient to walk on the street. One week later the headaches became more severe, and periorbital edema was noted in the mornings. There were no episodes of fainting and no epistaxis or symptoms of cerebrovascular accident, no chills, fever, orthopnea, edema of the ankles or increased abdominal girth and no known urinary disease or symptoms.

At the age of six the patient had had an attack of polyarthritis for which he was hospitalized and following which a diagnosis of rheumatic heart disease was made. He was kept out of competitive sports until the age of sixteen, but during the succeeding years he played baseball and filled a job requiring considerable physical effort with no difficulty. Five years before admission he was turned down by the Army because his blood pressure was "a little high."

Physical examination showed the patient to be pale and chronically ill. The eyes showed bilateral congenital zonular cataracts, which somewhat obscured the view of the fundi, nevertheless, numerous flame-shaped hemorrhages, many exudates and a Grade I papilledema were seen. The neck veins were dilated and pulsating. The lungs were clear except for some fluid at both bases. The heart was enlarged, the border of cardiac dullness extending to the left, the sounds were loud and snapping, and there was a widely transmitted Grade III apical systolic murmur. The liver edge was nontender and was felt one fingerbreadth below the costal margin. Shifting dullness and a questionable fluid wave were made out. There was minimal pitting edema of the ankles and sacrum. Chvostek and Trousseau signs were both present.

The temperature, pulse and respirations were within normal limits. The blood pressure was 210 systolic, 135 diastolic.

The hemoglobin was 8 gm, and the white-cell count 13,000. Urinalysis showed a specific gravity of 1.008 and a +++ test for albumin, the sediment contained 10 to 20 red cells, 5 to 10 white cells per high-power field and many granular casts. The nonprotein nitrogen was 90 mg per 100 cc, the total protein 4.48 gm per 100 cc, with an albumin-globulin ratio of 1:41, the serum calcium 5.8 mg and the phosphorus 9.7 mg per 100 cc, and the phosphatase 2.9 units. The sodium was 136.9, the chloride 98, the carbon dioxide 19, and the potassium 7.7 milliequiv per liter.

The patient's output of urine was very poor. He was given a small amount of 5 per cent dextrose in water intravenously and shortly thereafter suffered an attack of acute pulmonary edema. This was treated with morphine, cedilanid and tourniquets. He improved somewhat but then gradually lapsed into coma, developed numerous petechiae and died on the third hospital day.

#### DIFFERENTIAL DIAGNOSIS

DR BERNARD M JACOBSON: To summarize this patient's clinical course, we have the onset of probable rheumatic fever, with rheumatic heart disease many years before admission. Five years before admission he first learned that he had hypertension. About one year before admission he began to suffer dyspnea on exertion, in other words, the first indication of some complication of hypertension. For three months the symptoms consisted mainly of hypertensive encephalopathy and retinitis. We are dealing, then, with a young man who carried a hypertension for at least five years but who began to suffer from probable congestive heart failure one year prior to death.

We are told in the physical examination that the neck veins were dilated and pulsating. Physical signs of that sort make us think of right-sided heart failure or pericardial effusion or constrictive pericarditis. We think especially of tricuspid stenosis. Apparently no x-ray films of his chest were taken during the hospital stay. Is that right?

DR JOSEPH C AUB: Yes.

DR JACOBSON: We would be interested to see the configuration of the heart. We know that we can miss abnormal configurations by physical examination. The lungs were clear. I rather interpret the loud snapping first sound at the apex as probably due to hypertension and hypertensive heart disease. On the other hand, with the widely transmitted Grade III apical systolic murmur, one wonders if he had a diastolic blow. I am sure that we all can miss atypical diastolic blows, especially in a person who already has evidence of heart failure. We would also like to know whether the second aortic sound was louder than the pulmonic or vice versa.

We have evidence later of ascites. The Chvostek and Trousseau signs were undoubtedly due to hypocalcemia. The hemoglobin of 8 gm is not accompanied by a description of the stained smear, but I presume the red cells were fairly normocytic and normochromic, in other words, this was an anemia of the simple, chronic type seen in renal disease. From the study of the urine we get no specific diagnostic information. The picture of renal malfunction gives evidence of both diffuse glomerular and tubular irritation. The patient undoubtedly had been in renal failure for some time because of the nonprotein nitrogen of 90 mg per 100 cc by the time he came to the hospital. The total protein was rather low, 4.5 gm per 100 cc, and does not show the albumin-globulin reversal that we see in such conditions as subacute glomerulonephritis. There was no edema, and one wonders about the accuracy of the figure of 4.5 gm per 100 cc. There was a rather marked hypocalcemia — 5.8 mg per 100 cc, on the other hand, in view of the remainder of the picture, I doubt that we have to worry about primary hypoparathyroidism. This is a picture of hypocalcemia with secondary clinical evidence of tetany that we see every so often in terminal renal insufficiency, regardless of cause. The serum sodium and chloride were within normal limits. The potassium was high, undoubtedly due to renal retention. The carbon dioxide combining power compared with the normal of 25 milliequiv per liter was not markedly reduced. Most people in uremia at this stage of the game should have a more marked acidosis. The terminal episode of pulmonary edema following the intravenous infusion of dextrose and water is a common phenomenon in people with either congestive heart failure or severe renal insufficiency or both.

The presence of petechiae terminally is a common finding in renal insufficiency and denotes some type of vascular purpura. There is no question that the patient died of a combination of congestive heart failure — as evidenced by the symptoms and the distribution of the edema — and renal insufficiency or uremia.

What was the cause of the congestive heart failure? We know that this patient had hypertension long enough to produce hypertensive heart disease. At autopsy there may or may not have been evidence of myocardial infarction or myocardial fibrosis due to coronary-artery disease. What evidence have we that he had any other type of heart disease, such as rheumatic heart disease? I think it is of importance that he was told at the age of sixteen that he had rheumatic heart disease. He undoubtedly was known to have a murmur at that time. I think we have to say that he did have rheumatic heart disease, in addition to the hypertension. I do not believe there is any particular association in this case between the two conditions. Did he have mitral regurgitation, or did he have mitral

stenosis? A good deal of the murmur may have been due to congestive heart failure, part of it, at any rate, to old rheumatic heart disease, and part to hypertensive heart disease. I am a little surprised at not hearing anything about a gallop. Certainly in this terminal stage the patient should have had a gallop, and I would not be surprised if told that he had a pericardial friction rub during the last few days of life.

Certainly the two commonest types of renal lesions we have to consider are either chronic vascular nephritis or malignant hypertension and chronic glomerulonephritis with terminal renal insufficiency. I really do not see any certain way of differentiating these two conditions. Against glomerulonephritis is the fact that we have no history of acute glomerulonephritis or of subacute glomerulonephritis with edema. We have some evidence that the hypertension antedated any knowledge on his part of the urinary abnormalities, and from the level of the blood pressure recorded at entry in the presence of congestive heart failure, one wonders if he had not been carrying a much higher blood pressure during the previous year. This degree of hypertension would certainly be consistent with terminal vascular nephritis. There is nothing in the urinary picture that differentiates the two conditions.

With more renal studies, what other conditions might we encounter? We know that in our diagnoses we must mention chronic pyelonephritis. We have in this case no history of acute infection in the kidneys or a history of renal calculi. There is nothing in the urinary sediment at present that attracts our attention to chronic pyelonephritis. We have a definite statement of fever in the past history but no fever at the time of entry to the hospital. I think we have to discount the possibility of chronic pyelonephritis.

Could this have been an end result of congenital polycystic kidneys? Yes, they may first manifest their presence by the development of hypertension but are certainly far less frequent than malignant hypertension or glomerulonephritis.

Could this renal picture have been due to emboli from the valves of subacute bacterial endocarditis? It could be, but there is no evidence for it. There is no history of fever over a period of time before he came to the hospital and no elevated temperature on admission. There is no statement about any of the other symptoms or ordinary physical signs of subacute bacterial endocarditis. On the other hand, we will not be surprised if Dr. Mallory tells us that the patient had a terminal acute endocarditis.

Could this possibly have been a renal complication of lupus erythematosus? There is no evidence in the past to suggest lupus erythematosus, such as skin lesions, joint symptoms and leukopenia. Could this have been periarteritis nodosa? Again, the absence of fever in the history and the

presence of palpable arterial nodules and eosinophilia at the time of entry make me believe that there is nothing to substantiate that diagnosis. It is merely interesting to mention in passing.

I am going to conclude with a diagnosis of rheumatic heart disease, mitral regurgitation, congestive heart failure, malignant hypertension, chronic vascular nephritis and uremia.

A PHYSICIAN: May I ask whether the phosphatase determination was acid or alkaline?

DR JACOBSON: Undoubtedly it was alkaline phosphatase. The normal value for alkaline phosphatase is 2 to 5 Bodansky units. I suppose it is routine to ask for serum calcium, phosphorus and phosphatase in patients with renal failure. Is that not so, Dr. Aub?

DR AUB: Yes, I might say that I have never seen such a marked Chvostek sign in a uremic patient. He did not have such a very marked drop in calcium when allowance is made for the low plasma protein. Yet it was one of the most marked Chvostek signs that I have ever seen. I do not believe that it could have been due to low blood calcium but to the mechanical irritability that comes with uremia. There was one other sign not mentioned—when the patient was lying down the left upper lobe was full of rales and very congested, when he sat up they all vanished.

DR TRACY B. MALLORY: Is there any comment on the acute pulmonary edema following intravenous therapy with glucose?

DR AUB: In my note I said that it was dangerous to give it, but the only chance of survival was to make him urinate. I also recommended fluid, knowing that he might get pulmonary edema and thinking it was worth the risk.

A PHYSICIAN: How much fluid was given?

DR AUB: Not an enormous amount. He was given 1500 cc of 5 per cent dextrose in water.

DR JACOBSON: It may not be amiss at this point to comment to the effect that I had considered the possibility of lower-nephron nephrosis, such as sulfonamide sensitivity, but in view of the complete absence of such a history I did not discuss it.

A PHYSICIAN: In the face of congestion is it good therapy to give a man of that age intravenous fluids?

DR AUB: I thought it was. It was the only thing we could do for him.

A PHYSICIAN: Would you not use a more concentrated solution instead of so much water if you were trying to bring about diuresis?

DR AUB: You can have your choice. The patient was going to die anyhow.

#### CLINICAL DIAGNOSIS

Subacute glomerulonephritis?

Malignant vascular nephritis?

#### DR JACOBSON'S DIAGNOSES

Rheumatic heart disease  
Mitral regurgitation  
Congestive heart failure  
Malignant hypertension  
Chronic vascular nephritis  
Uremia

#### ANATOMICAL DIAGNOSES

Subacute glomerulonephritis  
Cardiac hypertrophy and dilatation, hypertensive type  
Pulmonary edema, severe  
Bronchopneumonia, slight  
Hydrothorax bilateral, slight

#### PATHOLOGICAL DISCUSSION

DR MALLORY: I think the autopsy showed conclusively that the patient was going to die, as Dr. Aub has said. I rather expected to find very contracted kidneys after reading through the record. At autopsy we found the kidneys to be larger than normal, weighing 450 gm (he was not a large man). They were very pale gray, with yellowish mottling, and the gross diagnosis was subacute glomerulonephritis, that was borne out by the microscopical examination. The other findings at autopsy were a very severe grade of pulmonary edema. The lungs weighed a little over 2000 gm, were very distended and failed to collapse when the thoracic cavity was opened. There was very little pleural fluid—150 cc on each side. Microscopically we found evidence of incipient pneumonia, but the major portions of the lung showed edema rather than infection. The heart did show recognized scars of previous rheumatic infection. The posterior leaflet of the mitral valve was distinctly shrunken, and the circumference of the valve was only 8.5 mm whereas the normal is considered 10 to 10.5 mm. There was a slight degree of mitral stenosis and a more significant degree of mitral regurgitation. The heart weighed 450 gm and the hypertrophy was about equally distributed on the right and left sides, so that I think the hypertrophy was secondary to hypertension as well as to the rheumatic valvulitis. The parathyroid glands were dissected and were not enlarged. Microscopically however, the fat, which is normally present within the parathyroid gland, had disappeared entirely indicating slight hyperplasia.

DR JACOBSON: Do you think that this was subacute bacterial endocarditis arising independently of the antecedent hypertension?

DR MALLORY: No, I think that the hypertension was probably due to the glomerulonephritis. I would have to admit that this was a slow and silent progression of glomerulonephritis, but one sees cases of this type on occasion.

DR JACOBSON: Was there any pericardial effusion?

DR MALLORY No, we found petechiae on many of the serous surfaces similar to those noted in the skin but no pericarditis, and there was no gastritis or colitis as there frequently is in the uremic state.

DR AUB Is there any reason for the bizarre clinical findings in the lungs?

DR MALLORY No, I think the immediate mechanism of death was probably pulmonary edema. The intravenous fluid had been given a full two days before death, however, and the pulmonary edema temporarily cleared, only to recur.

## CASE 34332

### PRESENTATION OF CASE

A sixty-eight-year-old woman entered the hospital complaining of easy fatigability.

About two months prior to admission the patient began to experience progressive weakness and easy fatigability. During this time she had been seen by two physicians, who had been unable to help her. A few hours before admission she developed a severe, steady pain in the right upper quadrant, not affected by breathing or by change in position, and lasting only a few hours. She had not noticed any jaundice, itching or changes in the urine or stools, and had not known of any weight loss.

At the age of thirty-eight she had undergone an apparently normal menopause.

Physical examination revealed a tired, weak, slightly jaundiced woman. A Grade II pulmonary diastolic murmur was heard. A tender, smooth, firm mass was palpated in the left upper quadrant. The edge was not well defined. The mass did not move with respiration and seemed to be medial to the spleen. There was slight erosion of the anterior lip of the cervix.

The temperature was 99.5°F, the pulse 105, and the respirations 24. The blood pressure was 125 systolic, 65 diastolic.

Examination of the blood revealed a red-cell count of 4,200,000, with 15 gm of hemoglobin, and a white-cell count of 11,700, with 79 per cent neutrophils, 13 per cent lymphocytes and 8 per cent monocytes. Examination of the urine showed a specific gravity of 1.020, a +++ test for albumin, acetone and bile, and a green color with a precipitate on sugar test. The serum nonprotein nitrogen was 41 mg, the total protein 5.9 gm, the cholesterol 610 mg and the cholesterol esters 125 mg per 100 cc. The fasting blood sugar was 100 mg, and the alkaline phosphatase 41.8 mg per 100 cc. A van den Bergh test was 6.4 mg per 100 cc direct and 8.2 mg total. The prothrombin time was 18 seconds (control, 19 seconds). The cephalin-flocculation test was + in twenty-four and forty-eight hours. A catheterized specimen

of urine revealed rare colon bacilli and a few non-hemolytic streptococci.

An x-ray film of the chest disclosed no abnormality of the bony thorax. There was some calcification in the right and left first interspaces. The right leaf of the diaphragm was quite high, obscuring the right lower-lung field. There were some linear areas of increased density. The left lung field was not remarkable. The heart appeared enlarged in the region of the left ventricle. A barium enema, with the patient unsatisfactorily prepared, showed no evidence of gross obstruction or gross filling defect in the large colon. A gastrointestinal series showed no esophageal varices. The stomach was displaced to the left and posteriorly by a greatly enlarged liver. No other masses could be made out though there was bulging in the left flank, possibly due to a mass other than the liver. There was flattening along the superior aspect of the proximal duodenum. On the second hospital day a biopsy of the cervix and a vaginal smear were done and both were reported negative.

On the eighth hospital day an operation was performed.

### DIFFERENTIAL DIAGNOSIS

DR JAMES H. TOWNSEND I would be interested to know whether the pain in the right upper quadrant lasted four hours, twelve hours or twenty-four hours. I take it it was the development of this pain, which she had not had before, that brought about the emergency situation that necessitated the patient's entry into the hospital. I should like to know whether the pain lasted for just a few hours before she came into the hospital, and then disappeared before she was seen, or whether, when she came in, the pain required morphine to relieve it. We are not given any information about that as yet. She had not noticed any jaundice, itching or changes in the urine or stools, and she had not known of any weight loss.

At physical examination on admission she was very jaundiced when first seen — I assume only a few hours after the pain developed. I think that is of importance.

The murmur I assume to have been an early diastolic murmur heard in the second left interspace. There was a wide pulse pressure that may have had significance in relation to the murmur.

Examination of the blood was essentially negative, with the white-cell count slightly on the high side, but no anemia.

Let us pause a moment. This patient had bile in the urine. She had acetone, which suggests that she had not been eating well or had been vomiting. She had albumin, which frequently accompanies bile and suggests that perhaps there had been bile there for some time. The green color on Benedict test, which is a frequent finding with

is not necessarily due to sugar, but may be due to some other substance

The cholesterol esters were at about a normal solute level, but the proportion was quite low in relation to the total. The phosphatase was high, and the van den Bergh within middle range. At this point are we told whether there were any cellular elements in the urine — white cells, red cells and so forth?

Presumably the linear areas of increased density described in the x-ray findings were caused by atelectasis associated with the high diaphragm. By x-ray interpretation the liver was greatly enlarged. We are not told on physical examination what the liver edge could be felt in the usual place. May we see the x-ray films at this point?

DR JOSEPH HANELIN: The chest film shows the elevated right leaf of the diaphragm, with a slight amount of linear streaking above it, probably representing atelectasis. The heart is probably enlarged somewhat although it is difficult to be certain of the exact size because the elevated diaphragm may increase the transverse diameter. The lungs otherwise are clear. This film includes the major portion of the abdomen and the barium-filled stomach, which is displaced to the left, presumably by the enlarged liver.

DR TOWNSEND: Can you see the lower border of the liver?

DR HANELIN: I would assume that it was opposite the third lumbar vertebra.

DR TOWNSEND: It is covered by gas so that you cannot define the lower edge too well as to position or exact shape.

DR HANELIN: That is right. We do not see the lower contour. The stomach is displaced somewhat to the left, and in the lateral projection the stomach is displaced posteriorly.

DR TOWNSEND: In the lateral view can you see where the liver is?

DR HANELIN: I cannot definitely outline it.

DR TOWNSEND: The liver is not sufficiently enlarged to push the hepatic flexure into the pelvis, is it?

DR HANELIN: No.

DR TOWNSEND: Most of the liver is above the iliac crest?

DR HANELIN: Yes.

DR TOWNSEND: There are one or two simple laboratory observations that we are not given. I wonder if they were done. We are given a good many blood chemical findings, but we are not told anything about the character of the stools, either the gross appearance or chemical reactions.

DR TRACY B. MALLORY: The stools were brown and guaiac negative. The urine contained a few pus cells, but the number was not estimated.

DR TOWNSEND: But no chemical test was done on the stool for bile pigment or urobilinogen? Was

there a test for urobilinogen in the urine? Evidently not.

We have, then, an elderly woman, with a two months' history of failing health, who had pain only a few hours before admission and at the time of admission was already clinically jaundiced. I am curious to know on which day the van den Bergh test was done, was that observation almost immediately after she came in or after the passage of some days?

DR MALLORY: The test was made on the day after entry.

DR TOWNSEND: She had a reasonably high van den Bergh reaction, which I do not believe developed in the twenty-four hours since she began to have pain. In other words, I believe she had jaundice before she had pain, and this has a different significance from jaundice appearing some days after pain.

The important features of the physical examination are jaundice, an abdominal mass and a diastolic murmur. The blood showed no anemia. We have many of the usual battery of tests done in an attempt to establish the cause of jaundice. In general, we divide these tests into those that point toward obstruction of the extrahepatic biliary passage and those that point toward disturbance of intrahepatic cellular function. Rarely do we get a clear-cut picture. The findings are usually mixed. In this case the high alkaline phosphatase and the high total cholesterol are strongly in favor of external obstruction (probably complete obstruction at these levels), although we would like very much to know whether there was complete obstruction demonstrated by the absence of bile pigment in the stools and the absence of urobilinogen in the urine. However, we do not have that information. The van den Bergh reaction is consistent with complete external obstruction. The slightly low total protein, on the other hand, the relatively low cholesterol esters and the + cephalin-flocculation test point toward damaged liver parenchyma. It was not damaged enough, however, to influence the prothrombin time, which in this case was normal.

The patient was operated on. We have to estimate what was most likely to be found at that operation. Let us look at it from the point of view of the mass described in the left upper quadrant. It was smooth, ill defined and tender. What masses of this sort occur in the left upper quadrant? The kidney is in that region. We have little information about the kidney. At least, there was no blood or pus coming from it. I assume that no intravenous pyelogram was done, or we would have been given that information. On the x-ray films I do not believe that we can see the kidney, and it was not described in the physical examination as a kidney mass would have been. Before examination at the hospital it was thought that it was definitely

not the spleen, and I do not believe that it was the spleen. Could it have been part of the larger mass that the roentgenologists thought might be liver? Yes, the left lobe of the liver might present such a mass, particularly if it was involved with metastatic disease, and that is a definite possibility.

What else could this mass have been? It could obviously have arisen in the pancreas, which is in that region, and pancreatic masses either solid or cystic type, benign or malignant, can present such a mass. They are usually not described as tender. However, I am sure I have seen cases of carcinoma of the pancreas that developed a large, tender mass before the patient died.

If this mass represented a metastasis in the left lobe of the liver, would it have been tender? Usually metastatic masses are not tender, and they are usually not painful. I think it is possible for such a mass to become tender if it is infarcted or has had a hemorrhage in it. I still think that this could have been the left lobe of the liver and that it could have been tender.

Our tests do not give us absolute proof as to whether we are dealing with a straight case of external obstruction or with damage to the liver parenchyma. They suggest a combination. I think that we have to look at the picture as a whole and consider the most probable diagnosis. I gather from the x-ray films that the liver was not tremendously large.

One can say almost with certainty that a liver of this size in a person of this age comes from metastatic carcinoma. The only other condition that frequently causes these very large livers at this age is leukemia, and that I think is ruled out by the blood picture. What was the probable source? We can pretty well rule out the colon. The patient had a pelvic examination, and although not specifically mentioned, I assume that no masses were felt. Probably these metastases did not arise from the pelvic organs, although that is a common source. A small tumor in the ovary can lead to tremendous metastases in the liver. It was apparently not in the stomach. I think it would have been seen if it had been in the stomach, although we all know that a tiny carcinoma in some part of the stomach may not be seen on x-ray study. But I think it is a very distant possibility when painless jaundice comes on at this age. I speak of this as painless jaundice because she was already jaundiced when she was first seen, and there was

not time to develop that degree of jaundice after the pain began. The tumor that causes such a situation usually originates either in the pancreas or in the bile duct. I do not believe that it is possible clinically to differentiate the two. Such liver cancer can also come from metastases from a lung tumor, but from what we can see of the lungs there appears to be no primary source in the nature of a bronchiogenic carcinoma. It is not necessary that the original tumor should have blocked the bile duct. Sometimes metastases themselves, in lymph nodes in the region of the bile duct, can cause such obstruction. I am assuming it was complete obstruction because of the finding of a very high alkaline phosphatase and high total cholesterol. However, the observation of brown stools suggests that it was not complete obstruction, that is a single finding and we cannot rely on it without more chemical tests.

Could this woman possibly have had the one condition that leads to external obstruction and that is amenable to surgery — a stone in the common duct? The possibility is very remote because she had been going downhill and feeling generally well for two months before the onset of pain and because she was jaundiced when first seen within a few hours after the onset of pain.

I shall, therefore, conclude by saying that the probability is that this woman had metastatic disease, presumably carcinoma, in the liver, probably arising from the pancreas, possibly the bile duct, and also possibly from some other source that I have mentioned. I do not believe that cirrhosis of the liver could produce such a picture. One almost never sees such a high cholesterol in cirrhosis of the liver. One can get pain like this in cirrhosis. Can it be a primary tumor in the liver? These are rare tumors usually arising in persons who already have had cirrhosis, of which we have no evidence here, whereas there is considerable evidence that she did not have cirrhosis. She had no esophageal varices. She did have a very high total cholesterol and no change in the prothrombin time. I therefore expect that whatever operation was done — whether it was an exploration, a punch biopsy or a peritoneoscopy — showed metastatic disease in the liver. As a probable source I should think that the pancreas was most likely. The painful mass may have been either the left lobe of the liver or the pancreas.

DR PERRY CULVER I saw this woman with the 4-year students. We were impressed with the severity of the patient's illness, and we were primarily concerned with the epigastric mass. We did not feel the liver at this examination, but in

Out-Patient Department the mass seemed to represent cancer of some sort. We thought it was probably metastatic neoplasm. We admitted the patient to the house immediately as emergency. That is as far as we went with the diagnosis at that time.

I should also like to say that we usually disregard a + cephalin-flocculation test as being within normal limits.

DR TOWNSEND I agree.

DR CULVER Another interesting point is that there is an occasional rare case with brown stools that, on repeated examinations, are completely devoid of bile pigment. Schiff\* has reported this same observation.

#### CLINICAL DIAGNOSES

Metastatic carcinoma of liver

Uremia

#### DR TOWNSEND'S DIAGNOSIS

Metastatic carcinoma of liver (probable primary source in pancreas or bile duct)

#### ANATOMICAL DIAGNOSES

*Carcinoma of gall bladder, with massive involvement of liver and metastases to adrenal glands*

Pulmonary congestion and edema

Cholelithiasis

Pulmonary tuberculosis, old

#### PATHOLOGICAL DISCUSSION

DR MALLORY The operation mentioned was a peritoneoscopy. There had been considerable discussion as to whether or not exploratory laparotomy or peritoneoscopy should be performed. Oddly enough it was the surgeons who did not wish to explore the patient and urged the peritoneoscopy. The liver was studded with tumor nodules. The

patient went rapidly downhill and died without any symptoms of note. At autopsy we found that almost all the liver tissue had been replaced by tumor. In cross-section the largest mass of this tumor was centered around the gall-bladder area, and in the gall bladder was a small papillary tumor, which we believed to be the primary site, with direct lymphatic spread throughout the liver substance. There were very few metastases in the body—two small ones in each adrenal gland and one small metastasis in the bone marrow, found more or less by accident in our microscopical sections. There were no metastases to the lung. The gall bladder contained numerous stones, and we also found three small stones in the common duct which however, was not dilated.

DR TOWNSEND I meant to say that sometimes patients have both carcinoma and gallstones and that perhaps the pain at the time she came in was due to gallstones but I did not believe that stones caused the whole picture.

DR MALLORY Cancer of the gall bladder almost never occurs in the absence of cholelithiasis.

DR TOWNSEND Was the large mass felt on the left side caused by metastases in the left lobe of the liver?

DR ROY V. BUTTLES I could not be sure that the mass felt on the left side was the lobe of the liver. It did not seem to be particularly enlarged.

DR TOWNSEND There was nothing else external to the liver or behind the liver?

DR MALLORY No.

DR JAMES HEIL May I ask about the pulmonary diastolic murmur?

DR TOWNSEND I meant to comment on that also. She may have had old rheumatic heart disease. I assume that a blood Hinton test was done, but I doubt very much the likelihood of a syphilitic process. She may have had sclerotic changes in the aortic valve, which could produce such a murmur in a patient of this age—probably calcific aortic valve disease, not marked.

DR MALLORY We did not find anything to explain the murmur. The heart was entirely normal.

\*Schiff L. *Differential Diagnosis of Jaundice* 313 pp Chicago Year Book Publishers Incorporated, 1946 P 250

# The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established 1828

Official Organ of

THE MASSACHUSETTS MEDICAL SOCIETY

and

THE NEW HAMPSHIRE MEDICAL SOCIETY

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND  
PUBLISHED WEEKLY UNDER THE JURISDICTION OF THE  
COMMITTEE ON PUBLICATIONS

James P. O'Hare, M.D. Richard M. Smith, M.D. *Chairman*  
Oliver Cope, M.D. Conrad Wesselhoeft, M.D.  
John Fallon, M.D.

Joseph Garland, M.D., *EDITOR*

*ASSOCIATE EDITORS*

Thomas H. Lanman, M.D. Donald Munro, M.D.

Henry Jackson, Jr., M.D.

Clara D. Davies, *EXECUTIVE EDITOR*

Robert O. Leary, *ASSISTANT EDITOR*

*EDITORIAL BOARD*

C. Guy Lane, M.D.  
Henry R. Viets, M.D.  
Robert M. Green, M.D.  
Dwight O'Hara, M.D.  
Fletcher H. Colby, M.D.  
Robert L. Goodale, M.D.  
Chester M. Jones, M.D.  
Harvey R. Morrison, M.D.

Maxwell Finland, M.D.  
James M. Faulkner, M.D.  
Carroll B. Larson, M.D.  
Francis D. Moore, M.D.  
C. Stuart Welch, M.D.  
Vernon P. Williams, M.D.  
Benjamin Castleman, M.D.  
Hugh R. Leavell, M.D.

SUBSCRIPTION TERMS: \$7.00 per year in advance, postage paid for the United States (medical students, \$4.00 per year); Canada, \$8.00 per year (Boston funds); \$9.50 per year for all foreign countries belonging to the Postal Union.

MATERIAL should be received not later than noon on Thursday three weeks before date of publication.

THE JOURNAL does not hold itself responsible for statements made by any contributor.

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts. Telephone KE 6-2094.

NEW ENGLAND ADVERTISING REPRESENTATIVE: Edwin B. Tyler, 89 State Street, Boston, Massachusetts. Telephone LA 3-5516.

## MEDICAL EXPERTS ON THE ATOMIC AGE

THE world terror characterizing the dawn of the Atomic Age seems at first glance to be something new and unique in human affairs. In a mood of incredulous despair the thoughtful people of the western world stand appalled at the magnitude of the danger. In quite a different mood, scientific experts are now beginning to preach a hard-headed gospel of preparedness. If our courage falters at the earnestness of their words it may be well for us to draw strength from a backward glance to another time when civilization found itself also in an evil case.

It was in the spring of 1242, eighteen years after the mysterious Mongol horde of Genghis Khan had irrupted into eastern Europe to massacre a Christian

army at the Kalka river, thirteen years after the dreaded horse archers had turned back to lay waste northern China while Europe shuddered through an uneasy lull, and three years after the Asiatic terror had again loomed across the Russian steppes.

These last three years had seen eastern Europe suffer the most fearful disasters—far worse than anything Attila and his Huns had brought. "The Mongols," according to Oman\* "represented not mere conquest but blind and wilful destruction, they left deserts behind them where there had been a civilized and thickly peopled group of states and killed for killing's sake." The armored chivalry of Christendom—the best that Europe could produce—melted before them. Nations in their path for got their local quarrels and united, but too late. Now led by Batu Khan, the horde trampled down Russia, Poland and Silesia. On April 5, 1241, they had annihilated an allied army of Germans, Moravians and Poles at Liegnitz and then had rapidly overrun the Balkan peninsula. Now indeed "a shock of terror went round the whole of Christendom." The last barrier was down, and with the approach of spring Batu Khan stood at the unprotected German border. Doubtless the unheeded warning of the River Kalka and the far-off fate of China were then remembered, and the thirteen wasted years of the "cold war" regretted. Western Europe saw its "atomic age" close at hand, and it was appalled.

But then, as now, there were experts to substitute reasoned action for despair. Observing siegecraft to be the weak side of Mongol tactics, military engineers advised building strong fortresses and castles—the people built them. Advised to unite for common defense, the nations united and braced themselves for inevitable disaster, but disaster never came. Batu Khan, after breaking his teeth on the first strongly fortified and defended cities suddenly faded into the east, and Western Europe, after a year of intense terror, finding itself inexplicably freed from all danger, was able to resume its endless local wars.

On August 6, 1945, a detonation over Hiroshima announced the advent of our own Atomic Age. Again the shock of terror, which is not new, is

\*Oman, C. *A History of the Art of War in the Middle Ages*. Second edition. 2 vol. London: Constable & Co. 1924.

ing felt round the world. And again the experts speaking.

Colonel Wesley C. Cox and Major A. J. Bauer, Army Medical Corps experts from the Surgeon General's Office, discussed "Military Epidemiology and Preventive Medicine in the Atomic Age" at the Harvard School of Public Health on May 26, 1948. Their remarks dealt with two aspects of the problem of preparedness: the immediate implications of an atomic bomb attack within the next five years, and the broader implications of producing a civilization capable of surviving the consequences of atomic bomb attacks in a more remote future.

They began by pointing out the enormous shocking power of the latest explosives, and the magnitude of the devastation one bomb can cause. Between 15,000 and 200,000 casualties can be expected in a city of 1,000,000 population. All the measures now taken in cases of widespread disaster will be needed, but on a vastly larger scale. Tremendous supplies of drugs, dressings and other medical equipment will be required. Blood transfusions will be used in fantastic numbers. Treatment of initial injuries will involve rescue, evacuation, sorting, nursing care, antibacterials, vitamin C, intravenous administration of fluids and blood and the surgery of trauma and burns. Later treatment of survivors may be directed to the effects of radiation illness, the radiation damage being evaluated by frequent lymphocyte counts. Agents of questionable value such as vitamin B<sub>12</sub>, toluidine blue, protamine sulfate, rutin and adrenocortical hormones may be used. "Of first importance following the rescue and first-aid ministrations to those known to have been exposed to excessive radioactivity is the administration of drugs to prevent the development of capillary and vascular fragility." Many laymen will have to be taught the technique of blood grouping, transfusion, cell counts and other medical skills to supplement the efforts of the physicians. Each community will have to organize a "civil-defense task-team" made up of experts in several fields as well as a civilian-defense force based on the experience of the English in World War II. A grim note is sounded by the statement that "the director of the emergency plan for one city must be a resident in some other community. Shelters, potable water,

waste disposal, food spoilage both by irradiation and by electric power disruption, detection and control of epidemics must also be envisioned. "The power of this weapon is so great that we cannot afford not to plan as long as any possibility of attack is present."

Colonel Cox and Major Bauer then spoke of the long-range plans that may be necessary if humanity is to survive in the Atomic Era.

The advent of the Atomic Period has oriented us to new concepts and wider horizons. We have adopted a broader view of democracy and fully recognize that although we are in a time of technocracy we have also entered into an era of renewed interest in the individual.

This leads them to discuss such apparently diverse subjects as trends in medical education, means of extending the span of economic usefulness in an aging population, the elimination of chronic diseases, eugenics, maternal health, periodic health examinations, prevention of dental caries, child psychology as an approach to reducing later neuropsychiatric instability, dietetics, and many others. "Only through such comprehensive National programs may we envision the development during the future Atomic Era of a physically strong, well-developed population, psychologically and mentally well conditioned and hardened and free of the preventable defects, disabilities and diseases which have so long plagued us."

Major Bauer ended with a thought that must surely have entered the minds of the thirteenth-century military experts while they were pushing their fortifications to completion.

The most important preventive measure in preparation for an atomic bomb attack is outside of our field. That is a national policy which will make all of our efforts superfluous.

## STREPTOMYCIN RESISTANCE OF TUBERCLE BACILLI

It is now well known that the development of resistance of the infecting organism is one of the most important limiting factors and the greatest cause of failures of streptomycin in the treatment of tuberculosis. Two recent studies shed further light on certain aspects of this phenomenon.

# The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established 1828

Official Organ of

THE MASSACHUSETTS MEDICAL SOCIETY

and

THE NEW HAMPSHIRE MEDICAL SOCIETY

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND  
PUBLISHED WEEKLY UNDER THE JURISDICTION OF THE  
COMMITTEE ON PUBLICATIONS

Richard M. Smith, M.D., Chairman

James P. O'Hare, M.D.

Oliver Cope, M.D.

Conrad Wesselhoef, M.D.

John Fallon, M.D.

Joseph Garland, M.D., Editor

ASSOCIATE EDITORS

Thomas H. Lanman, M.D.

Donald Munro, M.D.

Henry Jackson Jr., M.D.

Clara D. Davis, EXECUTIVE EDITOR

Robert O'Leary, ASSISTANT EDITOR

EDITORIAL BOARD

C. Guy Lane, M.D.

Henry R. Viets, M.D.

Robert M. Green, M.D.

Dwight O'Hare, M.D.

Fletcher H. Colby, M.D.

Robert L. Goodale, M.D.

Chester M. Jones, M.D.

Harvey R. Morrison, M.D.

Maxwell Finland, M.D.

James M. Faulkner, M.D.

Carroll B. Larson, M.D.

Francis D. Moore, M.D.

C. Stuart Welch, M.D.

Vernon P. Williams, M.D.

Benjamin Castleman, M.D.

Hugh R. Leavell, M.D.

SUBSCRIPTION TERMS: \$7.00 per year in advance, postage paid for the United States (medical students \$4.00 per year); Canada, \$8.00 per year (Boston funds); \$9.50 per year for all foreign countries belonging to the Postal Union.

MATERIAL should be received not later than noon on Thursday three weeks before date of publication.

THE JOURNAL does not hold itself responsible for statements made by any contributor.

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts. Telephone KE 6-2094.

NEW ENGLAND ADVERTISING REPRESENTATIVE: Edwin B. Tyler, 89 State Street, Boston, Massachusetts. Telephone LA 3-5516.

## MEDICAL EXPERTS ON THE ATOMIC AGE

THE world terror characterizing the dawn of the Atomic Age seems at first glance to be something new and unique in human affairs. In a mood of incredulous despair the thoughtful people of the western world stand appalled at the magnitude of the danger. In quite a different mood, scientific experts are now beginning to preach a hard-headed gospel of preparedness. If our courage falters at the earnestness of their words it may be well for us to draw strength from a backward glance to another time when civilization found itself also in an evil case.

It was in the spring of 1242, eighteen years after the mysterious Mongol horde of Genghis Khan had irrupted into eastern Europe to massacre a Christian

army at the Kalka river, thirteen years after the dreaded horse archers had turned back to lay waste northern China while Europe shuddered through an uneasy lull, and three years after the Asiatic terror had again loomed across the Russian steppes.

These last three years had seen eastern Europe suffer the most fearful disasters—far worse than anything Attila and his Huns had brought. "The Mongols," according to Oman\* "represented not mere conquest but blind and wilful destruction, they left deserts behind them where there had been a civilized and thickly peopled group of states and killed for killing's sake." The armored chivalry of Christendom—the best that Europe could produce—melted before them. Nations in their path for got their local quarrels and united, but too late. Now led by Batu Khan, the horde trampled down Russia, Poland and Silesia. On April 5, 1241, they had annihilated an allied army of Germans, Moravians and Poles at Liegnitz and then had rapidly overrun the Balkan peninsula. Now indeed "a shock of terror went round the whole of Christendom." The last barrier was down, and with the approach of spring Batu Khan stood at the unprotected German border. Doubtless the unheeded warning of the River Kalka and the far-off fate of China were then remembered, and the thirteen wasted years of the "cold war" regretted. Western Europe saw its "atomic age" close at hand, and it was appalled.

But then, as now, there were experts to substitute reasoned action for despair. Observing siegecraft to be the weak side of Mongol tactics, military engineers advised building strong fortresses and castles—the people built them. Advised to unite for common defense, the nations united and braced themselves for inevitable disaster, but disaster never came. Batu Khan, after breaking his teeth on the first strongly fortified and defended cities suddenly faded into the east, and Western Europe, after a year of intense terror, finding itself inexplicably freed from all danger, was able to resume its endless local wars.

On August 6, 1945, a detonation over Hiroshima announced the advent of our own Atomic Age. Again the shock of terror, which is not new, is

\*Oman, C. *A History of the Art of War in the Middle Ages*. Second edition. 2 vol. London: Constable & Co. 1924.

aced by a predominantly resistant one during course of treatment

### REFERENCES

- Sadusk, J. F. Jr and Swift, W. E. Jr. Sensitivity of tubercle bacillus to streptomycin before and during specific therapy. *J Clin Invest* 27 278 282 1948
- Pyle, M. M. Relative numbers of resistant tubercle bacilli in sputa of patients before and during treatment with streptomycin. *Proc Staff Meet. Mayo Clin* 22 465 473 1947

## TERATOGENETIC AND LETHAL EFFECTS OF EMBRYONIC INFECTIONS

THE recent observations on the occurrence of congenital defects in the offspring of mothers who have had rubella during pregnancy have stimulated interest in the whole subject of intrauterine or embryonic infections and of all types of infections and illnesses in the mother during pregnancy. An interesting experimental approach to this subject was made by Hamburger and Habel\* For their studies they used infections with influenza A and mumps virus in the developing hen's eggs

The chick embryo suggested itself as a suitable embryonic material since it is known that the tissues of the extraembryonic membranes of the chick embryo are a favorable medium for the culturing of a number of viruses. Furthermore, the absence of a placenta in the developing chick makes a direct infection of the embryo possible, thus avoiding the complications introduced by an extraembryonic barrier

The experimental evidence produced from these studies showed that the influenza A virus has teratogenic effects on the early chick embryo. It produced a specific syndrome comprising microcephaly and micrencephaly, twist of the axis and impairment of the growth of the amnion. Furthermore, the virus was lethal for early embryos within three days of infection. The mumps virus was likewise lethal for early embryos five days after infection, it did not produce specific abnormalities, but seemed to raise the incidence of malformations of the types that occasionally occur in uninfected chick embryos

The authors believe that their results place influenza A virus in a line with the rubella virus as a tera-

togenic agent. Their observations on influenza A infections in chick embryos also confirmed those on rubella in human beings in that only infections of early embryos resulted in abnormalities. Chick embryos of four days incubation were killed by the influenza virus, but it seemed that in that stage of development most organs have passed the critical period at which their morphogenesis could be directed into atypical channels

Their findings were also of interest in that the patterns of infectiousness were different for the embryo and for the fully developed structures. In the embryo the brain tissues seemed to be particularly susceptible to influenza A virus, whereas in the adult the respiratory mucous membranes were primarily affected. In mumps the infection of the salivary glands is not infrequently combined with meningitis, but no effect on the brain was found macroscopically in embryos. Hamburger and Habel regarded the situation with mumps in chick embryos as the same as that in rubella during pregnancy, in which the embryonic defects seem to have no obvious relation to the manifestations of rubella infections in older phases of life

## MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

### REIMBURSEMENT FOR HOSPITAL CARE

Reimbursement for the hospital care of a patient with venereal disease who cannot afford to pay for hospitalization has been increased from \$4.50 to \$6.50 per diem, in accordance with Chapter 669 of the Acts of 1948, the Massachusetts Department of Public Health announces. This increased rate, which became effective on July 1, 1948, shall constitute reimbursement in full for all services rendered the patient

## MISCELLANY

### NEW YORK UNIVERSITY HEALTH-EDUCATION INSTITUTES

A series of annual health-education institutes is to be held at New York University under the sponsorship of the School of Education. The first of these institutes to be held this summer from August 16 to September 3, 1948, under the Department of Physical Education and Health, School of Education in co-operation with the American Association for the Advancement of Science, the Research Council on Problems of Alcohol and other national agencies, will be devoted to problems in alcohol education

\*Hamburger A. and Habel E. Teratogenic and lethal effects of influenza A and mumps viruses on early chick embryos. *Proc Soc Exptl Biol & Med* 66 60-617 1947

Sadusk and Swift<sup>1</sup> tested the *in vitro* streptomycin sensitivity of tubercle bacilli isolated from sputum or gastric washings at monthly intervals in a group of 16 patients with pulmonary tuberculosis receiving 1.8 gm of streptomycin daily for a period of four months. In these cases 14 of the strains of bacilli isolated before treatment were sensitive to 0.5 microgm of streptomycin per cubic centimeter of the culture medium used, and 2 were sensitive to 1.0 microgm. Loss of sensitivity of the organisms, as evidenced by at least tenfold increase in resistance, began to appear by the end of the first month of therapy at a time when conversion of positive sputum or gastric washings to negative was observed in cultures of other cases. By the end of the third and fourth months of therapy 9 patients still had positive cultures, in 5 the organisms had increased tenfold to fiftyfold in resistance, and the remaining strains increased from one hundredfold to more than two thousandfold in resistance. There was no clear-cut correlation between resistance to streptomycin and the clinical course of these patients under therapy.

Another more detailed and somewhat more illuminating study was reported a few months previously by Pyle,<sup>2</sup> who made direct quantitative studies of the sputum of 8 patients with far advanced tuberculosis who were raising large amounts of sputum that was loaded with tubercle bacilli. These people were treated with streptomycin continuously with a dosage of 0.25 gm every six hours for four or five months. In each case the sediment from a twenty-four-hour specimen of sputum was concentrated to determine the total number of organisms present. The specimen was cultured on plates containing graded concentrations of streptomycin, and the number of organisms growing without the streptomycin and in varying concentrations of the agent was determined. This was repeated at weekly intervals throughout the course of treatment.

In 7 of the 8 cases a few relatively resistant organisms were found in the cultures of the sputum obtained before streptomycin was started. In each of these cases from four to forty-two colonies grew on plates of mediums containing 5 microgm, from one to eight colonies grew in 10 microgm of strep-

tomycin per cubic centimeter, and no colonies grew on mediums containing 25 or more microgm per cubic centimeter before treatment was started. The total bacterial count in the same amount of inoculum in 2 cases was in the vicinity of 100,000 and 350,000.

It was evident from these pretreatment studies that any large population of tubercle bacilli could be expected to contain organisms that are relatively resistant to streptomycin without having previously been exposed to the drug. In all 8 cases, however, the predominant strains of *Mycobacterium tuberculosis* were sensitive to from 0.6 to 1.25 microgm.

In 4 of the 8 cases the originally predominantly sensitive strains of tubercle bacilli were replaced during therapy by strains that were predominantly resistant to 1000 or more micrograms of streptomycin per cubic centimeter. In an additional case the strain became sensitive to 50 microgm at the end of eight weeks, in 2 cases the strains retained their original sensitivity throughout, and in the final case only a minimal degree of resistance occurred at the end of four and a half months of treatment.

In the 4 cases in which resistance developed the weekly cultures showed a more or less gradual increase in the number of resistant organisms and in the degree of resistance to streptomycin. This increase began within one to four weeks after treatment was begun, although the strains were not predominantly resistant until from six to thirteen weeks. For example, at the time when a number of colonies grew in medium containing as much as 100 microgm of streptomycin per cubic centimeter the vast majority of the bacterial population was still quite sensitive to streptomycin and the patients presumably could be expected to continue to receive benefit from chemotherapy.

From a practical point of view these findings suggest that most of the benefits that take place from streptomycin treatment in the majority of cases of tuberculosis will be obtained during the first month of treatment, and thereafter the effects of therapy decline so that probably no benefit is obtained after the end of two or three months. This is true, at least in the cases in which a sensitive flora is

iced by a predominantly resistant one during course of treatment

### REFERENCES

- adusk, J. F., Jr. and Swift, W. E. Jr. Sensitivity of tubercle bacillus to streptomycin before and during specific therapy *J Clin Investigation* 27 278-282 1948
- yle M. M. Relative numbers of resistant tubercle bacilli in sputa of patients before and during treatment with streptomycin *Proc Staff Meet Mayo Clin* 22 465-473 1947

## RATCGENETIC AND LETHAL EFFECTS EMBRYONIC INFECTIONS

THE recent observations on the occurrence of congenital defects in the offspring of mothers who have had rubella during pregnancy have stimulated interest in the whole subject of intrauterine or embryonic infections and of all types of infections and illnesses in the mother during pregnancy. An interesting experimental approach to this subject was made by Hamburger and Habel\* For their studies they used infections with influenza A and mumps virus in the developing hen's eggs

The chick embryo suggested itself as a suitable embryonic material since it is known that the tissues of the extraembryonic membranes of the chick embryo are a favorable medium for the culturing of a number of viruses. Furthermore, the absence of a placenta in the developing chick makes a direct infection of the embryo possible, thus avoiding the complications introduced by an extraembryonic carrier

The experimental evidence produced from these studies showed that the influenza A virus has teratogenic effects on the early chick embryo. It produced a specific syndrome comprising microcephaly and micrencephaly, twist of the axis and impairment of the growth of the amnion. Furthermore, the virus was lethal for early embryos within three days of infection. The mumps virus was likewise lethal for early embryos five days after infection, but did not produce specific abnormalities, but seemed to raise the incidence of malformations of the types that occasionally occur in uninfected chick embryos.

The authors believe that their results place influenza A virus in a line with the rubella virus as a tera-

togenic agent. Their observations on influenza A infections in chick embryos also confirmed those on rubella in human beings in that only infections of early embryos resulted in abnormalities. Chick embryos of four days' incubation were killed by the influenza virus, but it seemed that in that stage of development most organs have passed the critical period at which their morphogenesis could be directed into atypical channels.

Their findings were also of interest in that the patterns of infectiousness were different for the embryo and for the fully developed structures. In the embryo the brain tissues seemed to be particularly susceptible to influenza A virus, whereas in the adult the respiratory mucous membranes were primarily affected. In mumps the infection of the salivary glands is not infrequently combined with meningitis, but no effect on the brain was found macroscopically in embryos. Hamburger and Habel regarded the situation with mumps in chick embryos as the same as that in rubella during pregnancy, in which the embryonic defects seem to have no obvious relation to the manifestations of rubella infections in older phases of life.

## MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

### REIMBURSEMENT FOR HOSPITAL CARE

Reimbursement for the hospital care of a patient with venereal disease who cannot afford to pay for hospitalization has been increased from \$4.50 to \$6.50 per diem, in accordance with Chapter 669 of the Acts of 1948, the Massachusetts Department of Public Health announces. This increased rate, which became effective on July 1, 1948, shall constitute reimbursement in full for all services rendered the patient.

## MISCELLANY

### NEW YORK UNIVERSITY HEALTH-EDUCATION INSTITUTES

A series of annual health-education institutes is to be held at New York University under the sponsorship of the School of Education. The first of these institutes to be held this summer from August 16 to September 3, 1948, under the Department of Physical Education and Health School of Education in co-operation with the American Association for the Advancement of Science, the Research Council on Problems of Alcohol and other national agencies, will be devoted to problems in alcohol education.

\*Hamburger A. and Habel H. Teratogenic and lethal effects of influenza A and mumps viruses on early chick embryos *Proc Soc Exper Biol & Med* 66:602-617 1947

Sadusk and Swift<sup>1</sup> tested the *in vitro* streptomycin sensitivity of tubercle bacilli isolated from sputum or gastric washings at monthly intervals in a group of 16 patients with pulmonary tuberculosis receiving 18 gm of streptomycin daily for a period of four months. In these cases 14 of the strains of bacilli isolated before treatment were sensitive to 0.5 microgm of streptomycin per cubic centimeter of the culture medium used, and 2 were sensitive to 1.0 microgm. Loss of sensitivity of the organisms, as evidenced by at least tenfold increase in resistance, began to appear by the end of the first month of therapy at a time when conversion of positive sputum or gastric washings to negative was observed in cultures of other cases. By the end of the third and fourth months of therapy 9 patients still had positive cultures, in 5 the organisms had increased tenfold to fiftyfold in resistance, and the remaining strains increased from one hundredfold to more than two thousandfold in resistance. There was no clear-cut correlation between resistance to streptomycin and the clinical course of these patients under therapy.

Another more detailed and somewhat more illuminating study was reported a few months previously by Pyle,<sup>2</sup> who made direct quantitative studies of the sputum of 8 patients with far advanced tuberculosis who were raising large amounts of sputum that was loaded with tubercle bacilli. These people were treated with streptomycin continuously with a dosage of 0.25 gm every six hours for four or five months. In each case the sediment from a twenty-four-hour specimen of sputum was concentrated to determine the total number of organisms present. The specimen was cultured on plates containing graded concentrations of streptomycin, and the number of organisms growing without the streptomycin and in varying concentrations of the agent was determined. This was repeated at weekly intervals throughout the course of treatment.

In 7 of the 8 cases a few relatively resistant organisms were found in the cultures of the sputum obtained before streptomycin was started. In each of these cases from four to forty-two colonies grew on plates of mediums containing 5 microgm, from one to eight colonies grew in 10 microgm of strep-

tomycin per cubic centimeter, and no colonies grew on mediums containing 25 or more microgm per cubic centimeter before treatment was started. The total bacterial count in the same amount of inoculum in 2 cases was in the vicinity of 100,000 and 350,000.

It was evident from these pretreatment studies that any large population of tubercle bacilli could be expected to contain organisms that are relatively resistant to streptomycin without having previously been exposed to the drug. In all 8 cases, however, the predominant strains of *Mycobacterium tuberculosis* were sensitive to from 0.6 to 1.25 microgm.

In 4 of the 8 cases the originally predominantly sensitive strains of tubercle bacilli were replaced during therapy by strains that were predominantly resistant to 1000 or more micrograms of streptomycin per cubic centimeter. In an additional case the strain became sensitive to 50 microgm at the end of eight weeks, in 2 cases the strains retained their original sensitivity throughout, and in the final case only a minimal degree of resistance occurred at the end of four and a half months of treatment.

In the 4 cases in which resistance developed, the weekly cultures showed a more or less gradual increase in the number of resistant organisms and in the degree of resistance to streptomycin. This increase began within one to four weeks after treatment was begun, although the strains were not predominantly resistant until from six to thirteen weeks. For example, at the time when a number of colonies grew in medium containing as much as 100 microgm of streptomycin per cubic centimeter the vast majority of the bacterial population was still quite sensitive to streptomycin and the patients presumably could be expected to continue to receive benefit from chemotherapy.

From a practical point of view these findings suggest that most of the benefits that take place from streptomycin treatment in the majority of cases of tuberculosis will be obtained during the first month of treatment, and thereafter the effects of therapy decline so that probably no benefit is obtained after the end of two or three months. This is true, at least in the cases in which a sensitive flora is

replaced by a predominantly resistant one during the course of treatment

### REFERENCES

- 1 Sadusk, J. F., Jr., and Swift, W. E. Jr. Sensitivity of tubercle bacillus to streptomycin before and during specific therapy. *J Clin Investigation* 27:278-282 1948
- 2 Pyle M. M. Relative numbers of resistant tubercle bacilli in spots of patients before and during treatment with streptomycin. *Proc Staff Meet Mayo Clin* 22:465-473 1947

## TERATOGENETIC AND LETHAL EFFECTS OF EMBRYONIC INFECTIONS

THE recent observations on the occurrence of congenital defects in the offspring of mothers who have had rubella during pregnancy have stimulated interest in the whole subject of intrauterine or embryonic infections and of all types of infections and illnesses in the mother during pregnancy. An interesting experimental approach to this subject was made by Hamburger and Habel.\* For their studies they used infections with influenza A and mumps virus in the developing hen's eggs.

The chick embryo suggested itself as a suitable embryonic material since it is known that the tissues of the extraembryonic membranes of the chick embryo are a favorable medium for the culturing of a number of viruses. Furthermore, the absence of a placenta in the developing chick makes a direct infection of the embryo possible, thus avoiding the complications introduced by an extraembryonic barrier.

The experimental evidence produced from these studies showed that the influenza A virus has teratogenic effects on the early chick embryo. It produced a specific syndrome comprising microcephaly and micrencephaly, twist of the axis and impairment of the growth of the amnion. Furthermore, the virus was lethal for early embryos within three days of infection. The mumps virus was likewise lethal for early embryos five days after infection, it did not produce specific abnormalities, but seemed to raise the incidence of malformations of the types that occasionally occur in uninfected chick embryos.

The authors believe that their results place influenza A virus in a line with the rubella virus as a tera-

togenetic agent. Their observations on influenza A infections in chick embryos also confirmed those on rubella in human beings in that only infections of early embryos resulted in abnormalities. Chick embryos of four days' incubation were killed by the influenza virus, but it seemed that in that stage of development most organs have passed the critical period at which their morphogenesis could be directed into atypical channels.

Their findings were also of interest in that the patterns of infectiousness were different for the embryo and for the fully developed structures. In the embryo the brain tissues seemed to be particularly susceptible to influenza A virus, whereas in the adult the respiratory mucous membranes were primarily affected. In mumps the infection of the salivary glands is not infrequently combined with meningitis, but no effect on the brain was found macroscopically in embryos. Hamburger and Habel regarded the situation with mumps in chick embryos as the same as that in rubella during pregnancy, in which the embryonic defects seem to have no obvious relation to the manifestations of rubella infections in older phases of life.

## MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

### REIMBURSEMENT FOR HOSPITAL CARE

Reimbursement for the hospital care of a patient with venereal disease who cannot afford to pay for hospitalization has been increased from \$4.50 to \$6.50 per diem, in accordance with Chapter 669 of the Acts of 1948, the Massachusetts Department of Public Health announces. This increased rate, which became effective on July 1, 1948, shall constitute reimbursement in full for all services rendered the patient.

## MISCELLANY

### NEW YORK UNIVERSITY HEALTH-EDUCATION INSTITUTES

A series of annual health-education institutes is to be held at New York University under the sponsorship of the School of Education. The first of these institutes to be held this summer from August 16 to September 3, 1948, under the Department of Physical Education and Health, School of Education, in co-operation with the American Association for the Advancement of Science, the Research Council on Problems of Alcohol and other national agencies, will be devoted to problems in alcohol education.

\*Hamburger A. and Habel K. Teratogenic and lethal effects of influenza A and mumps viruses on early chick embryos. *Proc Soc Ex Biol & Med* 66:602-617 1947

## CORRESPONDENCE

## BOARD OF REGISTRATION IN MEDICINE

*To the Editor* At the annual meeting of the Board of Registration in Medicine held July 13, the following officers were elected for the ensuing year: George L. Schadt, M.D., Springfield, secretary, and Gordon M. Morrison, M.D., Boston, chairman.

The other members of the Board are as follows: Anthony O. Cardullo, M.D., Boston; Robert C. Cochrane, M.D., Boston; Charles E. Donovan, D.O., Salem; Roger T. Doyle, M.D., Boston; and Bancroft C. Wheeler, M.D., Worcester.

GEORGE L. SCHATZ, M.D. Secretary  
Board of Registration in Medicine

State House  
Boston

## STATISTICALLY SPEAKING

*To the Editor* I should like to call attention to the following facts in reference to the article, "Swimming Pools: Their relation to illness," by Dr. J. Roswell Gallagher, which appeared in the June 24 issue of the *Journal*.

Upon examination of the statistics presented in Table 1 of the article, one finds that the average number of hospital admissions for swimmers (0.354) is wrong. This average was obtained by adding the hospital admissions per swimmer (0.770 plus 0.290 and so forth) and dividing by 7. This is an unweighted average, since it does not take into account the number of swimmers in each year. The correct, weighted average is obtained by dividing the total number of hospital admissions (of swimmers) by the total number of swimmers. I have calculated these values and found that the total number of admissions (269) divided by the total number of swimmers (815) gives the true average of 0.330 hospital admissions per swimmer. Similarly, the figures for nonswimmers were calculated and the total number of admissions (1068) divided by the total number of swimmers (3500). Curiously enough, this weighted average equals the unweighted average of 0.305.

The percentage increase of admissions of swimmers over nonswimmers is now only 7.5 per cent. Upon closer statistical analysis of this figure it turns out that the standard deviation of the difference of the averages is 0.018. Since the difference of the average (0.330 minus 0.305) is only 0.025, the deviation from zero or 0.025-0/0.018 is 1.4 sigma. This means that the figure 7.5 per cent is statistically not significant. Thus the difference between swimmers and nonswimmers could easily occur by chance alone.

Since reference to Dr. Gallagher's article was made in the current issue of *Time* without Dr. Gallagher's cautious reservations regarding the validity of the figure 14 per cent, and since exact evaluation of the data yields only 7.5 per cent with a deviation of 1.4 sigma, making this figure without statistical significance, I believe that these findings should be brought to the attention of the editors of *Time* so that the lay population may not be misled. The readers of the *New England Journal of Medicine* might also be interested in these findings.

HANS W. NEUBERG '50

College of Physicians and Surgeons  
Columbia University

Mr. Neuberg's letter was referred to Dr. Gallagher whose comment is as follows:

*To the Editor* This is a valid comment. Through an oversight the raw data in Table 1 were not reduced to a "per boy" basis, the method that was used in the other similar tables in this paper. The discussion and summary, however, made it clear that the differences in illness were slight.

J. ROSWELL GALLAGHER, M.D.

## NOTICES

## ANNOUNCEMENT

Dr. Thomas B. Quigley announces the removal of his office to 319 Longwood Avenue, Boston.

## WANTED BY THE FBI

Hugo Bob Hubsch, with aliases of Robert C. Glass, R. C. Harris, Hogo Hobsch and Louis S. Miller, is being sought by the Federal Bureau of Investigation. On November 7, 1945, a Federal Grand Jury at Jackson, Mississippi, returned an indictment charging this man with a violation of the National Stolen Property Act. He is charged with another violation of the National Stolen Property Act in a complaint filed with a United States Commissioner at Birmingham, Alabama, on June 7, 1948. This man has defrauded numerous physicians and hospitals in the Eastern and Southeastern sections of the United States during the past few months through the medium of fraudulent checks.

Investigation has revealed that Hubsch has a chronic kidney ailment, and it has recently been ascertained that he has a large kidney stone in the right ureter about 10 cm. below the kidney. This condition has caused local inflammation, which, at varying intervals, results in almost unbearable pain. He has been advised that it will be necessary for him to undergo major surgery for the removal of the stone in the



near future, and until that surgery is performed he will need frequent, if not continuous medical attention. This fugitive moves about rapidly in the section of the United States east of the Mississippi River, and he has recently given numerous physicians and hospitals fraudulent checks in return for treatment, hospitalization, sedatives and narcotic prescriptions.

The following is a composite description of Hugo Bob Hubsch: age, about fifty-two (claims to have been born in Budapest, Hungary, on November 4, 1895); height, about 5 feet, 6 inches; weight, 140 to 170 pounds; hair, dark brown; graying eyes, brown build, medium; race, white; nationality, believed to be naturalized American; occupations, laborer, pharmacist; scars and marks, left arm partially paralyzed; needle scars on both arms, large scars above each hip resulting from kidney operations, shrapnel scars and two bullet scars on abdomen, bridge in upper front teeth characteristic, long nose, stooped posture.

Anyone having information concerning the whereabouts of this fugitive should immediately notify the nearest office of the Federal Bureau of Investigation or the local law-enforcement agency.

## ANNUAL MEETING OF NATIONAL COMMITTEE FOR MENTAL HYGIENE INC

The annual meeting of the National Committee for Mental Hygiene will be held on November 3 and 4 at the Hotel Pennsylvania, New York City. The program will consist of four scientific sessions during the mornings and afternoons, a business luncheon on the first day and the annual luncheon on the second day at which the presentation of the Lasker Award of \$1000, presented annually for outstanding service in the field of mental hygiene, will be made and the ten-day national program for mental health discussed.

Further information may be obtained from the National Committee for Mental Hygiene, 1790 Broadway, New York 19, New York.

(Notices concluded on page xiii)

## NOTICES (Concluded from page 282)

AMERICAN CANCER SOCIETY  
ANNOUNCEMENT OF GRANTS AND FELLOWSHIPS

The Committee on Growth of the National Research Council, acting for the American Cancer Society is entertaining applications for grants and fellowships. Applications for extension of existing grants in cancer research will be received until October 1, and applications for new grants until November 1. Final decision on applications submitted during this period will be made in most cases soon after February 1. Grants approved at this time ordinarily will become effective July 1, 1949.

Fellowship applications may be submitted at any time. Those received prior to November 1 will be acted upon by the Committee on Growth in December. Those received between November 1 and March 1 will be acted upon in April. Fellowships ordinarily will begin July 1, though this date may be varied at the request of the applicant.

During the past year the American Cancer Society, Inc., on recommendation of the Committee on Growth has approved research grants and fellowships totaling over \$2,000,000.

Communications regarding grants and fellowships should be addressed to Executive Secretary, Committee on Growth, National Research Council, 2101 Constitution Avenue, N.W., Washington 25, D.C.

## SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING  
THURSDAY, AUGUST 19

## FRIDAY AUGUST 20

\*10:00 a.m.-12:00 m. Medical Staff Rounds. Peter Bent Brigham Hospital

## TUESDAY AUGUST 24

\*12:15-1:15 p.m. Chiorocotogeological Conference. Peter Bent Brigham Hospital

\*1:30-2:30 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children. Massachusetts General Hospital

## WEDNESDAY AUGUST 25

\*12:00 m.-1:00 p.m. Chioral Conference. (Children's Hospital) Amphitheater. Peter Bent Brigham Hospital

\*Open to the medical profession

AUGUST 11-21. International Congress on Mental Health. Page 44 issue of March 4

AUGUST 23-26. International Society of Hematology. Page 419 issue of March 18

AUGUST 26-28. American Association of Blood Banks. Page 420 issue of March 18

SEPTEMBER 7-11. American Congress of Physical Medicine. Page 582 issue of April 15

SEPTEMBER 7-11. American Occupational Therapy Association. Page xv issue of July 8

SEPTEMBER 9. Some of the Advances in Surgery. Dr. Frank H. Lahey. Penitentiary Association of Physicians. 8:30 p.m. Haverhill

SEPTEMBER 13-15. American Academy of Pediatrics. Olympic Hotel. Seattle. Washington

SEPTEMBER 16-18. Vermont State Medical Society. Annual Meeting. Burlington

SEPTEMBER 20-23. American Hospital Association. Page 310 issue of February 26

SEPTEMBER 22. New England Conference of Industrial Physicians and Surgeons. Page 244 issue of August 5

SEPTEMBER 29. Mississippi Valley Medical Editors' Association. Page 170 issue of January 29

OCTOBER 6-9. American Board of Ophthalmology. Page 170 issue of January 29

OCTOBER 18-22. American College of Surgeons. Page 34 issue of July 1

OCTOBER 27. New England Obstetrical and Gynecological Society. Annual Meeting. Hotel Somerset. Boston

NOVEMBER 1-3. American Clinical and Climatological Association. Page 582 issue of April 15

NOVEMBER 3 and 4. Annual Meeting of National Committee for Mental Hygiene, Inc. Page 282

NOVEMBER 8-12. American Public Health Association. Page 420 issue of March 18

NOVEMBER 10-13. Association of Military Surgeons of the United States. Page 722 issue of May 13

NOVEMBER 20-23. American Academy of Pediatrics. Annual Meeting. Chalfonte Haddon Hall Hotel. Atlantic City. New Jersey

DECEMBER 7-9. Southern Surgical Association. Annual Meeting. Page 543 issue of April 8

DECEMBER 9 and 10. New York State Society of Anesthesiologists. Page 34 issue of July 1

FEBRUARY 4, 1949. American Board of Obstetrics and Gynecology, Inc. Page 244 issue of August 5

MARCH 28-APRIL 1, 1949. American College of Physicians. Page 138 issue of July 22

NOVEMBER 11-17, 1949. Third Inter American Congress of Radiology. Page 158 issue of July 22

## Washingtonian Hospital

41-43 WALTHAM STREET, BOSTON, MASS

Incorporated 1859

Conditioned Reflex, Psychotherapy, Semi-Hospitalization  
For Rehabilitation of Male Alcoholics

Treatment of Acute Intoxication and Alcoholic Psychoses  
Included

Outpatient Clinic and Social-Service Department for  
Male and Female Patients

JOSEPH THIMANN, M.D., Medical Director

Visiting Psychiatric and Neurologic Staff  
Consultants in Medicine, Surgery and the Other Specialties  
Telephone HA 6-1750

## VALLEYHEAD HOSPITAL

CONCORD MASSACHUSETTS

For the treatment of psychoneuroses, alcoholism, mild  
mental disorders and chronic diseases. Pleasant pastoral  
setting near historic Concord. Accepted modern therapies  
used. Complete occupational and recreational facilities  
available including outdoor swimming pool and tennis  
court.

S. GAGNON, M.D.  
Superintendent

J. BUTLER TOMPEKINS, M.D.  
Director of Clinical Psychiatry

J. P. THORNTON, M.D.  
Consultant in Neuro-  
psychiatry

IRVING KAUFMAN, M.D.  
Psychiatrist

Post Office, Box 151, Concord, Mass. Tel. Concord 1600

## TWO-WAY PROTECTION

## Tablets FERROSATE (Kenmore)

(Ferrous Sulfate gr. iv)

are coated twice to provide a doubly  
protected Ferrous Sulfate offering  
these therapeutic advantages

- 1 Inner coating prevents premature oxidation in vivo
- 2 Outer coating increases palatability and aids in preventing tooth discoloration

Write Dept. N  
for professional  
sample

**Kenmore Pharmacy, Inc.**  
500 Commonwealth Ave.  
Boston, Mass. U.S.A.



The Journal presents Dr. Wase  
(It hopes as a pleasant surprise)  
Who roars that it pays  
In a number of ways  
To use what our firms advertise

---

# BRIEF HISTORICAL NOTES ON MEAD'S CEREAL, PABLUM AND PABENA

---

**H**AND in hand with pediatric progress, the introduction of Mead's Cereal in 1930 marked a new concept in the function of cereals in the child's dietary. For 150 years before that, since the days of "pap" and "panada," there had been no noteworthy improvement in the nutritive quality of cereals for infant feeding. Cereals were fed principally for their carbohydrate content.

The formula of Mead's Cereal was designed to supplement the baby's diet in minerals and vitamins, especially iron and thiamine. How well it has succeeded in these functions may be seen from two examples:

(1) As little as one-sixth ounce of Mead's Cereal\* supplies over 50% of the iron and 20% of the thiamine minimum requirements of the 3-months-old infant. (2) One-half ounce of Mead's Cereal furnishes all of the iron and 60% of the thiamine minimum requirements of the 6-months-old baby.

That the medical profession has recognized the importance of this contribution is indicated by the fact that cereal is now routinely included in the infant's diet as early as the third or fourth month instead of at the sixth to

twelfth month as was the custom only a decade or two ago.

In 1933 Mead Johnson & Company went a step further, improving the Mead's Cereal mixture by a special process of cooking, which rendered it easily tolerated by the infant and at the same time did away with the need for prolonged cereal cooking in the home. The result is Pablum, an original product which offers all of the nutritional qualities of Mead's Cereal, plus the convenience of thorough scientific cooking.

During the last twelve years, these products have been used in a great deal of clinical investigation of various aspects of nutrition, which have been reported in the scientific literature.

Many physicians recognize the pioneer efforts on the part of Mead Johnson & Company by specifying Mead's Cereal and PABLUM—and also the new Pablum-like oatmeal cereal known as PABENA.

---

\*Pablum, the precooked form of Mead's Cereal, has practically the same composition: wheatmeal (farina), oatmeal, cornmeal, wheat embryo, beef bone, brewers yeast, alfalfa leaf, sodium chloride, and <sup>40%</sup> reduced iron.

# The New England Journal of Medicine

Copyright 1948 by the Massachusetts Medical Society

Volume 239

AUGUST 19, 1948

Number 8

## THE COUNTRY DOCTOR ON THE MAINE COAST\*

MARY ELLEN CHASE, PH D †

NORTHAMPTON, MASSACHUSETTS

MOST persons in my profession, which is the teaching of English Literature, cherish a devotion to the ancient Greeks of the fifth century B C, that golden age of poetry and drama. I share that devotion. My freshmen at Smith College always read with me a play or two of Euripides or of Sophocles, and I take great pleasure in reading to them the *Apology*, the *Crito* and the *Phaedo* of Plato so that they may know at least something about the life, the noble thoughts, and the death of Socrates.

But there is one Greek writer of this great and golden age of Pericles whom I do not share with my freshmen. He is reserved for my own delight, for those hours when one escapes from students either by going to bed with a book or by driving to the Berkshires in one's car, or by locking oneself within one's office and placing a curt sign upon the door. This ancient writer needs no introduction to this audience. You have been familiar with his name from the day you entered medical school. You are bound by his oath, and you doubtless know far more than I know about those books which he left behind him, some perhaps not written by him but all concerned with ancient medicine and all known by his name. I refer, of course, to Hippocrates, and to his books dealing with acute and chronic diseases, with fractures and head wounds, and swollen joints, with epilepsy, called by him "that sacred disease," with fevers, which seem to have been his chief interest, with childbirth and even with the common cold.

My first interest in Hippocrates began years ago in college when I had two passions: one the study of Greek, the other the dream of being a country doctor and ministering to the sick. The first in my youth was quite safe and sane, the second I kept discreetly to myself, for in those days, at least in rural Maine, the idea of a woman studying medicine was a completely insane notion. Needless to say, the second dream never came true. I must wait for another world for its realization, but the first pleasure—that of the study of Greek—has never

left me, although my early knowledge of that language has become tarnished and wasted with the years. I fortunately, however, possess the *Loeb Classical Library*, which gives me Hippocrates in four volumes, and I often delve into these, since the English translation is happily on each opposite page.

Hippocrates, as you know, came from the Island of Cos in the Aegean Sea. He must, therefore, have been reared among island people, fishermen and sailors, and I have a feeling that rural doctoring must have been interesting to him even after he went to Athens and became the great physician of his age and the teacher of young medical students as well. At all events among his many treatises, case histories and medical aphorisms, he has a good deal to say about the dignity of the profession in general, about the behavior of doctors toward their patients and about certain simple remedies that have always reminded me of the ones I grew up with as a child on the coast of Maine. I have chosen a few of these warnings and prescriptions to use as the framework to what I shall try to say about the country doctor as I knew him on the Maine coast many years ago.

Hippocrates says that doctors should always be clean and well dressed and smell pleasantly. The two country doctors, named, respectively, Dr. Rufus Grindle and Dr. Otis Littlefield, whom I knew for many years in the village of Blue Hill, Maine, and one of whom brought me into the world, were, I am sure, as clean as a Saturday night bath by the kitchen stove could make them. They dressed as well, I am sure, as their slender resources allowed, and they surely smelled strongly and, to me, at least, pleasantly, since they always carried about with them the smell of the barn where they cared for their horses and cows, of the old laprobes, which they sat under all winter on their household calls—in other words, of harnesses, manure, hay and grain bins.

Hippocrates says in several places that nature is the best doctor and that most sick people recover anyway of most ailments simply by the wise provi-

\*Presented in part at the annual meeting of the Massachusetts Medical Society, Boston, May 26, 1948.

†Professor of English Language and Literature, Smith College.

sion of the gods who have made us as we are. We surely believed that doctrine on the Maine Coast in my childhood. We depended on the body to right itself by itself, and the remedies we used to help it along were, for the most part, those of nature herself, gathered from her own fields and pastures. A great-aunt of mine was a faithful herb gatherer, bringing home all summer apronfuls of pennyroyal, wintergreen, wormwood, camomile, thoroughwort and mullein, and, whether we were ill or not, we drank huge quantities of the liquids brewed from these just as a precautionary measure against any diseases that might be lurking about. In addition, our home like most others kept on hand a bottle of Jamaica ginger, one of castor oil, one of Johnson's horse liniment, some spirits of niter, some essence of peppermint, some paregoric, and plenty of homemade cough syrup made by boiling molasses and vinegar together. There were plenty of onions for poultices, and the salt pork barrel in the cellar could always provide a generous slice, which, sprinkled with pepper and bound about a sore throat, was almost certain to cure it.

In fact, when I was a child, to call the doctor in was a momentous family decision. In the first place, it meant that the case was too serious to depend any longer on nature, assisted only by household remedies. In the second place, it meant that you were financially prepared for an unusual expenditure of money. Of course, if you were at all able, you went to the doctor's office at his house, a much confused room in which there was everything under the sun from an old couch, on which you might be asked to stretch yourself, to a checkerboard, upon which, after your professional interview was over, the doctor might ask you to try a game with him. Such an office visit cost you only fifty cents whereas a call at one's home cost a dollar. And in the third place, to call the doctor in meant that you were pleasantly prepared to receive great importance and concern in the eyes of your neighbors. When I was a child, the saying, "She's Had the Doctor," was one to conjure with. A child who had the doctor for anything short of a broken leg or a bad case of measles was raised to indescribable importance among his playmates, and a country woman who had the doctor for anything but the advent of a baby was assumed to be at the door of death.

When the doctor was once summoned, which meant a journey to his house in pre-telephone days or, if you lived far in the country, a message carried by a worried neighbor who was driving to the village, the whole family prepared for him in hushed silence. Clean sheets were put on the bed of the patient, who himself was in a dither of excitement and importance, the house was tidied up, clean towels were placed by the kitchen sink, a kettle of water was kept boiling on the stove, and the best sauce dishes were laid out to receive the doctor's pills and powders. Meanwhile all the unoccupied

members of the family found some excuse to call upon the neighbors to give the ominous word that the doctor had actually been called.

The doctor always took his time in coming. He had, of course, to get his black bag ready, to harness his horse and perhaps to drive several miles over all manner of roads. I remember the untold excitement that prevailed when at last he drove into our yard, hitched his horse to the barn door, or left him standing unhitched, and came through the side door into the kitchen. We all stood about in awed silence. My mother in a clean white apron stood ready to execute his commands and to conduct him to the sickroom. He always rubbed his hands over the kitchen stove if it were winter, then washed them at the kitchen sink, and dried them on the best towel laid out for him. Then he was likely, before he was taken to the patient, to have a word with each of us, to chat pleasantly about the weather or town affairs, and even, in spite of his Hippocratic oath, to gossip a bit about his other patients, who were, of course, known to us.

My mother always accompanied him to the sickroom, carrying a tumbler of fresh water, a towel and a spoon, by which he could look down his patient's throat. The first thing, as I remember it, that the doctor always said, after he had shaken hands cheerfully with the patient and inquired minutely about all his symptoms, was a remark I rarely, if ever, hear today: "Let's see your tongue." After the tell-tale member had been scrutinized, and the pulse and temperature taken, the doctor began thumping and prodding most of one's anatomy, looking for rashes, feeling one's feet.

This done he made a pleasant social visit with his patient, to whom he was careful to say nothing alarming about his condition. He talked of village affairs and coming events, ball games and horse races, or anything else that might be diverting. It was characteristic and, I may say, wise of our country doctors, if the patient happened to be the head of the family, to say nothing of politics. As a matter of fact, although Dr. Rufus Grindle was a staunch Republican, Dr. Otis Littlefield was an equally staunch Democrat in an overwhelmingly Republican community. Most heads of families who employed him deplored his politics, but welcomed his skilful ministrations and admired him in spite of his unfortunate political principles, which he was careful never to bring into a Republican sickroom lest mounting fever should result. Dr. Rufus Grindle was equally careful not to argue on politics with any rare patient who was a Democrat.

When the doctor emerged at last from the sickroom, my mother led him to the parlor, where behind closed doors they conferred together. Both our doctors, and I am sure all others on the Maine coast in those days, had high regard for the common sense, skill and even medical knowledge of country mothers and always treated them with

great respect Neither of our doctors really approved of my mother's homeopathic case, which contained little bottles of pleasant pills marked "Aconite," "Belladonna" and "Nux Vomica," but she used it all the same The doctors did approve however, of various other treatments, in fact, my mother, like many other New England women, was known far and wide for her knowledge of how to treat the sick

For earache she used a large raisin, which she heated on a hatpin over a kerosene lamp and placed in the ear, followed by a bit of cotton This operated, I presume, on the principle of a fireless cooker, and I remember many an earache soothed by it The great Galen, physician to the Roman Emperor, Marcus Aurelius, is said to have prescribed for toothache and swellings of the face tiny frogs boiled until they were steaming hot and like the raisins, capable of retaining heat For chest colds my mother first rubbed us lavishly with hot grease (goose or duck grease, if it were at hand) and then put on a stinging plaster made of mustard and white flour Even Hippocrates, who depended a great deal on sweating, did not regard it more highly than my mother and our country doctors We used to sit for half an hour before bedtime with our feet in a pail of hot mustard water Then we were put to bed surrounded by hot soapstones and in the morning we were damp but cured

Hippocrates has a great deal to say about gruel He believed it should be made of barley meal, either thick for nourishment or thin for sweats Our doctors agreed with him, and so did my mother "Give her some gruel all she wants," our doctors used to say I never hear a doctor use this old word nowadays, nor can I find a recipe for gruel in my modern cookbooks, but it used to be delicious in a yellow bowl and always gave one that pleasant sense of being ill and, therefore, important

When all these prescriptions had been suggested and the doctor had left his medicines, pink pills in one saucer, some neatly folded white powders in another, he prepared to take his departure, although he never seemed to be in the least of a hurry While he was strapping up his black bag, my mother produced his dollar, for most families preferred to pay him on the spot He always stuffed the bill into a pocket as though he were not much concerned with it

My mother and I a few years ago had an amusing time reckoning the doctor's bills of our family of six children over a period of sixteen years, from 1886 to 1902 According to our good memories assisted by some accounts of hers they all amounted to the sum of \$105 This amount had paid for the advent of six babies, six cases of measles, one serious case of rheumatic fever, one very bad cut with an axe six vaccinations for smallpox and a supply of medicine for the sixteen years I came into the world at a cost of \$8 00 — \$5 00 for my birth and

three follow-up visits to my mother at \$1 00 each My brothers and sisters cost the same, which meant an outlay of \$48 to start the Chase family The measles, since we all had them at once, cost \$4 00 for four visits, and the axe injury set us back \$7 00, the vaccinations performed in the doctor's office cost 50 cents each, and the rheumatic fever, which gave us enormous social prestige since the doctor came every day for a month, cost \$31 The rest of the \$105 paid for all the medicine, not of our own making I do not know the cost of a brother and sister born after 1902, but I do not assume that it was much higher I may add that all eight of us flourish today in spite of our humble beginnings and modest cash price!

Hippocrates and the great Galen after him, in ages rife with superstition and quackery, did not like superstitions, and yet they say that sometimes a belief in them proves helpful to the patient either in curing disease or in warding it off Our doctors did not like them either, though they laughingly tolerated them, but yet we flourished on them We wore each year a camphor bag all winter on a string around our necks, in the spring we were fed a tablespoonful of sulfur and molasses according to the mystic formula of three days and skip three, in the summer we were solemnly warned, and as solemnly believed, that the eating of chokecherries followed within three hours by a glass of milk meant certain death, and we just as solemnly believed that a horse chestnut, carried in one's pocket, would ward off rheumatism and any number of other disasters A black cotton stocking, worn for at least a week without washing, was believed to cure a sore throat, if it were bound around one's neck at bedtime with the heel against the Adam's apple I have gone to bed many times with one around mine

Hippocrates says that of all professions that of medicine is the most distinguished since it aims not only to heal the body but also to calm the mind and spirit This truth the country doctors of the Maine coast, and elsewhere of course, understood well They had never heard of psychiatry, but they knew people, their families, their circumstances, and their worries and they seemingly had all the time in the world to "talk things over" with their patients Dr Rufus Grindle often brought books along, which he thought his patients might enjoy, and while his old white horse often got tired of waiting and ambled home without him, he might be playing a game of checkers with someone not long for this world Money never seemed to worry either of our doctors They cheerfully took their pay, if necessary, in potatoes, lobsters, or a day's labor in their gardens or at their woodpiles In terms of affection and understanding as well as of healing, they cared for their patients

Even now along the outhing districts of the long Maine coastline, they are not extinct They go hither and yon in their old Fords, chug out to

lonely islands in motorboats, still know their patients as their friends. One of them told me recently that he was still delivering babies on wide-leaved kitchen tables and that he still sometimes resorted to a feather stuck in the patient's nose to induce helpful sneezings. And Dr. Otis Littlefield, who died six years ago at over eighty, full of years and good works, told me a short time before his death, with pardonable pride, that over a practice of fifty years he had brought nearly 1000 babies into the State of Maine and had never lost one of them—or a mother. Quite a record for a country doctor.

Thus is Maine today not bereft of her country doctors. In a State almost wholly rural, except for four or five considerable cities and towns, the doctors are general practitioners rather than specialists, although we boast of some eminent specialists and surgeons also in our hospitals and our cities. We are proud, too, of our small hospitals as well as of our large ones in Portland, Bangor and Lewiston. In my native village of Blue Hill we have a small but beautifully equipped hospital under the able charge of Dr. Raymond Bliss, who for twenty-five years has had an eminent name as a skillful surgeon as well as a general practitioner. Many of our summer residents on the coast, who have been most generous with financial help in building our hos-

pitals, show their confidence in our Maine village doctors and dentists by coddling along their ailing teeth, their appendixes and their gall bladders until the summer comes and they can have their earthly tabernacles depleted, renovated or refurnished by our country dentists and doctors. Our Maine country doctors still have time for their patients' troubles as well as for their bodily ills, and they are still looked up to and honored by us all.

I should like to say a few words in closing—making myself for the moment as spokesman for our small Coast hospitals and our village doctors—in gratitude for a service given here from 34 Bennet Street under the Bingham Foundation. I am told by Maine doctors that the courses given under this Foundation to doctors and technicians is the greatest single help the doctors in Maine have ever had, services that have inestimably benefited the Maine physicians, laboratory technicians and hospitals, and therefore Maine people at large. For this the doctors and the people of the State of Maine are grateful to the State of Massachusetts—states that, until 1820, were both the State of Massachusetts and, even today, in the character of their people, in their coastlines, and in their country villages and their country doctors, are still one and the same.

## SERUM CONCENTRATIONS OF PENICILLIN FOLLOWING THE ADMINISTRATION OF CRYSTALLINE PROCAINE PENICILLIN G IN OIL\*

WILLIAM L. HEWITT, M.D.,† PHILIP WHITTLESEY, M.D.‡ AND CHESTER S. KEEFER, M.D.§

BOSTON

THE use of peanut oil and beeswax suspensions of amorphous calcium penicillin and of the sodium and potassium salts of crystalline penicillin G for delaying its absorption when injected intramuscularly is well known. The recent preparation of the crystalline procaine salt of penicillin G has afforded the opportunity for studying the absorption of a relatively insoluble salt.<sup>1,2</sup> Procaine penicillin is a true salt derived by the stoichiometric combination of procaine hydrochloride and sodium penicillin G. Calculated on the basis of a potency for crystalline sodium penicillin G at 1667 units per milligram, the theoretical potency of crystalline procaine penicillin G would be 1041 units per milligram. The

solubility of this salt in water has been found to be about 7000 units per cubic centimeter. This is in marked contrast to the solubility of the sodium and potassium salts of penicillin G. Since procaine hydrochloride and sodium penicillin G combine on a molecule-to-molecule basis, each milligram of procaine penicillin G is equivalent to 0.42 mg of procaine base. The amount of salt, therefore, possessing an activity of 300,000 units contains about 120 mg of procaine base.

The activity of procaine penicillin *in vitro* and its pharmacology in laboratory animals has been defined by Hobby et al.<sup>2</sup> The antibacterial spectrum was shown to be qualitatively similar to that of the water-soluble salt, although quantitative differences were observed in that all the bacteria tested were slightly more sensitive to crystalline sodium penicillin G than to crystalline procaine penicillin G. The latter was shown to be a highly effective agent in controlling experimental pneumococcal and streptococcal infections in mice.

\*From the Robert Dawson Evans Memorial, Massachusetts Memorial Hospitals and the Department of Medicine, Boston University School of Medicine.

†Instructor in medicine, Boston University School of Medicine, National Institute of Health fellow in medicine, Robert Dawson Evans Memorial, Massachusetts Memorial Hospitals.

‡Assistant in medicine, Boston University School of Medicine, assistant resident in medicine, Robert Dawson Evans Memorial, Massachusetts Memorial Hospitals.

§Professor of medicine, Boston University School of Medicine, physician-in-chief, Massachusetts Memorial Hospitals.

The purpose of this report is to present pharmacologic data concerning the use in man of crystalline procaine penicillin G suspended in oil

### MATERIALS AND METHODS

#### *Antibiotic Agents*

Crystalline procaine penicillin G suspended in vegetable oil was available in a concentration of 300,000 units per cubic centimeter.\* Sesame oil was employed almost uniformly although a small number of observations were made after the injection of preparations suspended in cottonseed oil. All preparations were quite fluid at room temperature.

#### *Method of Administration*

The following single intramuscular injections were employed: 1 cc of procaine penicillin G in oil — 300,000 units per cubic centimeter, and 2 cc of procaine penicillin G in oil — 300,000 units per cubic centimeter.

A uniform suspension, obtained by vigorous shaking for at least two minutes, was withdrawn from rubber-capped bottles into a dry, sterile 2-cc to 5-cc syringe through a dry, sterile 18-gauge needle, which was replaced by a 20-gauge needle for injection. The mixture was injected in the conventional manner, the needle being inserted with an empty, dry, sterile syringe with which it was possible to ascertain that the needle was not in a blood vessel. Administration of the mixture in disposable cartridges containing 1 cc was performed without difficulty.

#### *Experimental Subjects*

Adult male and female human subjects were used who presented no evidence of impaired cardiac, renal or hepatic function. Post-partum female patients and young adults recovering from acute illnesses were in preponderance. In a number of cases the preparations were employed in the treatment of various acute illnesses as the definitive form of therapy.

#### *Determination of Serum Penicillin Concentrations*

The serum penicillin concentrations were determined by the method described by Rammelkamp,<sup>3</sup> using a beta-hemolytic streptococcus as the test organism.

### RESULTS

#### *Administration of 300,000 Units of Crystalline Procaine Penicillin G in Oil*

Fifty-seven subjects received intramuscularly 1 cc of sesame oil containing 300,000 units of crystalline procaine penicillin G. The serum concentrations of penicillin during the forty-eight hours following administration of this dose are shown in Figure 1. In

19 cases the concentration was determined half an hour after administration and varied from 0.04 to 0.64 units per cubic centimeter of serum. Of the 19 determinations, 16 (84 per cent) were 0.08 units per cubic centimeter or greater, and 9 (47 per cent) were 0.32 units or more. In the subjects in whom serum penicillin concentrations were determined at half an hour and four hours after injection the maximum level occurred uniformly at four hours and varied from 0.08 to 2.5 units per cubic centimeter of serum. The maximum level obtained after a given injection persisted for twelve hours in only 2 cases. Twelve hours after this injection all subjects had demonstrable concentrations of penicillin in the serum, and 34 patients (72 per cent) had levels of at least 0.08 units per cubic centimeter of serum. Assayable amounts of penicillin were present twenty-four hours

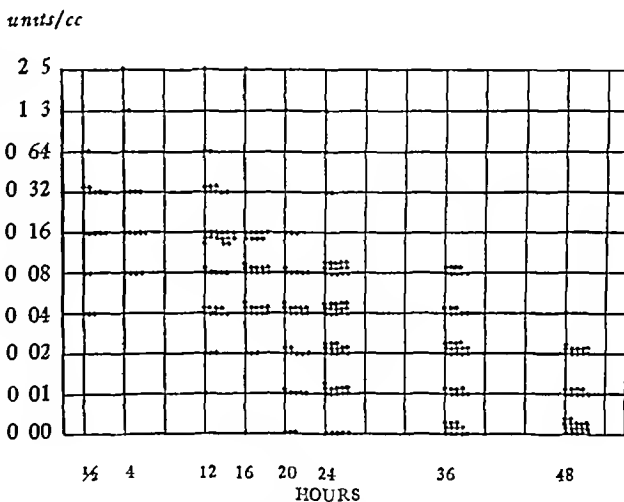


FIGURE 1. Serum Penicillin Concentrations Following the Administration of 300,000 Units of Crystalline Procaine Penicillin G in 1 cc of Sesame Oil

after administration in 58 of 63 patients (92 per cent). Forty-eight hours after administration 21 subjects (55 per cent) had assayable concentrations of serum penicillin.

#### *Administration of 600,000 Units of Crystalline Procaine Penicillin G*

Forty-eight subjects received intramuscularly 2 cc of sesame oil containing 600,000 units of crystalline procaine penicillin G. The serum penicillin concentrations present in these patients during the forty-eight hours following administration are shown in Figure 2. Half an hour after administration the serum contained 0.02 to 1.30 units per cubic centimeter of serum. Sixteen patients (80 per cent) had serum penicillin concentrations of 0.08 units or greater, and 10 patients (50 per cent) concentrations of 0.32 units per cubic centimeter of serum or greater. In all but 2 subjects from whom specimens were so taken the maximum serum con-

\*We are indebted to Eli Lilly and Co., Indianapolis, Indiana; Charles Pfizer and Co., Brooklyn, New York; and Schenley Laboratories Incorporated, New York City, for supplying the crystalline procaine penicillin G in oil employed in these studies.

lonely islands in motorboats, still know their patients as their friends. One of them told me recently that he was still delivering babies on wide-leaved kitchen tables and that he still sometimes resorted to a feather stuck in the patient's nose to induce helpful sneezings. And Dr. Otis Littlefield, who died six years ago at over eighty, full of years and good works, told me a short time before his death, with pardonable pride, that over a practice of fifty years he had brought nearly 1000 babies into the State of Maine and had never lost one of them—or a mother. Quite a record for a country doctor.

Thus is Maine today not bereft of her country doctors. In a State almost wholly rural, except for four or five considerable cities and towns, the doctors are general practitioners rather than specialists, although we boast of some eminent specialists and surgeons also in our hospitals and our cities. We are proud, too, of our small hospitals as well as of our large ones in Portland, Bangor and Lewiston. In my native village of Blue Hill we have a small but beautifully equipped hospital under the able charge of Dr. Raymond Bliss, who for twenty-five years has had an eminent name as a skillful surgeon as well as a general practitioner. Many of our summer residents on the coast, who have been most generous with financial help in building our hos-

pitals, show their confidence in our Maine village doctors and dentists by coddling along their ailing teeth, their appendixes and their gall bladders until the summer comes and they can have their earthly tabernacles depleted, renovated or refurnished by our country dentists and doctors. Our Maine country doctors still have time for their patients' troubles as well as for their bodily ills, and they are still looked up to and honored by us all.

I should like to say a few words in closing—making myself for the moment as spokesman for our small Coast hospitals and our village doctors—in gratitude for a service given here from 34 Bennet Street under the Bingham Foundation. I am told by Maine doctors that the courses given under this Foundation to doctors and technicians is the greatest single help the doctors in Maine have ever had, services that have inestimably benefited the Maine physicians, laboratory technicians and hospitals, and therefore Maine people at large. For this the doctors and the people of the State of Maine are grateful to the State of Massachusetts—states that, until 1820, were both the State of Massachusetts and, even today, in the character of their people, in their coastlines, and in their country villages and their country doctors, are still one and the same.

## SERUM CONCENTRATIONS OF PENICILLIN FOLLOWING THE ADMINISTRATION OF CRYSTALLINE PROCAINE PENICILLIN G IN OIL\*

WILLIAM L. HEWITT, M.D.,† PHILIP WHITTLESEY, M.D.‡ AND CHESTER S. KEEFER, M.D.§

BOSTON

THE use of peanut oil and beeswax suspensions of amorphous calcium penicillin and of the sodium and potassium salts of crystalline penicillin G for delaying its absorption when injected intramuscularly is well known. The recent preparation of the crystalline procaine salt of penicillin G has afforded the opportunity for studying the absorption of a relatively insoluble salt.<sup>1,2</sup> Procaine penicillin is a true salt derived by the stoichiometric combination of procaine hydrochloride and sodium penicillin G. Calculated on the basis of a potency for crystalline sodium penicillin G at 1667 units per milligram, the theoretical potency of crystalline procaine penicillin G would be 1041 units per milligram. The

solubility of this salt in water has been found to be about 7000 units per cubic centimeter. This is in marked contrast to the solubility of the sodium and potassium salts of penicillin G. Since procaine hydrochloride and sodium penicillin G combine on a molecule-to-molecule basis, each milligram of procaine penicillin G is equivalent to 0.42 mg of procaine base. The amount of salt, therefore, possessing an activity of 300,000 units contains about 120 mg of procaine base.

The activity of procaine penicillin *in vitro* and its pharmacology in laboratory animals has been defined by Hobby et al.<sup>2</sup> The antibacterial spectrum was shown to be qualitatively similar to that of the water-soluble salt, although quantitative differences were observed in that all the bacteria tested were slightly more sensitive to crystalline sodium penicillin G than to crystalline procaine penicillin G. The latter was shown to be a highly effective agent in controlling experimental pneumococcal and streptococcal infections in mice.

\*From the Robert Dawson Evans Memorial Massachusetts Memorial Hospitals and the Department of Medicine, Boston University School of Medicine.

†Instructor in medicine, Boston University School of Medicine, National Institute of Health fellow in medicine, Robert Dawson Evans Memorial Massachusetts Memorial Hospitals.

‡Assistant in medicine, Boston University School of Medicine, assistant resident in medicine, Robert Dawson Evans Memorial, Massachusetts Memorial Hospitals.

§Professor of medicine, Boston University School of Medicine, physician-in-chief, Massachusetts Memorial Hospitals.

The purpose of this report is to present pharmacologic data concerning the use in man of crystalline procaine penicillin G suspended in oil

MATERIALS AND METHODS

Antibiotic Agents

Crystalline procaine penicillin G suspended in vegetable oil was available in a concentration of 300,000 units per cubic centimeter \* Sesame oil was employed almost uniformly although a small number of observations were made after the injection of preparations suspended in cottonseed oil All preparations were quite fluid at room temperature

Method of Administration

The following single intramuscular injections were employed 1 cc of procaine penicillin G in oil — 300,000 units per cubic centimeter, and 2 cc of procaine penicillin G in oil — 300,000 units per cubic centimeter

A uniform suspension, obtained by vigorous shaking for at least two minutes, was withdrawn from rubber-capped bottles into a dry, sterile 2-cc to 5-cc syringe through a dry, sterile 18-gauge needle, which was replaced by a 20-gauge needle for injection The mixture was injected in the conventional manner, the needle being inserted with an empty, dry, sterile syringe with which it was possible to ascertain that the needle was not in a blood vessel Administration of the mixture in disposable cartridges containing 1 cc was performed without difficulty

Experimental Subjects

Adult male and female human subjects were used who presented no evidence of impaired cardiac, renal or hepatic function Post-partum female patients and young adults recovering from acute illnesses were in preponderance In a number of cases the preparations were employed in the treatment of various acute illnesses as the definitive form of therapy

Determination of Serum Penicillin Concentrations

The serum penicillin concentrations were determined by the method described by Rammelkamp,<sup>3</sup> using a beta-hemolytic streptococcus as the test organism

RESULTS

Administration of 300,000 Units of Crystalline Procaine Penicillin G in Oil

Fifty-seven subjects received intramuscularly 1 cc of sesame oil containing 300,000 units of crystalline procaine penicillin G The serum concentrations of penicillin during the forty-eight hours following administration of this dose are shown in Figure 1 In

19 cases the concentration was determined half an hour after administration and varied from 0.04 to 0.64 units per cubic centimeter of serum Of the 19 determinations, 16 (84 per cent) were 0.08 units per cubic centimeter or greater, and 9 (47 per cent) were 0.32 units or more In the subjects in whom serum penicillin concentrations were determined at half an hour and four hours after injection the maximum level occurred uniformly at four hours and varied from 0.08 to 2.5 units per cubic centimeter of serum The maximum level obtained after a given injection persisted for twelve hours in only 2 cases Twelve hours after this injection all subjects had demonstrable concentrations of penicillin in the serum, and 34 patients (72 per cent) had levels of at least 0.08 units per cubic centimeter of serum Assayable amounts of penicillin were present twenty-four hours

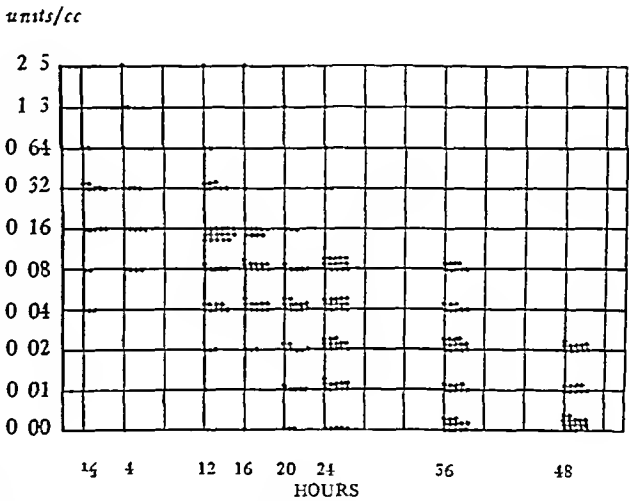


FIGURE 1 Serum Penicillin Concentrations Following the Administration of 300,000 Units of Crystalline Procaine Penicillin G in 1 cc of Sesame Oil

after administration in 58 of 63 patients (92 per cent) Forty-eight hours after administration 21 subjects (55 per cent) had assayable concentrations of serum penicillin

Administration of 600,000 Units of Crystalline Procaine Penicillin G

Forty-eight subjects received intramuscularly 2 cc of sesame oil containing 600,000 units of crystalline procaine penicillin G The serum penicillin concentrations present in these patients during the forty-eight hours following administration are shown in Figure 2 Half an hour after administration the serum contained 0.02 to 1.30 units per cubic centimeter of serum Sixteen patients (80 per cent) had serum penicillin concentrations of 0.08 units or greater, and 10 patients (50 per cent) concentrations of 0.32 units per cubic centimeter of serum or greater In all but 2 subjects from whom specimens were so taken the maximum serum con-

\*We are indebted to Eli Lilly and Co., Indianapolis, Indiana; Charles Pfizer and Co., Brooklyn, New York; and Schenley Laboratories Incorporated, New York City, for supplying the crystalline procaine penicillin G in oil employed in these studies.

centration occurred four hours after administration. The penicillin concentration in 1 patient was less than and in another was the same half an hour after injection as that at the four-hour interval. The maximum serum concentration obtained with this dosage varied from 0.08 to 2.5 units per cubic centimeter of serum. The maximum level that occurred in a given subject during the first four hours following injection was present twelve hours after the administration in 12 of 31 cases. The serum concentrations of penicillin twelve hours after injection of this dose varied from 0.04 to 1.30 units per cubic centimeter of serum. Twenty-four hours after injection a concentration of 0.02 units or more was maintained in all cases. Forty-one patients (85 per cent) showed 0.08 units, and 15 patients (31 per cent) maintained 0.32 units per cubic centimeter. Forty-eight hours

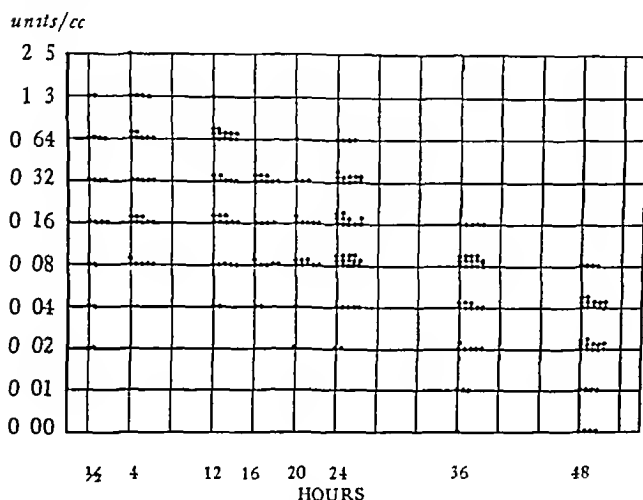


FIGURE 2 Serum Penicillin Concentrations Following the Administration of 600,000 Units of Crystalline Procaine Penicillin G in 2 cc of Sesame Oil

after administration 32 patients (89 per cent) had assayable serum penicillin concentrations, 28 patients (78 per cent) 0.02 units per cubic centimeter or more, and 4 patients (11 per cent) 0.08 units per centimeter or greater.

#### Local Reactions

Administration of this material was easily performed in the conventional manner, provided the suspension was thoroughly and vigorously shaken prior to withdrawal from the bottle. Delay in carrying out the injection after withdrawal of the preparation into a syringe resulted in early separation of the suspension and clogging of the injecting needle. There was an almost complete absence of pain at the site of injection, and subjects who had the opportunity to compare the local reaction with peanut oil and beeswax mixtures reacted uniformly in favor of the former. In only 1 of the group of 111 subjects who received well over three hundred injections was a persistent nodule palpable at the site of administra-

tion, probably owing to administration of the mixture subcutaneously instead of intramuscularly. No allergic reactions were noted.

#### Discussion

The serum penicillin concentrations following the injection of 300,000 and 600,000 units of procaine

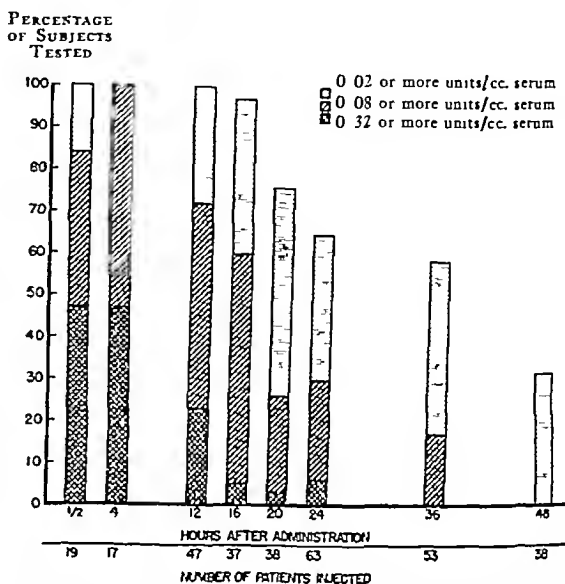


FIGURE 3 Incidence of Given Serum Penicillin Concentrations Following the Administration of 300,000 Units of Crystalline Procaine Penicillin G in 1 cc of Sesame Oil

penicillin are summarized in Figures 3 and 4. A comparison of the concentrations obtained in this

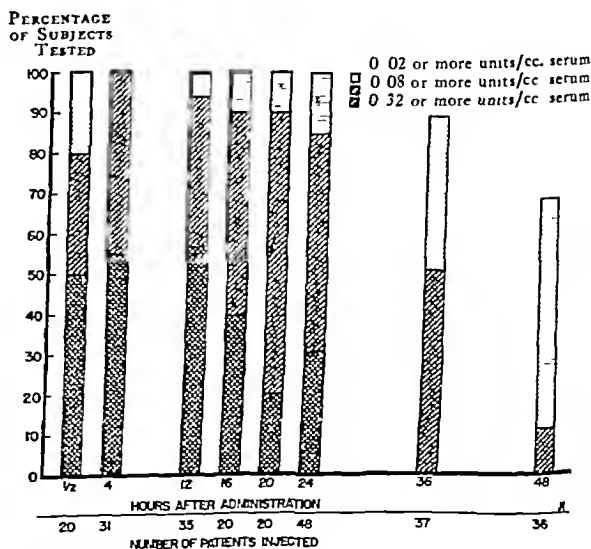


FIGURE 4 Incidence of Given Serum Penicillin Concentrations Following the Administration of 600,000 Units of Crystalline Procaine Penicillin G in 2 cc of Sesame Oil

laboratory with procaine penicillin G in sesame oil and crystalline sodium penicillin G in peanut oil and

beeswax is made in Table 1.<sup>4</sup> In contrast to the peak levels obtained after the injection of peanut oil and beeswax mixtures, there is a distinct tendency for the concentrations of penicillin to rise more slowly after the administration of procaine penicillin G. The four-hour levels were higher than those obtained half an hour after administration. The maximum serum penicillin concentrations obtained after the administration of procaine penicillin G are distinctly lower than those that follow the administration of the same dose of peanut oil and beeswax mixtures of crystalline sodium or potassium penicillin G.

tion during the twenty-four hours following administration,<sup>4</sup> the result of increased dosage of crystalline procaine penicillin G is largely one of prolongation of an effective concentration rather than an increase in the magnitude of the level during the four hours following administration. The superiority of procaine penicillin G in oil over crystalline sodium penicillin G in peanut oil and beeswax for maintaining an effective serum penicillin concentration for a period of twenty-four hours after administration is evident from the data presented in Table 1. The effective concentration varies with the infecting bac-

TABLE 1. *A Comparison of the Serum Penicillin Concentrations Following the Administration of Crystalline Sodium Penicillin G in Peanut Oil and Beeswax (POB) and Crystalline Procaine Penicillin G in Oil (PP)*

Dose	No of Patients		Interval after Administration	Serum Penicillin Concentrations			
	PP	POB		PP 0.08 unit/cc or over	POB	PP demonstrable	POB
600,000 units	35	30	12	94	90	100	100
	48	31	24	85	52	100	84
	57		36	51		97	
	36		48	11		89	
	47	30	12	72	70	100	93
300,000 units	63	20	24	10	10	92	70
	53		36	17		74	
	38		48	0		55	

Thus, the maximum concentrations obtained after the administration of 1 cc of peanut oil and beeswax containing 300,000 units of crystalline sodium penicillin G varied from 0.08 to 5.0 units per cubic centimeter of serum as compared with concentrations varying from 0.04 to 0.64 unit after the administration of a similar dosage of crystalline procaine penicillin G in sesame oil. Even more striking is the range of maximum penicillin concentration following the administration of 600,000 units. With the peanut oil and beeswax mixtures the concentration varied from 0.63 to 20 units per cubic centimeter of serum, whereas a concentration of 0.08 to 2.5 units followed the injection of the same amount of procaine penicillin G. There is a tendency, particularly with a dosage of 600,000 units, for the serum penicillin concentrations to be more uniform during the first twenty-four hours following injection of procaine penicillin G than sodium penicillin G in peanut oil and beeswax. It appears reasonable to assume that the difference in solubility of these two salts of penicillin is at least a major factor in producing this characteristic difference. The influence of solubility as a limiting factor may be further manifest in the comparison of the serum penicillin concentrations obtained with a dosage of 300,000 and 600,000 units. Whereas a dosage of 600,000 units of crystalline sodium penicillin G in peanut oil and beeswax produces a considerable increase in the magnitude of the serum penicillin concentrations during the first four hours after injection, as well as an increased incidence of an effective serum penicillin concentra-

tion and character of the infectious process present. Thus, while the penicillin concentrations required for the treatment of most of the infections caused by the gonococcus, alpha-hemolytic and beta-hemolytic streptococcus and the pneumococcus fall within the ranges obtained in this study, higher penicillin concentrations than can be obtained with this preparation may be necessary for the treatment of overwhelming infections, bacterial endocarditis, chronic osteomyelitis and infections due to organisms of high penicillin resistance, such as certain staphylococci. It is conceivable that under some circumstances the higher penicillin concentrations that result intermittently from the administration of crystalline sodium penicillin G in peanut oil and beeswax mixture might make this preparation more effective than procaine penicillin, with which an effective level was not obtained even intermittently.

Another advantage of procaine penicillin G in oil for prolonging therapeutic blood levels of penicillin over peanut oil and beeswax preparations is the elimination of beeswax, which has been cited as a cause of a number of unfavorable local reactions. The local reactions following the administration of procaine penicillin were significantly less than those that followed the use of peanut oil and beeswax.

Allergic reactions after the administration of penicillin in peanut oil and beeswax are higher than those following the use of aqueous penicillin. The incidence of such reactions after administration of procaine penicillin in oil remains to be determined. The activity of procaine penicillin G presumably depends

upon the dissociation of the molecule into its respective members, and patients who are allergic to penicillin or to procaine will probably be sensitive to this preparation. The toxicity of procaine itself is of interest in this regard inasmuch as some persons are hypersensitive to this agent. Furthermore, the toxicity of procaine penicillin G is determined by the amount of procaine base present in the compound.<sup>2</sup> This conforms to previous studies with soluble salts of penicillin in which it was shown that the toxicity of various salts was determined by the cation present.<sup>5</sup> Three hundred thousand units of procaine penicillin G contains approximately 120 mg of procaine base. Toxicity to procaine is dependent upon its rate of absorption and its concentration.<sup>6</sup> Inasmuch as the absorption of procaine penicillin into the circulation is so slow, it is unlikely that appreciable amounts of procaine would be present after the administration of therapeutic doses of procaine penicillin G. An intradermal sensitivity test with 1 per cent procaine solution should, however, be performed when suspicion of procaine allergy exists.

#### SUMMARY

Administration of 300,000 units of crystalline procaine penicillin G in sesame oil produced demonstrable serum penicillin concentrations at twelve hours after administration in all and at twenty-four hours after injection in 92 per cent of subjects studied.

Administration of 600,000 units of this material produced demonstrable serum penicillin concentrations twenty-four hours after injection in all and at

forty-eight hours after injection in 89 per cent of subjects studied.

The maximum serum penicillin concentrations obtained with procaine penicillin G in oil were distinctly lower than those following a similar dose of sodium penicillin G in peanut oil and beeswax. The concentrations following administration of the former preparation, particularly with a dose of 600,000 units, showed considerably more uniformity throughout the twenty-four hours following injection.

A comparison of the serum penicillin concentrations obtained after a dose of 300,000 and 600,000 units of procaine penicillin G revealed the most characteristic difference to be a prolongation of a given effective penicillin level rather than an increase in the magnitude of the penicillin concentration during the early period after administration.

Crystalline procaine penicillin G in oil was superior to crystalline sodium penicillin G in peanut oil and beeswax for maintaining an effective serum penicillin concentration for twenty-four hours after injection.

We are indebted to Miss Doris McCarthy for technical assistance.

#### REFERENCES

1. Salivar C J, Hedger F H and Brown E V. Crystalline procaine penicillins. *J Am Chem Soc* 70 1287, 1948.
2. Hobby G L, Brown E, and Patelski R A. Biological activity of crystalline procaine penicillin in vitro and in vivo. *Proc Soc Exper Biol & Med* 67 6-14 1948.
3. Rammelkamp, C H. Method for determining concentration of penicillin in body fluids and exudates. *Proc Soc Exper Biol & Med* 51 95 1942.
4. Hewitt W L. Serum concentrations of penicillin following administration of crystalline penicillin G in peanut oil and beeswax. *Am Practitioner* 2 247-252 1947.
5. Welch H, Chandler V L, Davis R P., and Price C W. Study of seven different salts of penicillin. *J Infect Dis* 76 52-54 1945.
6. Graubard, D J, Robertazzi R W, and Peterson, M. C. Intravenous procaine: preliminary report. *New York State J Med* 47 2187-2192 1947.

## PAROXYSMAL HYPERTENSION IN SPINAL-CORD INJURIES\*

CHARLES E THOMPSON, M D,<sup>†</sup> AND CAPTAIN A CALHOUN WITHAM, M C, A U S<sup>‡</sup>

MEMPHIS, TENNESSEE

THE purpose of this paper is to report on the clinical significance of a little known, but constantly occurring, phenomenon in high spinal-cord lesions. Mass sympathetic discharge, occurring either in conjunction with "mass reflex" or alone in response to various stimuli, has been noted for many years and was first clinically recorded in the classic papers of Head and Riddoch.<sup>1</sup> Since sweating is the most obvious manifestation of this activity, the mass sympathetic discharge has usually been incompletely designated and has received much attention as "spinal reflex sweating."<sup>2</sup> That the vasomotor component and in particular the severe hypertension may well be the most important part of the syndrome from the standpoint of managing the patient is pointed out below.

The trigger mechanisms that set off the general sympathetic response may be summarized briefly in the words of Head,<sup>1</sup> the first to describe it: "There is scarcely a stimulus, cutaneous, proprioceptive or visceral, that may not be followed by an outburst of sweating appropriate to the lesion in each case." Distention of the bladder, and sometimes of the rectum, has been universally the most common cause in the experience of all.<sup>1-3</sup> The syndrome is manifested by excessive sweating, flushing of the face, congestion of the nasal passages, pilomotor erection, sometimes shivering and a feeling of dullness in the head, which may progress to a severe, throbbing, bitemporal, occipital or frontal headache. Blurring of vision is not uncommon. Objectively the pulse may become slow, irregular and more forceful. The blood pressure climbs almost immediately to precipitous heights, and, if the stimulus is continued, convulsions and loss of consciousness may occur. These changes are quickly reversible when the offending stimulus is removed. Details of the sweating have been adequately described elsewhere.<sup>2</sup> This discussion is confined to the description of accompanying hypertension, which we believe to have been neglected as a field of study. Recent American reviews of the treatment of various stages of paraplegia, or observations of the related sympathetic phenomena, do not mention its occurrence.<sup>3-5</sup> Physicians who have spent much time with paraplegic patients have noted, however, that fluctuations of blood pressure are not uncommon although they

have observed no particular pattern to these variations. It appears from our studies that these wide variations in blood pressure are an integral part of a sympathetic response to various stimuli, principally vesicular and rectal in origin. This response has been described as being a component of the mass spinal reflex,<sup>2</sup> a release phenomenon induced by any afferent stimulus acting on the distal portion of the cord, the efferent path being through the thoracolumbar outflow of the autonomic system.

While our work was under way, Whitteridge and Guttmann,<sup>9</sup> who had previously made independent observations along the same lines, published a summary of their studies indicating a profound redistribution of blood flow. This might have been suspected from clinical observations. These authors noted greater blood-pressure changes when the cord lesion was above the level of the sixth dorsal segment. This fact they attributed to an inability of the organism to compensate by selective redistribution of blood flow when the large splanchnic bed was cut off from control of the vasomotor center. Changes in blood flow of the extremities in response to various nociceptive stimuli occur in normally innervated people.<sup>10</sup> Distention of the viscera in normal people also causes vasoconstriction in the fingers and toes.<sup>11</sup> A brief summary of the work of Whitteridge and Guttmann<sup>9</sup> follows.

In lesions above the sixth dorsal segment they noted a slight rise in rectal temperature and a greater rise in skin temperature of the neck and ears upon bladder distention. As measured plethysmographically, there was a decrease in volume of fingers and toes. There was an initial sharp decrease in pulse rate followed by a normal rate as bladder pressure was maintained. Pulse volume and temperature increased in the ears, meanwhile, temperature of the lower extremities fell.

In lesions below the sixth dorsal segment they found the same fall in temperature of the lower extremities combined with a profound fall in pulse volume of toes, but the blood flow increased in fingers and the blood pressure rose no more than 30 mm in contrast to increases of 100 mm or more in the higher lesions. They concluded that in the lower lesions there were still splanchnic areas under vasomotor center control available for compensatory vasodilatation. Distention of the rectum caused a similar syndrome, but the effects were more transient.

\*From the Paraplegia Service, Veterans Administration Medical Teaching Group, Kennedy Hospital.

Published with permission of the chief medical director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or the conclusions drawn by the authors.

<sup>†</sup>Chief, Paraplegia Service, Veterans Administration Medical Teaching Group, Kennedy Hospital.

<sup>‡</sup>Ward physician, Veterans Administration Medical Teaching Group, Kennedy Hospital.

We have confirmed these observations with the exception of the plethysmographic recordings, which we were unable to do at this hospital. Typical experimental studies at various levels of the spinal-cord injury are discussed below.

### METHOD

The patients were placed in recumbent position, and a tidal drainage apparatus with a cystometric manometer attached to a No. 16 Foley catheter

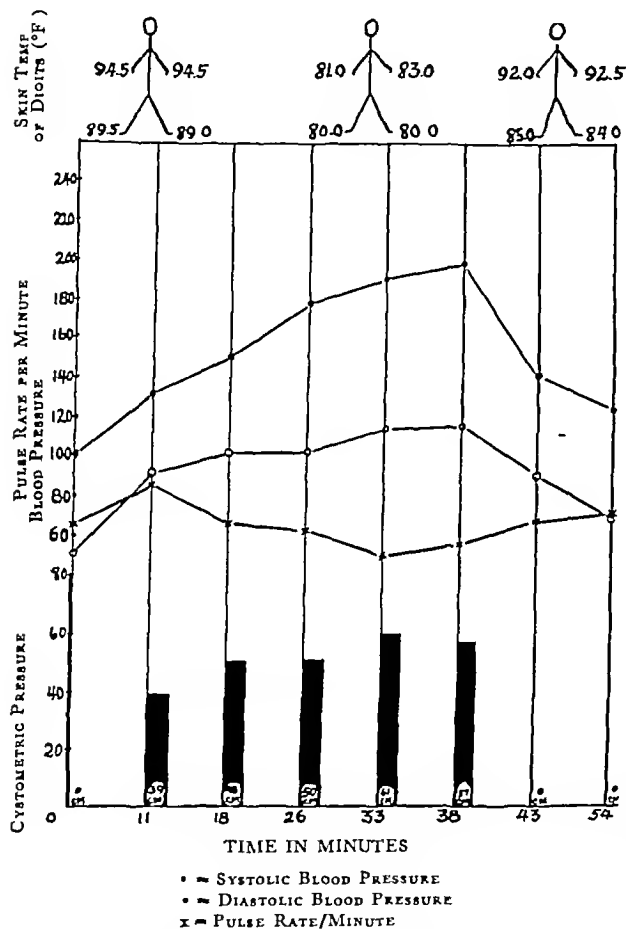


FIGURE 1 Pertinent Data in Case 1

previously inserted into the bladder. Skin temperatures were measured directly by a thermocouple (U.M.A. corporation). The subject was placed in a thermostatically controlled room at a constant temperature of 70 to 72°C for an hour before the procedure, to permit the skin temperature to become stable. Readings were made from the palmar surfaces of the distal phalanges of several digits of each extremity. Since no essential difference in direction of change occurred among the several digits of any one extremity, the first digit was arbitrarily chosen to be used in the illustrations. Blood pressures were measured indirectly by a cuff and mercury manometer. On certain patients, electrocardiographic and oscillometric records were taken. Observations were made of the blood pressure, pulse

rate, gross sweating, pilomotor changes and skin temperatures as the bladder was slowly filled with an irrigating solution ("G solution").<sup>12</sup> Subjective sensations, such as headache, palpitation, rigor and flushing were noted.

The following case reports are illustrative of the type of blood-pressure response that may be experimentally produced by distention of the bladder at the various levels of spinal-cord injury.

**CASE 1** E. J. C., a 22-year-old man, with traumatic transverse myelitis of 40 months' duration, had a physiologically complete lesion at the level of the fifth cervical segment. He gave a history of spinal sweating, headache and sometimes convulsions of short duration associated principally with urinary-tract infections while he was at another hospital. The blood pressure was not recorded at that time, and no cause for the convulsions was found. The attacks subsided spontaneously when the infections had ended. The blood pressure, cystometric pressure, pulse rate and skin temperatures of the digits are shown in Figure 1. For the last few months the patient has been symptom free.

During this procedure, although no convulsion occurred, the patient stated that the headache and chilliness that appeared with the rise in blood pressure were similar to his difficulties some months previously, which had sometimes caused loss of consciousness and generalized convulsions of a few minutes' duration.

**CASE 2** H. R., a 22-year-old man, with traumatic myelitis incurred in June, 1945, had a lesion neurologically complete at the level of the seventh dorsal segment and had exhibited

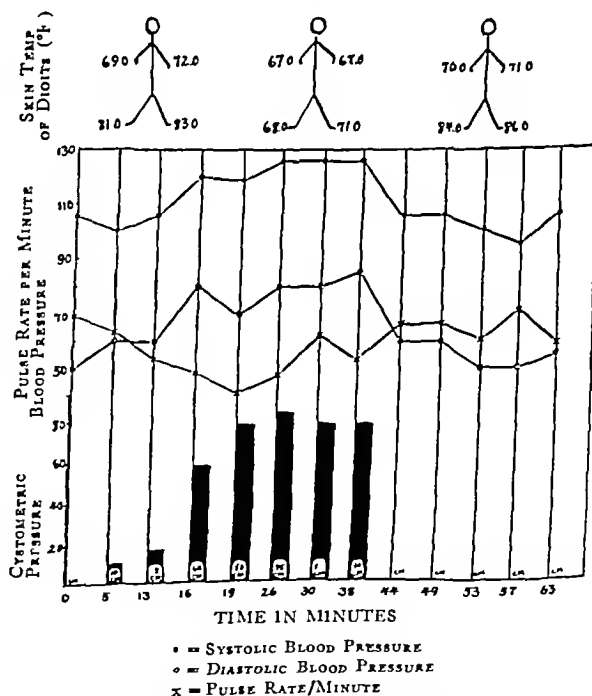


FIGURE 2 Pertinent Data in Case 2

reflex sweating since a few weeks after injury. He had had no cerebral symptoms. Laminectomy done in June, 1947, demonstrated a complete absence of the cord at the level of the seventh dorsal segment. The blood pressure, cystometric pressure, pulse rate and skin temperatures of the digits are shown in Figure 2.

Bladder sensation was completely absent in this patient. The appearance of sweating and pilomotor erection was prompt and severe on both legs but predominantly right-sided.

on the trunk as high as the level of anesthesia. Dermographia was striking above and below the sensory level, whereas the bladder pressure was high and disappeared promptly when pressure was released.

**CASE 3** G. L., a 31-year-old man, with incomplete transverse myelitis at the level of the second lumbar segment of 19 months' duration, had developed an automatic bladder but had never noticed the sympathetic discharges associated with distended bladder in patients with higher lesions. Thermoregulatory sweating was normal above and below the

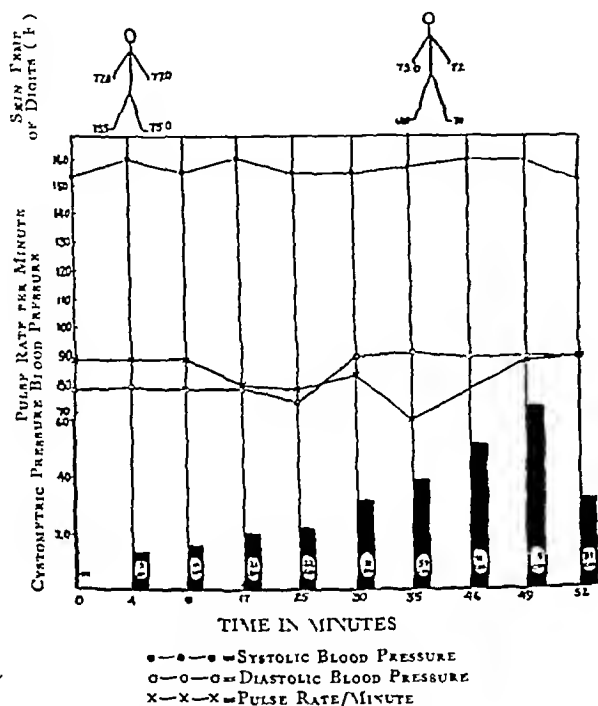


FIGURE 3 Pertinent Data in Case 3

lesion. The blood pressure, cystometric pressure, pulse rate and skin temperatures of the digits are shown in Figure 3.

In this patient, the central pathways of the autonomic system were apparently undamaged. No spinal sweating, pilomotor phenomena or hypertension occurred although from the skin-temperature changes, it seemed that vasoconstriction was taking place in the extremities although the systemic arterial pressure remained essentially the same. This case illustrates the effect of bladder distention in a patient with an intact autonomic nervous system.

In the following cases the vasomotor disturbances were of clinical importance in the care of the patient.

**CASE 4** E. D., a 22-year-old man, with a physiologically incomplete lesion below the level of the fifth cervical segment, since July, 1946, had the following interesting history. A few weeks after traumatic spinal-cord injury, not involving the head, the patient began to have periods of dimness of vision, sometimes severe headache with loss of consciousness and clonic movements of the left upper extremity and facial musculature. In retrospect the patient associated these "attacks" with change of catheter, sudden changes of position and enemas. Complete initial study failed to assign an etiology to this syndrome although electroencephalographic findings suggested "a focus of activity in the right fronto-temporal region without seizure discharges." Consultation with the ophthalmologist revealed normal funduscopic findings. "Seizures" were interpreted as epileptiform or its equivalent. There was no other neurologic evidence of intracranial disease. In April, 1947, a suprapubic cystostomy was performed because of postoperative hemorrhage following a litholapaxy. There was a complete and dramatic cessation

of these attacks. Repeat electroencephalogram showed no essential change from the previous record.

In retrospect, the possibility that these symptoms were produced by bladder spasm was considered after the patient had been symptom free for 8 months with the suprapubic tube in situ. Consequently we attempted to reproduce these symptoms experimentally by the methods outlined above. The blood pressure promptly rose to 220/115 when a pressure of 90 cm of water was present in the bladder. The usual autonomic phenomena were noted, and in addition, the pupils became bilaterally dilated, more so on the left. The patient complained of dimness of vision and headache and the facial muscles began to twitch. As the patient began to lose consciousness and became cyanotic, the bladder pressure was released. The patient's symptoms promptly disappeared in 3 minutes, and the blood pressure fell to 110/60 — his basal reading.

**CASE 5** T. B., a 25-year-old man with an incomplete lesion at the level of the fifth cervical segment since September 11, 1946, experienced sudden throbbing, bitemporal headache with flushing of the face, pilomotor erection, excessive sweating and symptoms of mental confusion and loss of consciousness each time an enema was administered. Other stimuli such as bladder distention and sudden changes in position from recumbent to upright and turning on the face, invoked the same chain of events innumerable times during the day and night. The symptoms had become more frequent and severe during the last few months. Blood pressures recorded during these attacks consistently ranged as high as 260/140. (This patient had undergone a progressive deterioration of mental outlook because of despair over this severe, additional incapacity.) Tetraethyl ammonium chloride, administered before these procedures, consistently prevented the attacks. This effect was maintained for less than 1 hour, however, and on account of the severity, frequency and persistence of the symptoms, a surgical attack on the sympathetic ganglions is being considered.

**CASE 6** W. H., a 22-year-old man with incomplete paraplegia below the level of the third dorsal segment, was first

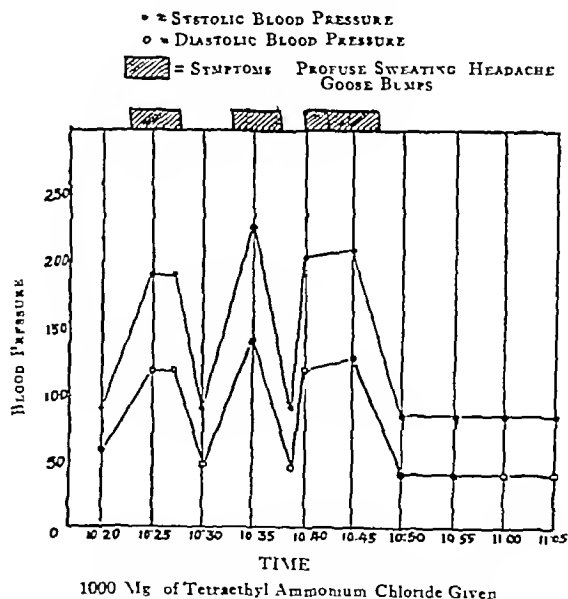


FIGURE 4 Effect of Tetraethyl Ammonium Chloride in Case 6

afflicted with excruciating, throbbing, bitemporal headache with the attending evidence of sympathetic discharge while suprapubic cystostomy was being performed. For several days postoperatively the same syndrome occurred every 15 or 20 minutes during the day — somewhat less frequently at night. This was always associated with severe bladder spasm that blocked the urinary outflow at the catheter but subsided spontaneously when flow was re-established. The blood pressure rose as high as 220/140 from a basal pressure of 90/70. Tetraethyl ammonium chloride intramuscularly in a dose of

0.8 to 1.0 gm dramatically stopped the headache, lowered the blood pressure and abolished the sweating. The patient usually remained symptom free for 4 to 6 hours after injection of the drug, in spite of persistent bladder spasm obstructing the free flow of urine, although spasms were less frequent. After 4 days the bladder spasms became so infrequent that the use of the drug was no longer necessary (Fig 4).

These blood-pressure recordings were made on the 3rd postoperative night, and the frequency of attacks had gradually increased until one had barely ceased when another occurred.

### CLINICAL SIGNIFICANCE OF THE HYPERTENSIVE COMPONENT

Since the blood pressures are more labile in lesions above the level of the fifth dorsal segment and since these patients usually have more complications that can provoke the reaction, the hypertension and its concomitant symptoms obviously play a more significant role in this type of case.

The appearance of severe, intermittent headache in high cord lesions should cause the physician to note whether or not this often easily recognizable series of events is in progress. Attention should immediately be directed to the bladder or bowel. The observation has been repeatedly made that blocking of a catheter, acute genitourinary infections and distention of the bowel are attended by hypertension and its concomitants. It should be pointed out that the intracerebral vasomotor change may progress to loss of consciousness and occasionally to the convulsive state, as in Cases 1, 4 and 5. On occasion this may simulate organic brain disease, as in Case 4.

It may easily be seen that the instability of blood pressure in high cord lesions may assume importance in surgical procedures. Paroxysmal hypertension during operation not infrequently taxes the ingenuity of surgeons in control of hemostasis. This is particularly true in resection of hypertrophic bladder neck when the bladder is mechanically distended by hydrostatic pressure. During long operative procedures care should be taken that the bladder does not overdistend. Distention of the bladder sometimes accounts for the hypertension seen toward the end of long plastic and orthopedic procedures in high cord lesions. There is some evidence that a postoperative cerebrovascular accident is provoked by this mechanism.

### TREATMENT

The obvious treatment is removal of the stimulus but this is often impossible, as in Case 4, in which the administration of an enema became an extremely painful process. It is for such patients that we began to search for an agent to block the reflex. Tetraethyl ammonium chloride (Parke-Davis)<sup>13</sup> has admirably filled this need, as indicated in Figure 4. This experience has been duplicated repeatedly in natural and artificially induced attacks. None of the usual sedatives and analgesics had any noticeable effect. In some patients as little

as 400 mg of tetraethyl ammonium chloride, administered intramuscularly, was immediately effective although for a much shorter time than with larger doses.

Preliminary, and as yet incomplete, studies with paravertebral procaine blocks indicate that bilateral lumbar sympathetic blocks are insufficient to stop the reflex. Relatively small amounts of procaine injected in the lumbar subarachnoid space, however, were effective in 2 cases.

In only 1 patient were symptoms sufficiently severe, prolonged or frequent for sympathectomy to be considered. Successful segmental sympathectomy for excessive spinal reflex sweating has been done,<sup>2</sup> but its effect on the paroxysmal hypertension has not been recorded. We suspect, however, that in these few cases an extensive procedure of the Smithwick type should be considered.

### SUMMARY

Attention is called to the phenomenon of paroxysmal hypertension associated with mass sympathetic discharge in high cord lesions. We have confirmed certain aspects of recent studies regarding the accompanying vasomotor changes. The diagnostic and therapeutic importance of this syndrome is emphasized. Tetraethyl ammonium chloride is an effective drug in its symptomatic control. The possibility that an occasional patient may require surgical sympathectomy for relief of symptoms is proposed. A few typical cases are presented. The controversial physiologic interpretations are not discussed. A number of lines of investigation suggest themselves. These include the effect of autonomic drugs and further studies of the hemodynamics.

### REFERENCES

1. Head, H. and Riddoch, G. Automatic bladder excessive sweating and some other reflex conditions in gross injuries of spinal cord. *Brain* 40: 188-263 1917.
2. Lait, C. G. and Pimenta, A. D. Sweat secretion in man. VI Spinal reflex sweating. *Arch Neurol & Psychiat* 51: 501-507 1944.
3. Martin, J. and Davis, L. Studies upon spinal cord injuries. I. Development of autonomic micturition. *Ann Surg* 126: 472-477 1941.
4. Kennedy, R. H. New viewpoint toward spinal cord injuries. *Acta Surg* 124: 1057-1065 1946.
5. Kuhn, W. G. Jr. Care and rehabilitation of patients with injuries of spinal cord and cauda equina: preliminary report on 113 cases. *J Neurosurg* 4: 40-68 1947.
6. Munro, D. Rehabilitation of patients totally paralyzed below waist, with special reference to making them ambulatory and capable of earning their living. III. Tidal drainage, cystometry and bladder training. *New Eng J Med* 236: 223-235 1947.
7. Sabs, A. L. and Fulton, J. F. Somatic and autonomic reflexes in spinal mankeys. *J Neurophysiol* 3: 258-268 1940.
8. Symposium. War wounds of spinal cord paralyzed patient. *J A M A* 129: 154-165 1945.
9. Whitteridge, D. and Guttmann, L. Symposium on paraplegia. *Proc Roy Soc Med* 40: 222 and 229 1947.
10. Kunkel, P., Stead, E. A. Jr., and Weiss, S. Blood flow and vasomotor reactions in hand, forearm, foot and calf in response to physical and chemical stimuli. *J Clin Investigation* 18: 223-235, 1939.
11. Carmichael, E. A., Doupe, J., Harper, A. A., and McSwiney, B. A. Vasomotor reflexes in man following duodenal distention. *J Physiol* 95: 276-281 1939.
12. Saby, H. I., Suby, R. M., and Albright, F. Properties of organic acid solutions which determine their irritability to bladder mucous membranes and effect of magnesium ions in overcoming this irritability. *J Urol* 48: 549-562 1942.
13. Lyons, R. H., et al. Effects of blockade of autonomic ganglia in man with tetraethylammonium: preliminary observations on its clinical application. *Am J M Sc* 213: 315-323 1947.

## PUBLIC HEALTH TODAY AND TOMORROW IN MASSACHUSETTS\*

V A GETTING, M D , D R P H T

BOSTON

PUBLIC health is primarily the responsibility of state and local governments. This responsibility, however, must be shared by the medical profession and hospitals if the benefits from recent advances in the medical sciences are to be extended to all the people. For over seventy-five years the Massachusetts Department of Public Health has been serving the people of the Commonwealth in an effort to prevent disease, prolong life and promote optimal health. Almost a hundred years ago Lemuel Shattuck, alarmed at the unusually high death rate among those in the prime of life in the Commonwealth, conducted a sanitary survey. Shocked by the untimely deaths of the inhabitants, he realized that the essentials required for healthful living should be made available to all people. Nineteen years later this survey culminated in the creation of the first state department of health. The Massachusetts Medical Society vigorously supported the creation of the Department and throughout the ensuing years has co-operated in the extension and improvement of public-health services in the Commonwealth.

## PUBLIC HEALTH TODAY

The evolutionary development of the Department from the small nucleus of 1869 has been a gradual but constant process. Today, it employs approximately 1,800 people and expends an annual appropriation of approximately \$7,250,000. In addition to its other activities, the Department is responsible for the operation of five institutions, eight branch offices and seven laboratories. The federal Government, recognizing its responsibility in the general welfare of the people, annually makes available to Massachusetts approximately \$2,500,000 through grant-in-aid programs.

Both the scope and the character of the work of the Department have changed with the passing of years. Primarily concerned with environmental sanitation and the abatement of nuisances, the Department is now engaged in activities pertaining to all aspects of public health. These include the administration of medical care programs, administration of federal grants-in-aid for the construction of hospitals and health centers, the operation of hospitals, supervision and licensing of clinics and hospitals, epidemiology of disease, manufacture and distribution of prophylactic and therapeutic biologic products and processing and fractionation of human blood. The development and pro-

motion of programs dealing with maternal and child health, tuberculosis, venereal diseases, control of cancer and chronic diseases and the research and development of new public-health methods and technics are daily responsibilities of the Department.

*Recess Commission on Public Health*

A special commission authorized to make a study relative to certain public-health matters was established by Chapter 73 of the Resolves of 1947. This commission was charged not only with the responsibility of considering the licensing of hospitals, convalescent and nursing homes and the co-ordination of local, state and federal activities in the field of public health but also with the laws and policies of the Commonwealth relating to public health. The Commission consisted of Senator Richard H. Lee, Newton, chairman, Representative George W. Dean, Oakham, Representative Joseph D. Rivist, Northampton, Representative Fred C. Harrington, Everett, Dr. Henry D. Chadwick, Waltham, former commissioner of the Massachusetts Department of Public Health, Dr. L. Jackson Smith, commissioner of public health of Springfield, and Professor Curtis M. Hilliard, professor of public health at Simmons College and supervisor of the Board of Health of Wellesley and Weston. The report of this special commission has been published as House Document No. 1766 of the current legislative session.

The Commission organized two technical advisory committees. Dr. Hugh R. Leavell, of Cambridge, professor of public-health practice, Harvard School of Public Health, was appointed chairman of the Committee on Local Health Units, and Dr. Conrad Wesselhoef, of Boston, clinical professor of infectious disease, Harvard School of Public Health, chairman of the Committee on Preventable Diseases. These committees are continuing their work in anticipation of the continuation of the Special Recess Commission, which submitted a progress report to the legislature on December 3, 1947 (H 1766). The activities of the Commission were directed toward certain major objectives, as follows: the administrative changes in the Department of Public Health, the development of some equitable plan for the establishment of full-time health units throughout the Commonwealth in areas of such population as may be reasonably and economically administered, relocation of the chronic-disease hospital, the licensing and regulation of certain hospitals, sanatoriums and nursing homes by the

\*Presented at the annual meeting of the Middlesex South District Medical Society, Cambridge, April 21, 1948.

†Commissioner, Massachusetts Department of Public Health.

Department of Public Health, and consideration of legislation requiring the x-ray examination of schoolteachers and other school employees

The Commission employed as a consultant Dr Carl E. Buck, field director of the American Public Health Association, who, with his assistant, Dr Robert E. Rothermel, contributed valuable aid and consultative advice. The Commission requested its technical advisory committee to make an extensive study of the organization of the Department and to prepare recommendations to the Commission regarding the simplification of the table of organization. As a result of this study, it was recommended by the Commission that assistant commissioners of public health be appointed who would devote their entire time to the administrative duties associated with the five major units into which the Department would be divided. The Commission recommended the consideration of reclassification of both titles and salaries of professional personnel in the field of public health. The Commission became fully cognizant of the fact that the salaries paid professional personnel in Massachusetts do not and cannot assure the people of the Commonwealth the leadership necessary to provide these basic medical services essential to the health of the people. Legislation implementing the recommendations by the Commission and by Dr Buck was introduced and is now pending in the current legislative session.

### *Local Health Services*

Perhaps the major assignment of the Commission has been the development of an equitable program for the creation of local health units throughout the Commonwealth. The greatest need in public health today in Massachusetts, as well as in the United States, is the development of full-time, adequately staffed local health departments for population groups sufficiently large to enable efficient and economic administration. A preliminary study of legislation pertaining to local health departments and unions of health departments, their duties, responsibilities and services rendered the people has been made in a report submitted. The Technical Committee on Local Health is continuing its work in this field.

Massachusetts may well take pride in the fact that in its health responsibilities, including the provision of tuberculosis hospitals, and in its vital statistics, which reveal a low infant and maternal mortality, absence of smallpox and low typhoid-fever morbidity, it compares very favorably with other sections of the country. However, the Commission has not considered that doing a good job is sufficient. Its report indicated that only the best possible public-health program should continue to evolve in Massachusetts.

Although the Commonwealth has been and is still far ahead of most of the country in such important

activities as cancer and tuberculosis control and in environmental sanitation, Massachusetts, as well as the remainder of New England, is far behind the rest of the country in the development of full-time, adequately staffed local health departments for units of sufficient population size to be susceptible of reasonably economic and efficient administration. In the Commonwealth today there are but eleven cities and towns and one county that provide full-time medical health officers not engaged in private practice. These include Boston, Brookline, Cambridge, Fall River, Falmouth, Lowell, Newton, North Adams, Pittsfield, Springfield, Worcester and Barnstable County. There are today in Massachusetts twenty communities of 35,000 population or more not served by full-time medical health officers. Such a condition exists despite the fact that practically all public-health administrators are agreed that the most important public-health need today is the development of adequately staffed full-time health departments. Dr Carl Buck, of the American Public Health Association, who has recently reviewed the status of local health services in the Commonwealth and who bases his opinion upon the "Evaluation Schedule of Local Health Services," has reported that there are but four health departments in all of Massachusetts that would be judged "good" on the basis of these accepted standards.

Why are the physicians and the people of the Commonwealth so apparently satisfied with the situation as it exists? Simply because Massachusetts rates for preventable causes of death are somewhat better than the average of the country as a whole? Perhaps this is being satisfied rather easily, for in the Commonwealth during the five-year period 1941-1945 inclusive more than 1,500 persons died from the following "preventable causes": diphtheria, 50, measles, 71, whooping cough, 142, syphilis, 1238, typhoid fever, 20, bacterial dysentery, 26, tetanus, 29, and undulant fever, 7. For the same period (1941-1945) over 70,000 deaths from controllable causes occurred as follows: cancer, 37,361, tuberculosis, 7888, lobar pneumonia, 3962, premature births, 4696, accidents, 14,670, meningitis, 279, scarlet fever, 63, maternal deaths, 934, and diarrhea and enteritis (in patients under two years of age) 693. If the knowledge concerning the prevention and control of these diseases that we have at hand could be universally applied throughout the Commonwealth, the saving in lives would be tremendous. Practically all the deaths from preventable causes could have been avoided, and it has been very conservatively estimated that at least a third of all cancer deaths and at least half of all other deaths from controllable causes could have been avoided. Thus, in Massachusetts alone, the saving of over 30,000 lives over a five-year period, or an annual saving of 6000 lives, could have been effected. If a human life is valued at only \$5000, this would result in an annual saving to the Com-

monwealth of over \$30,000,000 Obviously, the Commonwealth is currently and continuously experiencing an irreparable loss in lives and money. If the essential developments of modern medicine, preventive procedures and programs developed through public health could be made available to all the people these lives would not be lost but would continue to contribute to the assets of the Commonwealth.

In such a program the Government alone cannot succeed. The annual saving of over 6000 lives is a challenge not only to the government but also to the public-health and medical professions. Imagine the sacrifice of 30,000 people every five years in the Commonwealth — a population equivalent to that of the cities and towns of Revere, Belmont, Weymouth and Melrose! It must be borne in mind, however, that these figures represent but a portion of the entire problem. They include no estimate of the amount and extent of sickness or economic loss resulting from cases that do not terminate in death. For example, it is estimated that the annual loss of income of the Commonwealth due to disability from chronic disease is \$50,000,000. Is it a wonder then, that the medical profession and the public are expressing a growing concern about this unnecessary loss of lives and income?

Medical and other professional schools are now training physicians, dentists, nurses and health officers, in an effort to supply the personnel necessary to provide basic health services. Through local resources, voluntary and governmental hospitals and health centers are in the process of construction throughout the Commonwealth. The Department of Public Health is assisting this expansion of physical facilities through the administration of the Survey and Plan for Construction of Hospital and Health Centers in the Commonwealth. By means of this program financial assistance will be offered to some of these projects through a federal grant amounting to \$8,000,000, which will extend over five fiscal years beginning on July 1, 1947.

The greatest single need in Massachusetts, however, is the development of local health units, adequately staffed and efficiently serving all the people of the Commonwealth. If full-time health departments are to be established, certain basic essentials must be met.

A sound state-wide program of health education to accomplish as soon as possible a universal understanding of the needs and value of full-time health services.

An active department of health adequately staffed. This is essential for the proper leadership and stimulation of activities throughout the cities and municipalities.

Basic legislation permitting and facilitating the establishment of full-time health departments through unions of towns on a voluntary basis.

Approval of the state health agency of such departments would be necessary that no section of the Commonwealth would eventually be without such services. Compulsory formation of such unions may be required if they are not formed voluntarily within a period of five to ten years.

A plan for state and federal subsidy for the maintenance of full-time local health departments.

The training of adequate health officers, public health nurses, sanitarians, nutritionists and medical social workers required for the local health units.

The provision of adequate compensation to qualified public-health personnel. This is an essential, since the recruitment and retention of good personnel depend first and foremost upon good salaries, reasonable tenure of office, opportunities for advancement and reasonable plan of retirement. The last three, of course, may be effectively obtained through a well conducted civil-service system.

Periodic evaluation of services rendered by the community health agencies preferably through some method of study as that devised in the evaluation schedule of the American Public Health Association. Evaluations of this type have many uses, among them being provision of a base line for future measurement, calling attention to achievements and unmet needs, and furnishing a foundation for future planning.

Of these seven basic essentials necessary to the establishment of full-time local health departments, Massachusetts is lacking in all. Perhaps the best way of meeting the need for the dissemination of health information is through the creation of a state-wide health committee designed to achieve real understanding on the part of the people and the professions of the services and benefits that can be obtained through the extension of adequate local health services.

Although existing legislation permits the establishment of unions of towns for health purposes, such unions have not been successful in the past because of their effervescent nature and failure of financial support from either state or federal appropriations. A plan must be devised for providing various alternate methods for these unions of towns on a county or district basis, which will ensure complete coverage of the Commonwealth within a reasonable time, or the alternative of such a program must be introduced — namely, that such unions be formed after public hearings throughout the Commonwealth have been held by the Department of Public Health.

At present there are but nine states in the entire United States that do not make available state funds to local health departments. Massachusetts is one of these.

### *The Private Practitioner and the Health Department*

Efficient local health departments have always called attention to the need for more adequate medical services. It has been my experience and that of most public-health officials that the more conscious the public becomes of health, the more it utilizes available local health facilities and services. Therefore, the formation of adequately staffed health units throughout the Commonwealth would increase the utilization of services of physicians, dentists and hospitals. Although physicians may as a result of this become more overworked than they are now, such services would consist primarily of preventive measures and the diagnosis and treatment of early illnesses or disabilities rather than the providing of terminal care, which has unfortunately occurred too often. To be sure, prolonged illness and chronic disability will still occur, but effective preventive measures, early diagnosis and prompt and adequate treatment may greatly reduce the incidence.

A private practitioner of medicine has, therefore, a moral obligation to the people to assist in furthering community health programs. At the same time he will contribute to the economic improvement not only of himself but also of his entire community.

### *Long-Term Illness*

Physicians are all concerned with the task of prolonging life and improving the health of patients. Today, with the life expectancy of a newborn infant amounting to almost seventy years, the doctor's responsibility for this life is greater. With advancing age the human body tends to succumb to a host of chronic diseases, such as heart disease, vascular disease, cancer and diabetes, any one of which may be not only prolonged but also often disabling. The medical and public-health professions have made outstanding advances in the control of infectious diseases and the diseases of early life, which must continue, but they must also acquire further knowledge and develop better methods for the early diagnosis of preclinical long-term illnesses. New procedures for the prevention, early diagnosis and amelioration of chronic diseases must be the next major development. Although it may be impossible to prevent heart disease per se, it may be possible not only to reduce its incidence

but also to delay the onset of symptoms, postpone the disability period and prolong life for many productive and happy years. By similar methods, the patient with cancer or diabetes may look forward to a longer productive life. This will occur, but the essential prerequisite is that health departments and the medical profession, through co-ordinate action, make available to the people the benefits of new medical knowledge as soon as it is of proved value.

Here again the private practitioner receives a challenge — a challenge not only to promote greater health in the aging population but also to realize and accept the changing goal in his daily practice. Health supervision, through periodic, thorough examination and care of the patient, becomes a physician's increasing responsibility.

### PUBLIC HEALTH TOMORROW

The education of the patient in healthful living is the dual responsibility of the doctor and the health department. The doctor of tomorrow must not only prescribe well but also inform well. Patients want to know what can be done to improve their health. Today, more than ever before, the public is conscious of its health, people are making greater demands for services upon the Government, hospitals and the medical profession. The future of public health is therefore encouraging. Programs for the maintenance and preservation of health are both improving and increasing in scope. The people, by demanding basic health services, will secure coverage of the nation with adequately staffed local health departments. Improved facilities of hospitals and clinics, the workshops of physicians, will serve more people. The school child will be offered a better opportunity to attain adult life without physical or mental disability, and as an adult, he will be convinced that good health cannot be taken complacently but can be assured only through diligent care under the direction of competent physicians.

Thus, by striving toward the common objective of improving the health of the people the doctor, hospital and health officer may bring to every person the basic essentials, diagnostic, preventive and therapeutic measures that will enable him to enjoy a more productive life and become a greater asset to the community.

## MEDICAL PROGRESS

## CHEMOTHERAPY OF NEOPLASTIC DISEASE

## III. Agents of Clinical Value

DAVID A. KARNOFSKY, M.D.\*

NEW YORK CITY

From the large array of substances under laboratory and clinical study, several have been established as useful in the management of patients with inoperable neoplastic disease. These agents are discussed in the order of their value to the clinician, as judged by their unique therapeutic activity and their general clinical effectiveness.

*Estrogens*

Estrogens are useful in the treatment of carcinoma of the prostate and, to a considerably lesser extent, in carcinoma of the breast. With the fundamental work of Huggins<sup>214</sup> in establishing the role of the steroid hormones in prostatic physiology, the therapeutic value of castration and estrogen therapy in carcinoma of the prostate was rapidly established.<sup>215</sup> Bilateral orchidectomy or estrogen therapy, in 50 to 75 per cent of patients with prostatic carcinoma, will produce rapid and remarkable effects—a decrease in the size of the enlarged prostate, degeneration of many of the neoplastic cells, a diminution in the size of metastases and recalcification of bone lesions, a fall in an elevated serum acid phosphatase level and a relief of pain, urinary-tract obstruction and disability. Hormonal therapy is not curative, however, and the patient ultimately becomes resistant to therapy, but life is often appreciably prolonged.<sup>216, 217</sup> This work has been reviewed by Nathanson.<sup>218</sup>

In the past two years the chief problem in estrogen therapy has been to establish the indications for its use in the proper management of prostatic carcinoma. Colston and Brendler<sup>219</sup> have recommended the use of stilbestrol, 1 to 2 mg daily, prior to radical prostatectomy. This procedure may possibly convert a localized but moderately advanced inoperable carcinoma into an operable one, and simplify the removal of an operable tumor. Herger and Sauer<sup>220</sup> believe that estrogen therapy is of no prophylactic value in slowly progressing, asymptomatic but inoperable carcinoma of the prostate, and they suggest that its early use may destroy the subsequent estrogen sensitivity of the disease. They have recommended that hormonal therapy be withheld until the disease is extensive or disabling symptoms are present. Deming<sup>221, 222</sup>

however, sanctions the use of estrogen therapy in all stages of inoperable prostatic carcinoma. It is generally agreed that since estrogens will produce therapeutic effects equal to castration, their use is to be preferred.<sup>217, 220-222</sup> When immediate relief is necessary, castration is indicated since its therapeutic effects appear within thirty-six hours, whereas estrogens require seven to ten days. Castration is also indicated in patients unable or disinclined to take estrogens, or in those who have relapsed under adequate estrogen therapy. It is not considered likely that castration will help the latter group, but the rare beneficial reports that have appeared seem to justify its trial.<sup>217, 220</sup> Conversely, in cases of castration relapse, estrogen therapy is sometimes effective.<sup>217</sup> There appears to be no good evidence of additive benefits from simultaneous therapy by castration and estrogens.

The estrogen preparations most frequently used are stilbestrol, 1 to 5 mg daily, and ethinyl estradiol, 0.1 to 0.5 mg daily. Dean<sup>217</sup> is of the opinion that ethinyl estradiol may be given in larger estrogen equivalent doses than stilbestrol, with less severe gastrointestinal symptoms. Other side effects of therapy are signs of feminization, particularly enlargement and tenderness of the breasts, and a decrease in libido.

The use of estrogens in the palliative treatment of mammary carcinoma is still in the experimental stage, but extensive clinical work is in progress.<sup>223-229</sup> Estrogens do not appear to be active<sup>227, 228</sup> against osseous metastases, which occur chiefly in the younger age groups, and they rarely exert a favorable effect on the disease in this group.<sup>224</sup> Indeed, there is evidence that estrogens sometimes accelerate the course of mammary cancer in young patients.<sup>227</sup> For these reasons, the use of estrogen therapy is entirely confined to postmenopausal patients, and it has been suggested that its use be restricted to women at least five years beyond the menopause.<sup>229</sup> In this group, 30 to 40 per cent of the patients have been found to show some temporarily favorable, but often only slight, response to therapy.<sup>224, 227</sup> This may consist of subjective improvement, regression of local tumors, shrinkage and healing of ulcers, reduction in the size and redness of skin metastases and decrease in the size of lymph-node and lung metastases. The usual

\*Associate, Sloan Kettering Institute for Cancer Research, fellow in medicine, Memorial Hospital Center for Cancer and Allied Diseases, fellow Jane Coffin Childs Memorial Fund for Medical Research.

dosage is 5 to 20 mg of stilbestrol daily.<sup>229</sup> These large doses may induce gastrointestinal disturbances, with nausea and vomiting, weight loss, diarrhea and uterine bleeding, edema and skin eruptions.

In mammary carcinoma in the male, estrogen therapy has not been tried extensively, but Nathanson<sup>226</sup> has recorded his impression that castration may be therapeutically more effective. Estrogens have been reported to produce tumor regressions in bladder papilloma and subjective improvement in bladder carcinoma.<sup>230</sup>

### *Nitrogen Mustard*

Gilman et al,<sup>231</sup> early in 1943, first reported, in a confidential military communication, on the clinical use of a nitrogen mustard compound, *tris* (beta-chloroethyl) amine hydrochloride in the treatment of neoplastic disease. Jacobson and his co-workers,<sup>232</sup> shortly afterward, began the clinical use of another nitrogen mustard, methyl-bis (beta-chloroethyl) amine hydrochloride, also known as DEMA or HN2, and this work was extended to two other clinics.<sup>233, 234</sup> Similar work was initiated in England by Wilkinson and Fletcher.<sup>235</sup> Because of military restrictions on the nitrogen mustards, none of the information could be reported until the end of World War II.<sup>114</sup> When these restrictions were lifted in 1946, an official statement was published<sup>236</sup> summarizing the clinical information available at that time, and distribution of the agent for clinical investigation was begun.<sup>237</sup> Since the inception of this study a number of clinical reports have appeared.<sup>238-250</sup>

HN2 must be given intravenously and, therefore, exerts its therapeutic action throughout the body. Recovery from the toxic effects of HN2 is more rapid than that from total body exposure to an equivalent effective dose of x-rays. This makes it possible to control HN2 dosage somewhat more closely than total body irradiation by x-rays or radioactive isotopes.

HN2 therapy has not proved to be a cure in any type of neoplastic disease, in leukemic mice, for example, four to ten times a lethal dose of HN2 *in vivo* is required to destroy the viability of the leukemic cells, a strain of cells considered to be unusually sensitive to HN2.<sup>28</sup> The rationale of HN2 therapy, therefore, consists in attempting to give the largest amount of HN2 consistent with doing no serious harm to the patient. The amount of HN2 that can be safely given varies considerably in different patients. Important factors in dosage are the patient's general condition, his hematologic status and his immediate prognosis—that is, greater risks can be taken if the immediate prognosis is poor.

The usual course of HN2 therapy consists of the intravenous injection of 0.1 mg per kilogram of body weight daily for four days, a total of 0.4 mg per kilogram. This is usually a safe dose, but in

some patients with depression of the hematopoietic system, especially that due to bone-marrow involvement with disease, or with very extensive, massive tumors, toxic effects may occur, and the drug should, therefore, be given more cautiously. A course of 0.4 mg per kilogram of body weight usually produces a moderate leukopenia, which develops gradually within seven to fourteen days, the white-cell count reaching a maximum of 1000 to 3000, followed by a relatively prompt recovery. There may be a mild depression in the platelet count, and usually the hemoglobin level is unaffected. The changes in the peripheral blood are paralleled in the bone marrow.<sup>238</sup> In selected cases the total course of HN2 may be given in two injections of 0.2 mg per kilogram of body weight or in a single dose of 0.4 mg per kilogram of body weight. If the usual total course of 0.4 mg of HN2 does not produce a satisfactory therapeutic result, and the peripheral-blood picture is relatively unchanged or has recovered, within two or three weeks, further HN2 may be given cautiously. In some patients, as a result of experience, it has been found that a total course of 1.0 mg per kilogram of body weight can be given safely in a three-week period—an amount of HN2 that would prove fatal in other patients.

If an excessive dose of HN2 is given, a characteristic toxicologic picture develops within seven to fourteen days, consisting of severe leukopenia, thrombocytopenia, with petechiae or purpura, a rapidly developing anemia, fever and weakness. The patient may bleed extensively from the nose, gums, kidneys and bowel, or into the skin, and even death may occur. Usually, however, recovery begins within four to ten days. Blood transfusions, as well as penicillin to ward off infections, appear to be the only agents of value in the treatment of this condition.

HN2 has two unpleasant incidental side effects. In many cases it produces thrombosis of the injected vein. This seems to occur more frequently when it is given by the direct syringe method than when injected into the tubing of a freely flowing intravenous infusion. Since the former method is simpler, it is more frequently used. If HN2 escapes from the vein it will produce an extensive local area of erythema, induration and eventually fibrosis. Within one to eight hours after an injection of HN2 most patients feel nauseated, and about 50 per cent vomit.<sup>234</sup> During the course of treatment, the patient may complain of weakness, anorexia and weight loss.

HN2 is not recommended for localized neoplastic disease, which can be treated more effectively with x-rays, with less discomfort to the patient and with longer clinical remissions. The agent has not been in use long enough to permit a definitive statement of its clinical value and the indications for its use.

but the available reports agree about its clinical effects

HN2 has found its most useful therapeutic role in the treatment of Hodgkin's disease<sup>232-233, 246, 247, 249</sup> It will induce a consistent clinical improvement in 80 to 90 per cent of treated patients The most striking effect is detoxification of the patient, with a prompt fall in fever increase in strength, appetite and weight Objectively, there may be a decrease in the size of enlarged lymph nodes, spleen and liver, clearing of pulmonary infiltrations and resorption of ascitic or pleural effusion Less consistently, there may be relief of bone pain or pruritus, shrinkage of involved, massively infiltrated tissues and recalcification of osseous lesions A remission may last from two weeks to more than a year, but the average duration is about six weeks The longer the remission from an adequate single course of therapy, the more favorable the outlook When the patient begins to relapse, another course of HN2 is usually indicated Some patients have received more than ten courses of treatment with repeated clinical responses, and with no definite evidence of cumulative damage to the bone marrow In most cases, however, the disease progresses, and the patient gradually becomes unresponsive to therapy

HN2 is suggested for the treatment of generalized Hodgkin's disease with systemic symptoms, and for use in patients believed to be "x-ray fast" A significant group of the "x-ray fast" patients may be salvaged for several months or longer by a course of mustard therapy This does not necessarily mean that the tissue in Hodgkin's disease unresponsive to x-rays can be affected by HN2, it probably does mean that the x-rays were not applied to the areas of active disease whereas a systemic form of therapy could ferret out these areas After satisfactory response of an "x-ray fast" patient to HN2 therapy, x-rays may then be used to treat localized disease There is no evidence that HN2, given early or late in Hodgkin's disease, alters the general course of the disease or prolongs life significantly It does, however, have an important and unique place in the management of the disease

HN2 has a definite palliative effect in mycosis fungoides<sup>244</sup> It will temporarily cause a regression of the skin lesions in patients no longer responding to or unsuitable for x-ray therapy The duration of remission to a course of treatment is variable, from only several days to six months or longer

Some patients with lymphosarcoma may respond to HN2 in a truly remarkable fashion, with rapid shrinkage of the enlarged lymph nodes, liver and spleen, and subjective improvement persisting for six months to a year or longer<sup>231-233, 235-237</sup> Another group with very aggressive disease may also show a marked but unsubstantial therapeutic response, relapsing within one or two weeks In

general, x-ray therapy is more satisfactory for the control of lymphosarcoma In some patients with extensive but relatively slowly progressive lymphosarcoma, HN2 may give remissions sufficiently long to make it a satisfactory alternative to x-ray therapy

Consistent clinical remissions can be induced in chronic myelogenous leukemia, with a fall in the white-cell count, a rise in hemoglobin level, a decrease in the size of an enlarged spleen and general improvement in the patient The remission usually continues for two or three months, and relapse is then fairly rapid Patients will continue to show some response to treatment until they reach the terminal stage Wintrobe et al<sup>238</sup> successfully maintained over many months 2 patients by periodic injections of HN2 There is little evidence that HN2 will prove effective in the treatment of patients unresponsive to adequate x-ray therapy In fact, in patients with very large spleens, greater relief is obtained from splenic irradiation than from systemic HN2 therapy

The results of HN2 therapy in chronic lymphatic leukemia have not been consistent These patients seem to have a greater tendency to develop a toxic reaction to HN2, which should therefore be given cautiously<sup>231</sup> Occasionally a patient may show a surprisingly good response, with a spontaneous rise in hemoglobin As Wintrobe<sup>238</sup> points out, however, patients in good condition usually show a good response to HN2, whereas those in poor condition, with generalized lymphadenopathy and anemia, do poorly

The acute leukemias do not show a satisfactory clinical response to HN2, although a fall in the white-cell count can be produced Relief of bone pain has been reported<sup>239</sup>

HN2 will induce a clinical remission in polycythemia vera<sup>17, 246</sup> similar to that produced by radioactive phosphorus It is too early to draw any conclusions regarding the consistency of this therapeutic effect, or the relative merits or hazards of HN2 therapy compared to other methods of treatment

In common with other agents, HN2 may cause some relief of pain in multiple myeloma, but there is no substantial evidence that the osseous lesions or the course of the disease is altered

HN2 has been found to produce transient symptomatic and occasional objective improvement in about 50 to 70 per cent of patients with inoperable carcinoma of the lung<sup>126, 241, 247</sup> These effects consist of relief of dyspnea and cough, decrease of sputum and hemoptysis and an increase in strength, appetite and weight The primary tumor and the metastases may show some decrease in size, and absorption of pleural effusions and aeration of atelectatic areas may occur There is occasionally relief of chest pain, and symptoms from obstruction of the superior vena cava may be markedly alleviated These therapeutic effects usually last

for from two weeks to two months only, and relapses develop rapidly. Patients with anaplastic carcinoma of the lung show a very dramatic symptomatic improvement, but they relapse quickly. Subsequent courses of treatment are usually not so successful, and HN2 therapy does not seem to cause a significant prolongation of life.

Circumscribed, inoperable carcinomas of the lung are best treated by x-rays. HN2 appears to be useful when the disease is extensive or severe symptoms are present. There does not appear to be any real evidence that its use in early carcinoma of the lung will significantly check the course of the disease.

In other types of carcinoma and sarcoma transient beneficial results have occasionally been reported, but these effects do not appear to be consistent. Further clinical investigation may disclose conditions in which HN2 will produce some consistent palliation.

Three general points about further indications for the use of HN2 may be considered, as follows:

HN2 does not seem to produce edema in tissues immediately following treatment, such as may occur after x-ray therapy. In obstructive tumors, such as lymphosarcoma pressing on the trachea, or obstruction of the superior vena cava from carcinoma of the lung, HN2 may be indicated prior to x-ray therapy.

Since the effects of HN2 are rapidly exerted it may be used as an emergency measure in selected cases. In patients in *extremis* from advanced but possibly responsive disease—and this situation has arisen chiefly in patients with lymphosarcoma or carcinoma of the lung—HN2 may produce remarkable improvement within twenty-four hours. Subsequently, a more considered program of therapy can then be started.

Studies are in progress to determine the value of combining the systemic effects of HN2 with localized x-ray therapy. In laboratory experiments, it has been shown that if HN2 is given before x-ray therapy an additive effect results, if given in the reverse sequence, x-rays seem to interfere with the action of HN2.<sup>28</sup> On the basis of these laboratory data, it seems reasonable, in the proper situation, to give HN2 prior to x-ray therapy.

### Radioactive Iodine

In 1940 Hamilton, Soley and Eichorn<sup>251</sup> demonstrated the selective deposition of radioactive iodine in human thyroid tissue, but only an insignificant amount was found in 2 carcinomas of thyroid origin studied. Metastatic thyroid carcinomas that selectively concentrate radioactive iodine were subsequently described.<sup>252, 253</sup> This concentration of radioiodine produces an intense and destructive local irradiation of thyroid tissue. Functional

thyroid tumors are rare, and it is estimated that only about 15 per cent of the tumors of thyroid origin will concentrate iodine.<sup>254</sup> In 19 selected thyroid tumors studied for their ability to take up radioactive iodine, 9 tumors, showing an orderly cell arrangement in a follicular pattern and containing colloid-like material, were capable of concentrating the iodine. These included 5 benign metastasizing strumas and 4 follicular adenocarcinomas. Of the remaining 10 solid alveolar or more anaplastic carcinomas, only 1 showed any evidence of iodine uptake.<sup>254</sup>

Thus far, only 1 patient has been reported in detail as having been treated successfully with radioactive iodine,<sup>255</sup> although additional reports are in press.<sup>256</sup> The selection of patients suitable for radioactive-iodine therapy is made by histologic examination of the tumor and by its ability to concentrate tracer doses of radioactive iodine. In patients with highly functional thyroid tumors, radioactive iodine will concentrate in the metastases. In most cases of functional thyroid tumors, however, the selective uptake of radioactive iodine is not great. The avidity of these tumors for radioactive iodine may be increased in some cases by surgical thyroidectomy, or "medical thyroidectomy" with radioactive iodine.<sup>257</sup> The radioactive iodine generally used is  $I^{131}$ , with a half-life of eight days. Large doses up to 200 millicuries have been given during a single course of treatment. The hazards of therapy are due to the radiation effects from radioactive iodine and the rapid destruction of active thyroid tissue.<sup>258</sup> In suitable cases, radioactive iodine will produce extraordinary tumor regressions and relief of pain and disability and will result in considerable prolongation of life. It is emphasized that patients must be carefully selected for treatment, and  $I^{131}$  administered with knowledge of the principles of thyroid physiology and radiation effects.

### Androgens

Androgenic substances have not been found to have such wide or specific applications as the estrogens in the treatment of cancer. Evidence is now accumulating that they have occasionally a temporary therapeutic effect on osseous metastases from carcinoma of the breast.<sup>256, 258, 265-267</sup> Although only a small number of cases have been reported in each series, certain preliminary generalizations appear justified. The preparation of androgen usually used is testosterone propionate. The premenopausal or younger patients with metastatic mammary carcinoma are considered most suitable for treatment. In about 50 per cent of the patients there will be some subjective improvement, with relief of pain and an increase in activity, appetite and a feeling of well-being. In 20 to 30 per cent of the patients with bone lesions, there will be x-ray evidence of regression and recalcification of the bone metastases. Less commonly, the primary

tumor or soft-tissue metastases will undergo regression<sup>225, 263</sup> If favorable clinical effects develop, they usually appear within two or three weeks of treatment and continue for variable but often short periods in the range of two to six months Under testosterone therapy the bone metastases may sometimes remain quiescent while the soft-tissue metastases progress Data are inadequate for discussion of the relative therapeutic merits of surgical or x-ray castration, alone or in combination with androgen therapy

A dosage schedule of 100 mg of testosterone propionate intramuscularly three times weekly has been suggested<sup>229</sup> This should be given for ten weeks and continued if improvement is satisfactory The side effects of testosterone administration — masculinizing effects, amenorrhea, edema and increased libido — should be taken into consideration in the decision to initiate therapy In patients with an elevated blood calcium level prior to treatment, testosterone therapy must be given with caution, since it may further raise the blood calcium to dangerous levels<sup>259</sup>

#### *Radioactive Phosphorus*

Radioactive phosphorus has been used clinically for almost ten years, and its therapeutic applications have been reviewed several times in the past three years<sup>8, 247, 264-270</sup> There is remarkable agreement concerning the place of this agent in the treatment of neoplastic disease It has not proved consistently useful in the treatment of Hodgkin's disease and lymphosarcoma, and it is without value in acute leukemia Its use is chiefly limited to certain disorders of the hematopoietic system

P<sup>32</sup> is considered by many to be the treatment of choice in polycythemia vera<sup>8, 247, 265, 266, 271, 272</sup> It will produce, almost invariably, marked symptomatic relief, a remission in the abnormal hematologic picture and a reduction in the size of an enlarged liver and spleen The usual duration of remission after an adequate single course of treatment is six to twelve months, but much longer remissions have occurred The serious complication of P<sup>32</sup> therapy is hematopoietic injury, with leukopenia, thrombocytopenia and anemia The usual dose is 4 to 7 millicuries intravenously, and further treatment may be given in one to three months if an adequate response has not been obtained The agent must be administered cautiously, since the maximum therapeutic and toxic effects usually do not appear before two weeks, and they may not reach maximum development for six months Furthermore, patients vary markedly in their sensitivity to P<sup>32</sup>, and an ineffective dose in one patient may be a toxic one in another There are some reservations about the use of P<sup>32</sup> in polycythemia vera Hall and Watkins<sup>266</sup> have suggested that the incidence of acute leukemia is higher in patients with polycythemia vera treated with P<sup>32</sup>, and Hahn<sup>177</sup> is of the opinion that P<sup>32</sup> is not necessarily

indicated in a disease that is treated so easily and effectively by other methods that have potentially less serious after effects

In chronic myelogenous leukemia, P<sup>32</sup> will induce typical clinical remissions, with a fall in white-cell count, rise in hemoglobin, reduction in the size of the spleen and symptomatic improvement The usual procedure is to administer P<sup>32</sup> cautiously, perhaps 1 to 2 millicuries twice a week until the white-cell count has begun to fall One patient may respond to a total dose of 5 millicuries, whereas another may need 25 millicuries When a clinical remission is induced, treatment is discontinued until relapse occurs<sup>265</sup> The nature and duration of remissions produced by P<sup>32</sup> are similar to those from x-rays, and, as with x-ray therapy, P<sup>32</sup> has only been found to produce a slight prolongation of life<sup>265</sup> Hall and Watkins<sup>266</sup> have raised the possibility that a greater number of cases of chronic myelogenous leukemia treated with P<sup>32</sup> terminate more frequently with acute leukemia than those treated by other means In chronic lymphatic leukemia P<sup>32</sup>, like other chemotherapeutic agents, does not produce clinical remissions as satisfactory or as consistently as in chronic myelogenous leukemia In many cases, however, a reduction in white-cell count, decrease in the size of enlarged nodes, liver and spleen, rise in hemoglobin and improvement in the general condition occur X-ray therapy is more effective in the treatment of large localized manifestations of lymphatic leukemia, but P<sup>32</sup> is of equal value in the therapy of generalized disease In multiple myeloma the drug has produced considerable relief of pain in 10 out of 14 patients in one series,<sup>266</sup> but it has not affected tumor growth or altered the progressive course of the disease

It is apparent that P<sup>32</sup> is neither unique nor irreplaceable in the treatment of neoplastic diseases of the hematopoietic system Its fourteen-day half-life sometimes makes the tissue radiation dosage difficult to regulate, and other radioactive isotopes may prove more satisfactory in certain cases

#### *Urethane*

Urethane was first tried clinically by Paterson et al<sup>146</sup> in the treatment of miscellaneous tumors, including carcinoma of the breast, but the results indicated only slight or inconstant chemotherapeutic activity Since some of these patients developed leukopenia, the drug was given to patients with chronic myelogenous and lymphatic leukemia and, in these diseases, characteristic temporary clinical remissions were obtained

Urethane is a drug of low toxicity, and in the past it has been used as a hypnotic The dose usually recommended for the treatment of leukemia is 2 to 4 gm daily for two to six weeks or until a therapeutic effect results It may be given orally<sup>146</sup> in an aqueous solution, by enteric coated capsules or parenterally<sup>273</sup> Nausea and occasionally vomit-

ing are complications of treatment, but this is rarely sufficiently severe to necessitate cessation of treatment. Larger doses up to 15 gm a day have been given.<sup>27</sup> The large doses have a hypnotic and moderately intoxicating effect. The results of excessive urethane therapy have not been definitely established, but the drug should be administered cautiously and the hematologic picture carefully followed. In patients with leukemia there is no doubt that urethane will produce a severe depression of the bone marrow.<sup>146, 273</sup> It seems likely that patients with normal bone marrow exposed continuously to large doses of urethane will show hematopoietic injury, with leukopenia, anemia, thrombocytopenia and bleeding. Moeschlin,<sup>148</sup> however, has been unable to produce any injury to the bone marrow of normal male patients by the continuous administration of urethane. Urethane has a moderately cumulative effect, and its hematologic action in leukemia varies with the total amount and the daily dosage of the drug administered. No evidence has been presented that urethane induces pulmonary adenomas in man, although this possibility must be considered.

Since the initial publication on the clinical effects of urethane in leukemia, several confirmatory reports have appeared.<sup>273-276</sup> The most successful results have been obtained in chronic myelogenous leukemia. Within one to three weeks after urethane treatment was begun, there was, in almost all cases, a fall in the white-cell count, a tendency of the differential to return toward normal, a rise in the hemoglobin and a reduction in the size of the spleen. The total dose required to accomplish this ranged from 19 to 325 gm, and remissions usually occurred within ten to thirty-one days. Patients relapse under treatment, however, and there is no evidence that life is appreciably prolonged or the course of the disease altered by the treatment. Patients in the terminal stage of chronic myelogenous leukemia do not respond well to urethane. In chronic lymphatic leukemia the results in general have not been so satisfactory as those in myelogenous leukemia, although in the majority of cases treated, a temporary remission of the disease has been induced, with regression in the size of diseased organs, a rise in hemoglobin level, a decrease in the white-cell count and an absolute increase in the polymorphonuclear leukocytes. In Paterson's<sup>274</sup> series 13 out of 23 patients showed improvement, 5 were unaffected, and 5 became worse. In a smaller series of 8 cases, Hirschboeck et al.<sup>275</sup> observed a satisfactory remission in 3 cases, a fair result in 2 and poor results in the remainder. No significant clinical improvement has been observed in acute leukemia, although the white-cell count may be lowered. There have been no consistent results from the use of the drug in lymphosarcoma or Hodgkin's disease.<sup>146, 276</sup> A remarkable remission in an anaplastic carcinoma metastatic to the skin has been reported.<sup>277</sup> In 4 patients with prostatic

carcinoma no longer responding to hormonal control, large doses of urethane caused some shrinkage of the primary tumor, a decrease in acid phosphatase, a relief of pain and a sense of well-being.<sup>278</sup> One of these patients died of hepatic necrosis, which could not definitely be attributed to the urethane therapy.

In general, in the treatment of chronic myelogenous and lymphatic leukemia, urethane can be expected to produce remissions similar to those effected by x-ray therapy, radioactive phosphorus, nitrogen mustard and Fowler's solution.<sup>276</sup> Its action is perhaps not so consistent, precise and predictable as that of the more toxic agents, and it is unlikely that urethane will be effective in patients in whom these other agents fail. Furthermore, at effective doses, it has a toxic effect on the bone marrow and should, therefore, be administered cautiously.

#### *Fowler's Solution*

Although there are no recent papers on the use of potassium arsenite in leukemia, it is well established as a useful agent for inducing clinical remissions in early and responsive cases of chronic myelogenous and lymphatic leukemia.<sup>279</sup>

\* \* \*

Only a small group of human neoplastic diseases is susceptible to the palliative effects of chemotherapeutic agents. In carcinoma of the prostate estrogens may temporarily halt the disease and prolong life, in an occasional patient with carcinoma of the thyroid gland radioactive iodine is effective in interrupting the disease and prolonging life, in Hodgkin's disease nitrogen mustard serves as a useful adjuvant to x-ray therapy, and this appears to be true, but to a lesser extent, in lymphosarcoma and mycosis fungoides, in chronic myelogenous and chronic lymphatic leukemia. Fowler's solution, urethane, nitrogen mustard and radioactive phosphorus are all capable of inducing clinical remissions when the patient is responsive to therapy, but they are all uniformly less effective when the patient approaches the terminal or acute stage, in polycythemia vera radioactive phosphorus and, possibly to a lesser extent, nitrogen mustard will induce excellent clinical remissions, in carcinoma of the lung nitrogen mustard may produce transient palliative effect, and in mammary carcinoma in postmenopausal patients estrogen therapy may produce temporary palliation and tumor regressions—in the premenopausal patient with osseous metastases androgens are more effective. Inconstant and unpredictable transient responses to some of these chemotherapeutic substances have been reported in a variety of other tumors.

It is to be hoped that in future reviews the great efforts of the laboratories and clinics in cancer therapy will result in a longer list of neoplastic diseases responsive to more effective chemotherapeutic agents.

## REFERENCES

- 214 Higgins C. Endocrine control of prostatic cancer. *Science* 97 541-544 1943
- 215 Ferguson J. D. Carcinoma of prostate treated with oestrogens. *Lancet* 2:551-556 1946
- 216 Nesbit, R. M. and Plumb R. T. Prostatic carcinoma follow-up on 795 patients treated prior to endocrine era and comparison of survival rates between these and patients treated by endocrine therapy. *Surgery* 20:265-272 1946
- 217 Dean A. L. Carcinoma of prostate. *Bull New York Acad Med* 23 454-471 1947
- 218 Nathanson I. T. Endocrine aspect of cancer. *New Eng J Med* 231 764-770 and 795-902 1944
- 219 Colston J. A. C. and Brendler H. Endocrine therapy in carcinoma of prostate: preparation of patients for radical perineal prostatectomy. *J A M A* 134 848-853 1947
- 220 Herger C. C., and Sauer H. R. Consideration of effect of androgen control treatment of carcinoma of prostate. *New York State J Med* 47 494-501 1947
- 221 Deming C. L. Hormonal treatment of prostatic malignancy. *Bull New York Acad Med* 22 88-101 1946
- 222 Idem. Present evaluation of response of prostatic cancer to hormone therapy. *South M J* 40:328-332 1947
- 223 Haddow A. Watkinson J. M. and Paterson E. Influence of synthetic oestrogens upon advanced malignant disease. *Brit M J* 2 393-408 1944
- 224 Ellis F. et al. Discussion on advanced cases of carcinoma of breast treated by stilboestrol. *Proc Roy Soc Med* 37 731-736 1944
- 225 Nathanson I. T. Endocrine aspects of human cancer. *Recent Progr Hormone Research* 1 261-291 1947
- 226 Idem. Hormonal alteration of advanced cancer of breast. *S Clin North America* 27 1144-1150 1947
- 227 Herrmann J. B., Adair F. E., and Woodard H. Q. Effect of estrogenic hormone on advanced carcinoma of female breast. *Arch Surg* 54 19, 1947
- 228 Escher G. C., Mellors R. C., Adair F. E., and Farrow J. H. Study of 50 cases of advanced mammary cancer treated with sex hormones. *Fourth International Cancer Research Congress* St. Louis September 1947. P 101
- 229 Nathanson I. T., Adair F. E., Allen W. M. and Engle E. T. Estrogens and androgens in mammary cancer. *J A M A* 135 987-989 1947
- 230 Lich, R. and Grant O. Use of estrogens in treatment of bladder tumors. *J Urol* 59 682-686 1948
- 231 Gilman A., Goodman L. S., Phillips F. S. and Dougherty T. Unpublished data
- 232 Jacobson L. O., et al. Studies on effect of methyl bis (beta-chloroethyl) amine hydrochloride on neoplastic diseases and allied disorders of hemopoietic system. *J A M A* 132 265-271 1946
- 233 Goodman L. S. et al. Nitrogen mustard therapy: use of methyl-bis (beta-chloroethyl) amine hydrochloride and tri (beta-chloroethyl) amine hydrochloride for Hodgkin's disease, lymphosarcoma, leukemia and certain allied and miscellaneous disorders. *J A M A* 132 126-132 1946
- 234 Karnofsky D. A., Craver L. F., Rhoads C. P. and Abels J. C. Evaluation of methyl-bis (beta-chloroethyl) amine hydrochloride and tri (beta-chloroethyl) amine hydrochloride (nitrogen mustards) in treatment of lymphomas, leukemia and allied diseases. In *Approaches to Tumor Chemotherapy* \* Pp 319-346
- 235 Wilkinson J. F. and Fletcher F. Effect of beta-chloroethylamine hydrochlorides in leukemia, Hodgkin's disease and polycythemia vera. *Lancet* 2 540-545 1947
- 236 Rhoads C. P. Nitrogen mustards in treatment of neoplastic disease. Official statement. *J A M A* 131 656-658 1946
- 237 Idem. Report on cooperative study of nitrogen mustard (H's) therapy of neoplastic disease. *Tr A Am Physicians* 60 110-117 1947
- 238 Spurr C. L., Jacobson L. O., Smith T. R., and Barron E. S. G. Clinical application of methyl-bis (beta-chloroethyl) amine hydrochloride to treatment of lymphomas and allied dyscrasias. In *Approaches to Tumor Chemotherapy* \* Pp 306-318
- 239 Jacobson L. O., Spurr C. L., Smith T. R., and Dick, G. F. Radioactive phosphorus (P<sup>32</sup>) and alkylamines (nitrogen mustards) in treatment of neoplastic and allied diseases of hemopoietic system. *M Clin North America* 31 5 18 1947
- 240 Wintrobe M. M., McLennan M. T. and Huguley C. M. Jr. Clinical experiences with nitrogen mustard therapy. In *Approaches to Tumor Chemotherapy* \* Pp 347-357
- 241 Alpert L. K. and Peterson, S. S. Use of nitrogen mustard in treatment of lymphomas. *Bull U S Army M Dept* 7 187-194 1947
- 242 ApThomas M. I. R., and Cullinbaine H. Nitrogen mustards in Hodgkin's disease: report on 21 cases and 4 of other leukoses. *Lancet* 1 899-901 1947
- 243 Wintrobe M. M., Huguley C. M. Jr., McLennan M. T. and de Carvalho Lima, L. P. Nitrogen mustard as therapeutic agent for Hodgkin's disease, lymphosarcoma and leukemia. *Ann Int Med* 27:529-540 1947
- 244 Henstell H. H., Tober J. N. and Newman B. A. Influence of nitrogen mustard on mycosis fungoides. *Blood* 2 546-577 1947
- 245 Osborne E. D., Jordan J. W., Hoak, F. C. and Pecherier F. J. Nitrogen mustard therapy in cutaneous blastomatous disease. *J A M A* 135 1123-1128 1947
- 246 Faloon W. W., and Gorham L. W. Clinical experience with nitrogen mustard. *New York State J Med* 48 612-616 1948
- 247 Craver L. F. Recent advances in treatment of lymphomas, leukemias and allied disorders. *Bull New York Acad Med* 24 5 25 1948
- 248 Urteaga B. O., Dieguez, J., Zavaleta, A. and Zubiate P. Tratamiento de las leucemias con alquilaminas. I. Leucemias crónicas. II. Leucemias agudas. *Arch peru pat y clin* 1 185-256 and 783-470 1947
- 249 Craver L. F. Nitrogen mustards: clinical use. *Radiology* 50 486-493 1948
- 250 Taffel M. Experiences in treatment of neoplastic disease with nitrogen mustard. *Lab J Biol & Med* 19 971-977 1947
- 251 Hamilton J. G., Soley M. H. and Eichorn K. B. Deposition of radioactive iodine in human thyroid tissue. *Uric California Publ Pharmacol* (no 28) 1 359-367 1940
- 252 Frantz, V. K., Ball R. P., Keston A. S., and Palmer W. W. Thyroid carcinoma with metastases studied with radioactive iodine. *Ann Surg* 119 668-689 1944
- 253 Leiter L., Seidlin S. M., Marinelli L. D. and Banmann E. J. Adenocarcinoma of thyroid with hyperthyroidism and functional metastases studied with thiouracil and radio-iodine. *J Clin Endocrinol* 6 247 261 1946
- 254 Marinelli L. D., Foote F. W., Hill R. F. and Hocker A. F. Retention of radioactive iodine in thyroid carcinomas: histopathologic and radio-autographic studies. *Am J Roentgenol* 58 17-30 1947
- 255 Seidlin S. M., Marinelli L. D., and Oshry E. Radioactive iodine therapy: effect on functioning metastases of adenocarcinoma of thyroid. *J A M A* 132 838-847 1946
- 256 Trunnell J. B., Hocker A. F. and Foote, F. W. Factors involved in experimental therapy of metastatic thyroid cancer with iodine-131. *Fourth International Cancer Research Congress* St. Louis September 1947. P 158
- 257 Rawson R. W., Dohyns B. M., Hill R., and Fluharty R. G. Collection of radioactive iodine by benign and malignant tumors of thyroid. *Fourth International Cancer Research Congress* St. Louis September 1947. P 156
- 258 Fels E. J. Treatment of breast cancer with testosterone propionate. *J Clin Endocrinol* 4 121-125 1944
- 259 Adair F. E. and Herrmann J. B. Use of testosterone propionate in treatment of advanced carcinoma of breast. *Ann Surg* 123 1023-1035 1946
- 260 Herrmann J. B., Adair F. E. and Woodard H. Q. Use of testosterone propionate in treatment of advanced carcinoma of breast. II. Treatment of osseous metastases. *Surgery* 22 101-119 1947
- 261 Adair F. E. Use of male sex hormone in women with breast cancer. *Surg, Gynec & Obst* 84 719-722 1947
- 262 Schwander H. and Marvin H. N. Treatment of carcinoma of human breast with testosterone propionate: report of five cases. *J Clin Endocrinol* 7 423-432 1947
- 263 Herrmann J. B., and Adair F. E. Effect of testosterone propionate on carcinoma of female breast with soft tissue metastases. *J Clin Endocrinol* 6 769-775 1946
- 264 Warren S. Therapeutic use of radioactive phosphorus. *Am J M Sc* 209 701-711 1945
- 265 Reinhard, E. H., Moore C. V., Bierbaum O. S. and Moore S. Radioactive phosphorus as therapeutic agent. Review of literature and analysis of results of treatment of 155 patients with various blood dyscrasias, lymphomas and other malignant neoplastic diseases. *J Lab & Clin Med* 31 107-215 1946
- 266 Hall B. E. and Watkins C. H. Radiophosphorus in treatment of blood dyscrasias. *M Clin North America* 31 810-840 1947
- 267 Idem. Medical use of radioactive isotopes. I. Radioactive isotopes in hematologic disturbances and neoplasms. *Am J M Sc* 213 621-628 1947
- 268 Lawrence, J. H., Dohson R. L., Low-Beer B. V. A. and Brown B. R. Chronic myelogenous leukemia: study of 129 cases in which treatment was with radioactive phosphorus. *J A M A* 136 672-677 1948
- 269 Reinhard E. H. and Womack, A. Treatment of blood dyscrasias, lymphomas and other malignant diseases with radioactive phosphorus: clinical and experimental results. In *Approaches to Tumor Chemotherapy* \* Pp 384-396
- 270 Doan C. A. et al. Radioactive phosphorus P<sup>32</sup>: six year clinical evaluation of internal radiation therapy. *J Lab & Clin Med* 32 945-969 1947
- 271 Erl L. W. Radiophosphorus as treatment of choice in primary polycythemia. *Am J Med* 1 362-366 1946
- 272 Erl L. A. Primary polycythemia: remissions induced by therapy with radiophosphorus. *Blood* 1 202-206, 1946
- 273 Webster J. J. Urethane in leukemia. *J A M A* 135 901-903 1947
- 274 Paterson E., ApThomas I., Haddow A. and Watkinson J. M. Further report on action of urethane in leukemia. In *Approaches to Tumor Chemotherapy* \* Pp 401-415
- 275 Hirschboeck, J. S., Lindert, M. C. F., Chase J. and Calvy T. L. Effects of urethane in treatment of leukemia and metastatic malignant tumors. *J A M A* 136 90-95 1948
- 276 Berman, L. and Axlerod, A. R. Effect of urethane on malignant diseases: hematologic and histologic observations on patients with carcinoma leukemia and related diseases. *Am J Clin Path* 18 104-129 1948
- 277 Goodman M. J. and Lewis H. P. Urethane in leukemia. *J A M A* 132 1105 1946
- 278 Higgins C. Y. S. T. and Jones R., Jr. Inhibitory effects of ethyl carbamate on prostatic cancer. *Science* 106 147 1947
- 279 Forkner C. E. *Leukemia and Allied Disorders* 353 pp. New York, Macmillan 1938

# CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

## Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

TRACY B MALLORY, M D, *Editor*

BENJAMIN CASTLEMAN, M D, *Associate Editor*

EDITH E PARRIS, *Assistant Editor*

### CASE 34341

#### PRESENTATION OF CASE

A forty-eight-year-old hide merchant was admitted to the hospital because of abdominal pain.

The patient developed vague, epigastric discomfort and nausea approximately forty-eight hours previous to admission following the ingestion of food. This subsided soon but recurred each time he ate. Three hours before admission the pain became severe, cramping and localized in the mid-abdomen, and was accompanied by vomiting. At times borborygmus was audible to the patient.

Approximately one year before admission an appendectomy was performed at another hospital. It was said to be a difficult operation and there was a question of the appendix having ruptured. An abscess of the abdominal wall complicated his convalescence. Three months after this the patient began having difficult bowel movements with occasional diarrhea and intermittent lower abdominal pain. A physician at this time noted a firm, tender mass in the right lower quadrant. The stools were not bloody or tarry. For several months before admission the patient had intermittent chills and fever. X-ray studies of the entire gastrointestinal tract six months before entry were reported to be negative. Three and a half years previous to admission the patient had a coronary occlusion. While convalescing from this he had one episode of hematemesis and repeated tarry stools presumed to be due to a peptic ulcer.

Physical examination revealed a pale man in no acute distress. The heart and lungs were normal. The abdomen was tympanitic. In the right lower quadrant a mass extended from beneath the appendectomy scar toward the pubis. It was 8 to 10 cm in diameter, firm, fixed and somewhat tender. There was also diffuse tenderness in the epigastrium. Peristaltic sounds were high-pitched. Bilateral, easily reduced inguinal hernias were present.

The temperature, pulse and respirations were normal. The blood pressure was 125 systolic, 75 diastolic.

The urine had a specific gravity of 1.026 and gave a ++ test for albumin, and the sediment contained frequent hyaline casts and 4 pus cells per high-power field. Examination of the blood disclosed a hemoglobin of 15.5 gm and a white-cell count of 15,100, with 90 per cent neutrophils. A stool specimen was guaiac negative. An electrocardiogram was suggestive of an old posterior myocardial infarct. An x-ray film of the abdomen showed gas scattered throughout the large bowel, and there appeared to be two dilated loops of small bowel in the midabdomen.

The patient was given fluids intravenously, and a Miller-Abbott tube was passed.

An operation was performed on the second hospital day.

#### DIFFERENTIAL DIAGNOSIS

DR HENRY H FAXON Shall we review the x-ray films, Dr Wyman?

DR STANLEY M WYMAN The loops of dilated bowel, apparently small bowel, are seen in the left middle and lower abdomen. I cannot see the gas described in the colon. There is a large collection of gas in the right upper abdomen, the location of which I cannot determine. This shadow may represent ileum but is probably colon, at least there are very few haustral markings. The stomach is seen in the upper midabdomen. There is an absence of any great degree of gas in the right lower abdomen, but there are a number of small collections of gas, the locus of which is not certain, and the appearance is quite atypical. The film taken the next day again shows several loops of gas-containing small bowel that do not appear so widely dilated as those at the last observation. Here again there are small collections of gas in the right lower abdomen in a rather atypical pattern.

DR FAXON Could this gas be free in the peritoneal cavity?

DR WYMAN I do not believe so.

DR FAXON Could the strange patches of gas that you speak of be in the subcutaneous tissue?

DR WYMAN They suggest gas outside the bowel somewhere, and they are quite consistent with what is seen in abscess.

DR FAXON Is there any gas in the rectum?

DR WYMAN No.

DR FAXON Can you see the kidney shadows?

DR WYMAN The left kidney shadow is quite well outlined, the right is less well outlined. Both are normal in size, shape and position.

DR FAXON The case falls into two separate parts: the nature of this chronic mass in the right lower quadrant and the acute episode that precipitated the hospital entry. Apparently, the mass appeared approximately nine months before entry, for he was operated on one year before entry and it was three months later that his doctor discovered a mass in the right lower quadrant. It is rather

surprising that more intensive studies had not been done to determine the correct diagnosis in the intervening months. So far as the mass in the right lower quadrant is concerned, it seems to me that we have to consider two main classifications—a tumor or an inflammatory mass. If a tumor, it may have been of the bowel or retroperitoneal space. In favor of its being a tumor is its long persistence with relatively little change. The age and general appearance of the patient are consistent with a malignant lesion of the right colon or of the bowel, and the law of averages favors its being a neoplasm. I mention this because I think that the burden of proof lies on the person who says that this was not a growth of some kind. Did he have a barium enema?

DR WYMAN: No.

DR FAXON: When one is in doubt a barium enema carries with it little risk and often gives much helpful information. The mass, from the description, seems to be fairly anterior and not to lie deep in the pelvis. X-ray studies should have been repeated even if they were negative six months before. It is notorious and readily admitted that the right colon is the portion of the gastrointestinal tract in which it is especially hard to visualize a malignant growth by x-ray study. The fact that six months before entry the mass was present and the roentgenologists were unable to say if it was an intrinsic lesion of the bowel does not rule out the possibility of its being inherent in the intestine but makes such localization of the lesion most unlikely.

There are a few points against the diagnosis of a malignant growth. In the first place if it had been of the bowel and possibly missed by the earlier x-ray examination, the patient should have shown anemia. Right-sided lesions are notorious for the anemia that they cause. But here we have a case in which examination of the stool was negative and the hemoglobin was 15.5 gm, although this may be accounted for in part by dehydration. We are not told how much he vomited.

The second argument against neoplasm is that within three months after the previous operation a mass was felt for the first time and had grown to a size that was easily palpable by the patient's physician. The description of the difficulties encountered by the surgeon suggest that the first operation very obviously might have been misdirected, and although he took the appendix out it is possible that the essential disease was neither dealt with nor recognized.

It could, of course, have been a retroperitoneal lymphoma, but again I think it is unlikely that the patient would have remained in such apparently good condition over such a long period.

In considering the second possibility, that the mass in the right lower quadrant was inflammatory, it should be pointed out that the symptoms

started as those of irritation of the lower bowel, with diarrhea and difficult bowel movements. The diarrhea and intermittent lower abdominal pain could have been caused by extrinsic pressure or infection on the lower bowel. This antecedent inflammatory process for which the patient had been operated upon would have given cause for the subsequent development of an inflammatory area in the right lower quadrant. We know that pus had been present in a sinus and that the wound had become infected and drained for a considerable period. It is interesting that the wound eventually healed, which would be unlikely with tuberculosis, actinomycosis or a spreading type of infection. He had chills and fever for several months, which again suggest an inflammatory process. The temperature was normal at the time of admission here, but I do not believe that would change our premise that this was an inflammatory mass, which had been present so long and was so completely walled off that he might have evinced his hyperthermia earlier and reached the stage where he had little or no fever. He had an elevated white-cell count, and of even more significance is the fact that the smear showed 90 per cent neutrophils. There is therefore much to suggest that this was an inflammatory lesion. The absence of blood in the stools is consistent with a mass outside the bowel, which I am postulating may well have been inflammatory. However, if it was an inflammatory process of the usual variety, it should not have persisted this long unless either some recurrent cause for the infection existed or a very unusual type of infection such as tuberculosis, actinomycosis, regional ileitis or diverticulitis was present. A foreign body might have been keeping the inflammation going. The patient was rather old for regional ileitis, and although diverticulitis often gives this type of picture it is in the left lower rather than the right lower quadrant. Meckel's diverticulum has little to recommend it as a diagnosis. Volvulus or intussusception would not have lasted this long. A foreign body, left at the previous operation, could quite readily have caused an inflammatory mass of this nature. A fecalith from the ruptured appendix might have persisted for a long time and would have kept an inflammatory reaction going.

I do not believe the mass on the right side was kidney, it seemed too low, and there was not enough wrong with the genitourinary tract to make it seem likely that that was the cause of the lesion. I do not believe the gastric ulcer three years previously was more than an incidental finding of the past, nor do I think that the inguinal hernia or the coronary disease had anything to do with the picture.

Regarding the symptoms that brought him into the hospital, I think that they were typical of small-bowel obstruction, in which there is either a paralytic, inflammatory type of obstruction, such as

# CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

## Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

EDITH E. PARRIS, *Assistant Editor*

### CASE 34341

#### PRESENTATION OF CASE

A forty-eight-year-old hide merchant was admitted to the hospital because of abdominal pain.

The patient developed vague, epigastric discomfort and nausea approximately forty-eight hours previous to admission following the ingestion of food. This subsided soon but recurred each time he ate. Three hours before admission the pain became severe, cramping and localized in the mid-abdomen, and was accompanied by vomiting. At times borborygmus was audible to the patient.

Approximately one year before admission an appendectomy was performed at another hospital. It was said to be a difficult operation and there was a question of the appendix having ruptured. An abscess of the abdominal wall complicated his convalescence. Three months after this the patient began having difficult bowel movements with occasional diarrhea and intermittent lower abdominal pain. A physician at this time noted a firm, tender mass in the right lower quadrant. The stools were not bloody or tarry. For several months before admission the patient had intermittent chills and fever. X-ray studies of the entire gastrointestinal tract six months before entry were reported to be negative. Three and a half years previous to admission the patient had a coronary occlusion. While convalescing from this he had one episode of hematemesis and repeated tarry stools presumed to be due to a peptic ulcer.

Physical examination revealed a pale man in no acute distress. The heart and lungs were normal. The abdomen was tympanitic. In the right lower quadrant a mass extended from beneath the appendectomy scar toward the pubis. It was 8 to 10 cm. in diameter, firm, fixed and somewhat tender. There was also diffuse tenderness in the epigastrium. Peristaltic sounds were high-pitched. Bilateral, easily reduced inguinal hernias were present.

The temperature, pulse and respirations were normal. The blood pressure was 125 systolic, 75 diastolic.

The urine had a specific gravity of 1.026 and gave a ++ test for albumin, and the sediment contained frequent hyaline casts and 4 pus cells per high-power field. Examination of the blood disclosed a hemoglobin of 15.5 gm. and a white-cell count of 15,100, with 90 per cent neutrophils. A stool specimen was guaiac negative. An electrocardiogram was suggestive of an old posterior myocardial infarct. An x-ray film of the abdomen showed gas scattered throughout the large bowel, and there appeared to be two dilated loops of small bowel in the midabdomen.

The patient was given fluids intravenously, and a Miller-Abbott tube was passed.

An operation was performed on the second hospital day.

#### DIFFERENTIAL DIAGNOSIS

DR. HENRY H. FAXON: Shall we review the x-ray films, Dr. Wyman?

DR. STANLEY M. WYMAN: The loops of dilated bowel, apparently small bowel, are seen in the left middle and lower abdomen. I cannot see the gas described in the colon. There is a large collection of gas in the right upper abdomen, the location of which I cannot determine. This shadow may represent ileum but is probably colon; at least there are very few haustral markings. The stomach is seen in the upper midabdomen. There is an absence of any great degree of gas in the right lower abdomen, but there are a number of small collections of gas, the locus of which is not certain, and the appearance is quite atypical. The film taken the next day again shows several loops of gas-containing small bowel that do not appear so widely dilated as those at the last observation. Here again there are small collections of gas in the right lower abdomen in a rather atypical pattern.

DR. FAXON: Could this gas be free in the peritoneal cavity?

DR. WYMAN: I do not believe so.

DR. FAXON: Could the strange patches of gas that you speak of be in the subcutaneous tissue?

DR. WYMAN: They suggest gas outside the bowel somewhere, and they are quite consistent with what is seen in abscess.

DR. FAXON: Is there any gas in the rectum?

DR. WYMAN: No.

DR. FAXON: Can you see the kidney shadows?

DR. WYMAN: The left kidney shadow is quite well outlined, the right is less well outlined. Both are normal in size, shape and position.

DR. FAXON: The case falls into two separate parts: the nature of this chronic mass in the right lower quadrant and the acute episode that precipitated the hospital entry. Apparently, the mass appeared approximately nine months before entry, for he was operated on one year before entry and it was three months later that his doctor discovered a mass in the right lower quadrant. It is rather

surprising that more intensive studies had not been done to determine the correct diagnosis in the intervening months. So far as the mass in the right lower quadrant is concerned, it seems to me that we have to consider two main classifications—a tumor or an inflammatory mass. If a tumor, it may have been of the bowel or retroperitoneal space. In favor of its being a tumor is its long persistence with relatively little change. The age and general appearance of the patient are consistent with a malignant lesion of the right colon or of the bowel, and the law of averages favors its being a neoplasm. I mention this because I think that the burden of proof lies on the person who says that this was not a growth of some kind. Did he have a barium enema?

DR WYMAN: No.

DR FAXON: When one is in doubt a barium enema carries with it little risk and often gives much helpful information. The mass, from the description, seems to be fairly anterior and not to lie deep in the pelvis. X-ray studies should have been repeated even if they were negative six months before. It is notorious and readily admitted that the right colon is the portion of the gastrointestinal tract in which it is especially hard to visualize a malignant growth by x-ray study. The fact that six months before entry the mass was present and the roentgenologists were unable to say if it was an intrinsic lesion of the bowel does not rule out the possibility of its being inherent in the intestine but makes such localization of the lesion most unlikely.

There are a few points against the diagnosis of a malignant growth. In the first place if it had been of the bowel and possibly missed by the earlier x-ray examination, the patient should have shown anemia. Right-sided lesions are notorious for the anemia that they cause. But here we have a case in which examination of the stool was negative and the hemoglobin was 15.5 gm, although this may be accounted for in part by dehydration. We are not told how much he vomited.

The second argument against neoplasm is that within three months after the previous operation a mass was felt for the first time and had grown to a size that was easily palpable by the patient's physician. The description of the difficulties encountered by the surgeon suggest that the first operation very obviously might have been misdirected, and although he took the appendix out it is possible that the essential disease was neither dealt with nor recognized.

It could, of course, have been a retroperitoneal lymphoma, but again I think it is unlikely that the patient would have remained in such apparently good condition over such a long period.

In considering the second possibility, that the mass in the right lower quadrant was inflammatory, it should be pointed out that the symptoms

started as those of irritation of the lower bowel, with diarrhea and difficult bowel movements. The diarrhea and intermittent lower abdominal pain could have been caused by extrinsic pressure or infection on the lower bowel. This antecedent inflammatory process for which the patient had been operated upon would have given cause for the subsequent development of an inflammatory area in the right lower quadrant. We know that pus had been present in a sinus and that the wound had become infected and drained for a considerable period. It is interesting that the wound eventually healed which would be unlikely with tuberculosis, actinomycosis or a spreading type of infection. He had chills and fever for several months, which again suggest an inflammatory process. The temperature was normal at the time of admission here but I do not believe that would change our premise that this was an inflammatory mass, which had been present so long and was so completely walled off that he might have evinced his hyperthermia earlier and reached the stage where he had little or no fever. He had an elevated white-cell count, and of even more significance is the fact that the smear showed 90 per cent neutrophils. There is therefore much to suggest that this was an inflammatory lesion. The absence of blood in the stools is consistent with a mass outside the bowel, which I am postulating may well have been inflammatory. However, if it was an inflammatory process of the usual variety, it should not have persisted this long unless either some recurrent cause for the infection existed or a very unusual type of infection such as tuberculosis, actinomycosis, regional ileitis or diverticulitis was present. A foreign body might have been keeping the inflammation going. The patient was rather old for regional ileitis, and although diverticulitis often gives this type of picture it is in the left lower rather than the right lower quadrant. Meckel's diverticulum has little to recommend it as a diagnosis. Volvulus or intussusception would not have lasted this long. A foreign body, left at the previous operation, could quite readily have caused an inflammatory mass of this nature. A fecalith from the ruptured appendix might have persisted for a long time and would have kept an inflammatory reaction going.

I do not believe the mass on the right side was kidney, it seemed too low, and there was not enough wrong with the genitourinary tract to make it seem likely that that was the cause of the lesion. I do not believe the gastric ulcer three years previously was more than an incidental finding of the past, nor do I think that the inguinal hernia or the coronary disease had anything to do with the picture.

Regarding the symptoms that brought him into the hospital, I think that they were typical of small-bowel obstruction, in which there is either a paralytic, inflammatory type of obstruction, such as

occurs in general peritonitis following ruptured appendix, or a mechanical obstruction. This man had plenty of reason for mechanical obstruction, both by the mass that was present, which might have involved the small intestine, and from the previous peritonitis, which might have left bands that could cause kinking. If this obstruction had been on a paralytic basis, the patient should have been sicker than he was and should have had absent peristalsis, and the abdomen should have been rigid. Furthermore, there should have been some good etiology such as a perforated ulcer, which I think in this case is highly unlikely. I do not believe that he fits the picture of a dynamic ileus. On the other hand, with mechanical obstruction of the small bowel, a patient is not of necessity especially ill until obstruction has gone on for such a long time that there is increased high-pitched peristalsis, persistent vomiting and dilated loops of small bowel by x-ray examination. Although it is tempting to say that this man had small-bowel obstruction, secondary to a neoplasm or a growth of some kind, I shall put down as my diagnosis mechanical small-bowel obstruction secondary to an inflammatory mass in the right lower quadrant caused by and persisting because of a foreign body retained at the first operation.

#### CLINICAL DIAGNOSIS

Inflammatory lesion, region of cecum, due to regional enteritis or foreign body

#### DR FAXON'S DIAGNOSIS

Small-bowel obstruction due to inflammatory mass caused by foreign body

#### ANATOMICAL DIAGNOSES

*Carcinoma of stomach, with peritoneal metastases*  
*Small-bowel obstruction*

#### PATHOLOGICAL DISCUSSION

DR TRACY B MALLORY Dr Claude Welch, who operated on this patient, is operating and unable to get here. He called me on the telephone, however, just before the conference and asked me to say that his preoperative diagnosis was an inflammatory lesion in the region of the cecum due (first choice) to regional enteritis or (second choice) to a retained foreign body. He was forced to operate on the patient without complete study because of the inability to control the intestinal obstruction in any other way.

At operation he found a mass in the region of the cecum, which appeared to be granulomatous and inflammatory. There were also, however, some nodules seen on the peritoneal surface elsewhere. When he explored further he found a large tumor mass in the pyloric portion of the stomach, occupying most of the lesser curvature. He felt reasonably sure from palpation that it was a neo-

plastic lesion in the stomach. He was still inclined to think that the lesion in the region of the cecum was inflammatory. He took a biopsy from that and also from one of the peritoneal nodules, and both showed metastatic carcinoma. He relieved the intestinal obstruction by doing a side-to-side anastomosis between the ileum and the sigmoid, since the lumen of the entire ascending colon was compromised by a mass, whatever it was. Subsequent x-ray examination of the stomach was done. That showed a fairly characteristic picture. Dr Wyman will show the films.

DR WYMAN The film demonstrates fairly well an annular carcinoma involving the distal third of the stomach.

DR FAXON Do you suspect that the bleeding of three years previously was related to the lesion found in the stomach at the time of operation?

DR MALLORY Probably.

Dr Welch has just arrived. We have just finished discussing your case, and Dr Faxon's diagnosis was an inflammatory lesion of the cecum, probably secondary to retained foreign body.

DR CLAUDE E WELCH I am sorry that I missed his discussion. I think that I might answer any questions that may have been raised by the brief summary of a quite confusing case. The things that impressed us before operation were the inflammatory mass in the right lower quadrant and the signs of intestinal obstruction, the history of which was rather chronic. We thought the best way to put the whole story together was on the basis of regional enteritis that had perforated, forming an abscess, first intraperitoneally and then perforating into the abdominal wall. We were not very happy about the diagnosis, but we had to operate on him on that basis.

DR FAXON Have you seen many cases of regional enteritis in this age group?

DR MALLORY It usually occurs in the twenties, although we do see it occasionally in older patients.

DR FAXON As a matter of curiosity, were the x-ray films of the gastrointestinal tract taken six months prior to operation reviewed?

DR WYMAN They have been since, and they appeared to be entirely normal.

#### CASE 34342

#### PRESENTATION OF CASE

A forty-six-year-old man entered the hospital because of hematuria.

The present illness began five weeks before admission with anorexia, nausea and occasional vomiting. At the same time he noted some red spots on his skin. These came and went and were slightly itchy but never tender. Four weeks before admission the urine was noted to be pink, and this sign also fluctuated in degree during the succeeding

period Three weeks before admission the family physician discovered albumin and red cells in the urine No history of other abnormal bleeding could be elicited, and there were no other urinary symptoms There had been some ulcer-like abdominal pain in the past, but this was not a part of the present illness nor were there any chills, fever or severe malaise

The past history disclosed rheumatoid arthritis, which had bothered the patient for eight years prior to admission but had never caused any severe pain or disability Three years before admission a diagnosis of pulmonary tuberculosis was made The disease was treated by thoracoplasty and considered quiescent one year later There was no history of rheumatic fever, scarlet fever or kidney disorders

Physical examination showed a well developed and well nourished man sitting up in bed On the skin there were purplish, nonblanching spots in small clusters and larger ecchymotic spots chiefly over the lower legs The mucous membranes and nailbeds were clear The thoracoplasty wound on the left side was well healed The breath sounds were slightly depressed on the right, but no rales or areas of dullness were made out The heart was normal except for a Grade II basal systolic murmur heard best along the left sternal border The liver edge was felt slightly below the costal margin, otherwise examination of the abdomen was negative Rectal examination was also negative The hands and feet showed slight rheumatoid changes

The temperature, pulse and respirations were within normal limits The blood pressure was 120 systolic, 75 diastolic

Examination of the blood disclosed a hemoglobin of 9.4 gm and a white-cell count of 13,500, with 84 per cent neutrophils The urine showed a specific gravity of 1.008, gave a +++ test for albumin, and the sediment was "loaded" with red cells A stool specimen was guaiac negative Culture of the sputum grew a rare beta-hemolytic streptococcus and abundant colonies of *Neisseria catarrhalis*, a concentration was negative for acid-fast bacilli Culture of the urine grew a few colonies of *Staphylococcus albus* The sedimentation rate was slightly elevated A tourniquet test was negative The nonprotein nitrogen was 136 mg, and the total protein 6.1 gm per 100 cc, with an albumin-globulin ratio of 1.78 The carbon dioxide was 21.3 and the chloride 84 milliequiv per liter The prothrombin time was 20 seconds (normal, 17 seconds) A congo-red test was unsatisfactory X-ray examination of the chest showed the thoracoplasty on the left, fibrosis with emphysematous blebs throughout both lungs and a soft mottling at the left hilus extending inferiorly Retrograde pyelograms showed a faint, irregular calcification overlying the upper third of the left kidney just

above the middle calyx, and constant beading of the ureters

In the hospital the patient's symptoms continued unchanged, and he developed hemoptysis, which gradually increased in severity until considerable respiratory difficulty was produced and clots were raised On auscultation of the lungs numerous rhonchi and moist medium rales were heard throughout, and a chest plate showed extensive mottling in both lung fields On the ninth hospital day his condition deteriorated rapidly, the pulse and respirations rising although the blood pressure remained stable and the temperature was normal He died the same day

#### DIFFERENTIAL DIAGNOSIS

DR REED HARWOOD Let us look at the x-ray films

DR STANLEY M WYMAN This is the old left thoracoplasty involving the upper ribs, and marked collapse of the upper half of the lung field is well demonstrated The diaphragm is low in position, being at the level of the twelfth rib There is fibrosis throughout both lung fields, most marked in the upper portion of the right There is probably a small quantity of fluid or possibly thickened pleura at the right base, and a fine, indefinite mottling in both lung fields, which may represent edema The heart shadow itself is not remarkable The film taken five days later shows this extensive, very pronounced change with a heavy, granular density throughout the central portions of both lung fields, sparing only the bases and the portion under the thoracoplasty The area of calcification in the left kidney is fairly well demonstrated The lesion in this area when injected with dye is seen to be present in the middle and upper calyces The remaining calyces are normal in appearance, and the beading of the ureter is well seen The spleen appears to lie unusually low and is probably enlarged The liver also extends well down and is also probably enlarged The right-kidney calyces and pelvis appear normal, but there are two or three small areas suggesting beading in the ureter

DR HARWOOD Is this picture typical of the kind of pulmonary edema that one often sees in uremia?

DR WYMAN Yes, it appears to be quite consistent

DR HARWOOD What is the significance of the beading of the ureter?

DR WYMAN It is usually thought to mean old infection, such as tuberculosis In keeping with that is the calcification apparently in the kidney parenchyma

DR HARWOOD We are faced with the problem of making a diagnosis of what type of renal disease this patient had What combination will commonly give nitrogen retention and hematuria? Cancer we can satisfactorily exclude Amyloid disease was thought of in this case but I believe

that hematuria is an unusual manifestation of amyloid disease. Prostatic hypertrophy and obstruction can produce hematuria and uremia, but there is no evidence of difficulty in urination in this case and no difficulty in passing the cystoscope. I think that that can be excluded. It is said that at least 10 per cent of patients with pulmonary tuberculosis have lesions in the kidney of greater or less severity. We cannot exclude the presence of tuberculosis in this patient. Indeed, I think it likely that he did have a tuberculous lesion of the left kidney. Hematuria, of course, is a common symptom of this disease, but there is another characteristic of renal tuberculosis—namely, that despite considerable destruction of the renal parenchyma, renal failure is rare. Furthermore, most cases of advanced renal tuberculosis also have tuberculosis in the bladder, which can be readily excluded by cystoscopy in this case, and by the lack of symptoms of cystitis. Pyelonephritis is another condition in which hematuria and albuminuria and nitrogen retention are found. It is distinctly unusual, though, to have blood alone without pus in the urine and very unusual not to have fever and cystitis. I therefore think that pyelonephritis is unlikely. Glomerulonephritis is next to be considered. Of course glomerulonephritis will produce hematuria and nitrogen retention. Casts are also commonly found in glomerulonephritis, but they are not mentioned in the record of the case under discussion. Hypertension, generalized edema and retinal hemorrhages were absent in this case. I do not believe that we can exclude the possibility of glomerulonephritis with terminal uremia, but it is unlikely.

The skin lesions may be an important clue. They suggest to me the possibility of two diseases: Henoch's purpura and periarteritis nodosa. A recent review of Henoch's purpura by Gairdner\* tells us that joint and skin lesions are the commonest manifestations of Henoch's purpura. Most cases also show evidence of renal involvement, and some patients die in renal failure. It is significant that the cases reported all show macroscopic hematuria. The condition usually occurs in young people, although cases have been reported in later life, and it is more common in males than females. Death from renal failure is not uncommon, and it is of interest that the autopsy reports show "glomerular nephritis." The negative tourniquet test in this patient does not exclude the diagnosis of purpura because sometimes the tourniquet test is positive. Possibly against the diagnosis of Henoch's purpura is the total absence of lesions of the gastrointestinal tract. Cases have been reported, however, in which only renal disturbance has been noted.

Periarteritis nodosa can involve any arteries in the body, and it is perfectly possible that the vessels of the kidney and skin were involved in periarteritis nodosa in this case. The absence of eosinophilia is possibly against this diagnosis. I have the feeling that this patient died of a generalized vascular disturbance. As Gairdner points out, the three conditions under discussion—purpura, periarteritis and nephritis—are closely allied in some respects, both pathologically and possibly etiologically. In my diagnosis I place Henoch's purpura as my first choice, periarteritis nodosa as my second, and acute glomerulonephritis as my third.

DR ALFRED KRANES: Are you able to make a diagnosis of Henoch's purpura anatomically?

DR TRACY B. MALLORY: I do not know how to.

DR DONALD S. KING: Would you get that much hemoptysis from pulmonary edema, Dr Harwood?

DR HARWOOD: How much was there?

DR KING: The patient raised clots.

DR JACOB LERMAN: One occasionally sees that much in rheumatic heart disease, but there is no evidence of that here.

DR KING: That is right, but this man had no mitral stenosis. Does hemoptysis occur in purpura?

DR HARWOOD: It must be distinctly unusual. I could find no mention of it in the literature.

DR KING: I cannot remember having seen any. I would almost have to get an infarct into this case to explain the hemoptysis.

DR HARWOOD: I would not go any farther than to say that it was a terminal event.

DR KING: Most of the cases here are that.

DR HARWOOD: I mean that the patient did not die from the hemoptysis.

DR PAUL C. ZAMECNIK: I think it is interesting that the purpura seemed to follow the scratch marks and that the purpuric spots did not fade very quickly. I saw them one day and about two days later they had not changed. The patient seemed to run a strikingly rapid downhill course. He was admitted on the genitourinary service with a question of renal stone. Once that was ruled out he was transferred to the medical service. It is interesting that at the time I saw him the non-protein nitrogen was 100 mg per 100 cc. He was relatively symptom free, and four days later he died. We had the feeling that we were missing something all along, but all we could put our finger on was the renal damage. In the absence of anything else we said it was acute or subacute glomerulonephritis.

DR LERMAN: In the presence of tuberculosis, as this kidney suggests, amyloid disease is always a good bet.

DR HARWOOD: He may have had some, but do you believe that he died from it?

DR LERMAN: No, he might have bled from the tuberculous focus in the lung.

\*Gairdner, D. Schönlein-Henoch syndrome (anaphylactoid purpura). *Quart J Med* 17:95-122, 1948.

DR KING That is what I was wondering about. Old tuberculous lesions with thoracoplasty bleed. However, we have no evidence for it.

DR MALLORY It was strongly considered on the wards to account for the hemoptysis.

#### CLINICAL DIAGNOSES

Pulmonary tuberculosis, with hemorrhage  
Subacute glomerulonephritis

#### DR HARWOOD'S DIAGNOSES

Henoch's purpura  
Periarteritis nodosa?  
Acute glomerulonephritis?  
Uremia  
Pulmonary edema

#### ANATOMICAL DIAGNOSES

*Subacute glomerulonephritis*  
*Pulmonary edema, with massive hemorrhage into lungs*  
*Purpura*  
Pulmonary tuberculosis, healed  
Operation thoracoplasty, left

#### PATHOLOGICAL DISCUSSION

DR MALLORY The striking lesion found at autopsy was in the kidneys. They were considerably enlarged, weighing 510 gm, with a grayish yellow cortex and peppered over with small red spots — a typical picture for subacute glomerulonephritis. That was confirmed microscopically. The only other findings of great interest at autopsy were in the lungs, and they were somewhat difficult to interpret.

The tuberculosis was on the whole very well healed. We found only two or three quite small lesions that showed any degree of activity, but none of them we felt could be responsible for the hemorrhage. On the other hand, the entire right lung and the uncollapsed portion of the left lung were filled with blood. Parts of this were of an almost solid consistence, practically consolidated, other parts were more fluid — a hemorrhagic lung with pulmonary edema.

Microscopical examination showed massive hemorrhage into the alveoli and rather minimal inflammatory reaction. There was some fibrin, some foci of hyaline membrane lining the alveoli and a beginning exudation of polymorphonuclear leukocytes. The inflammatory reaction looked more as if it were a reaction to hemorrhage than if it were primary. I am inclined to interpret this as a form of extremely severe pulmonary edema or

pneumonitis, which we do see from time to time in cases of active nephritis. I have seen it most often in cases of sulfonamide injury to the kidney, but I am quite sure that I have seen it in glomerulonephritis on a number of occasions as well. Whether there actually exists an entity that we call pneumonitis I am not sure. I have been tempted sometimes to think that there might be one. The picture is both grossly and histologically very similar to what is seen in a certain number of cases of acute rheumatic fever and ordinarily called acute rheumatic pneumonitis. I do not believe I can differentiate the two on the microscopical slides.

DR KING There is a hemorrhagic form of pulmonary edema with hemoptysis?

DR MALLORY Yes, one sees it occasionally.

DR KING It is rare.

A PHYSICIAN Were there any casts in the urine?

DR JAMES DAVIS Two urine specimens were searched for casts, but we found none — only red cells.

A PHYSICIAN Were there any lesions in the ureter?

DR MALLORY No.

A PHYSICIAN How are the skin lesions accounted for?

DR MALLORY Purpura is not rare with renal insufficiency. I would assume that that was the cause of it.

DR HARWOOD Gairdner reports a specific pathologic picture in Henoch's purpura as opposed to other kinds of bleeding in the skin, it might be interesting to know what the skin lesions showed histologically.

DR MALLORY The skin lesions were not examined. One frequently discovers that skin lesions that are conspicuous during life are hardly visible by the time of autopsy. Unless our attention is specifically called to them, we are apt to miss them.

DR ZAMECNIK Is there a pathological distinction in the kidneys between acute glomerulonephritis and purpura?

DR MALLORY I think there would be no question about that. I see no reason why one should have active lesions — the crescent formation and so forth — in purpura.

A PHYSICIAN Did the blood pressure go up?

DR MALLORY No, not in the period of observation. Of course that is unusual for glomerulonephritis, I must admit.

A PHYSICIAN Was there any lesion in the spleen?

DR MALLORY No, in the bone-marrow sections the megakaryocytes showed an unusual amount of pyknosis and degenerative change. Otherwise the bone marrow was not normal, it was a little hypoplastic.

# The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established 1828

Official Organ of

THE MASSACHUSETTS MEDICAL SOCIETY  
and  
THE NEW HAMPSHIRE MEDICAL SOCIETY

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND  
PUBLISHED WEEKLY UNDER THE JURISDICTION  
OF THE COMMITTEE ON PUBLICATIONS

Richard M. Smith, M.D., *Chairman*  
James P. O'Hare, M.D. Conrad Wesselhoef, M.D.  
Oliver Cope, M.D. John Fallon, M.D.

Joseph Garland, M.D. *Editor*

Associate Editors

Thomas H. Lanman, M.D. Henry Jackson Jr. M.D. Donald Munro, M.D.

Clara D. Davies, *Executive Editor*  
Robert O'Leary, *Assistant Editor*

Editorial Board

C. Gny Lane, M.D.	Maxwell Finland, M.D.
Henry R. Vieta, M.D.	James M. Faulkner, M.D.
Robert M. Green, M.D.	Carroll B. Larson, M.D.
Dwight O'Hara, M.D.	Francis D. Moore, M.D.
Fletcher H. Colby, M.D.	C. Stuart Welch, M.D.
Robert L. Goodale, M.D.	Vernoo P. Williams, M.D.
Chester M. Jones, M.D.	Benjamin Castleman, M.D.
Harvey R. Morrison, M.D.	Hugh R. Leavell, M.D.

SUBSCRIPTION TERMS: \$7.00 per year in advance, postage paid for the United States (medical students \$4.00 per year). Canada \$8.00 per year (Boston funds). \$9.50 per year for all foreign countries belonging to the Postal Union.

MATERIAL should be received not later than noon on Thursday, three weeks before date of publication.

THE JOURNAL does not hold itself responsible for statements made by any contributor.

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts. Telephone KE 6-2094.

NEW ENGLAND ADVERTISING REPRESENTATIVE: Edwin B. Tyler, 89 State Street, Boston, Massachusetts. Telephone LA 3-5516.

## DOWN EAST DOCTOR

MARY ELLEN CHASE, professor of English at Smith College, is a coast of Maine New Englander, a product of the sturdy traditions and the independence of that particular rock-bound section of the country's shore line. That she should read the Aphorisms of Hippocrates in the original Greek or deliver the address at the annual dinner of the Massachusetts Medical Society is no more unusual than that she should have grown up and left the region of Penobscot Bay to teach English in a leading woman's college. Women of the Maine coast are accustomed to doing a day's work in fair weather or foul.

Professor Chase's recollections of the character and activities of a country doctor a generation

ago will stir nostalgic memories in many who read her address in this issue of the *Journal*, for it deals with a period and a place whose spirit is that of hardihood and self-reliance and personal independence. The smells of harness leather and the grain bin still linger in the nostrils of many of her countrymen who have not yet passed their active years, other ancillary facilities of transportation contributed to the "smell" of the doctor, as Miss Chase so nicely phrased it — the carriage lap robe, sun-cured hay and, at times, that Augean aroma that characterizes certain phases of the nitrogen cycle conspicuously identified with hooved animals. There are frontiers, too, where cold drawn castor oil and sweet spirits of niter are still in daily use, and the onion poultice has been professionally applied within the memory of living man.

The costs of medical care rarely constituted a problem in the country districts a generation ago, — Miss Chase's family spent \$105 for medical care over a period of sixteen years, — and pay was likely to be in "kind" — in labor or lobsters, a load of wood or a barrel of potatoes. The practice of medicine was not entirely a profession, it was a way of life, as farming once was, and a kindly one.

Miss Chase's reminiscences furnish something besides entertainment, they are more than a pleasant interlude in one of memory's lanes. They are a reminder that the medicine of today, if it is to be effective and economical, must be brought to the patient through the medium of one who is both counselor and friend. More and more, as life becomes increasingly complicated and the science of medicine more intricate and more costly it is apparent that the resourceful family doctor must remain as the backbone of the profession. Medicine in its relation to its public and in the service that it can economically deliver will be on firmer ground if the family doctor is encouraged to resume his former pastoral position.

The greater the complexities of medical science and the greater the need for specialization on that account, the greater also is the need of the patient for wise and kindly guidance. If the family practice of medicine should disappear, a great loss would be sustained. Such a loss would also mean that a type of life in which these values were appreciated had gone.

## POLYMYXIN

THE almost universal tendency of streptomycin to give rise to resistant organisms, its significant toxicity and its relatively low activity against many common pathogens have resulted in a very intensive search for new antibiotics to replace streptomycin in the fields in which it has proved its greatest use—namely, against gram-negative bacilli and in tuberculosis. At least one agent, highly active against gram-negative bacilli, has become available and is having some clinical trials. This agent has been obtained in two separate laboratories<sup>1, 2</sup> in this country from several strains of *Bacillus polymyxa* and a very similar if not identical substance was obtained in England<sup>3</sup> from a related organism, *B. aerosporus*. Interestingly enough, the findings in all three laboratories were announced almost simultaneously.

The preparation, named polymyxin by the workers at the American Cyanamide Company and aerosporin by those of the Wellcome Laboratory, has interesting properties.<sup>2, 4-7</sup> It is a basic substance obtainable in the form of crystalline hydrochloride and is water soluble. Its activity is not affected by reactions between pH 2 and 7 and is only slightly affected by blood, serum or other mediums at physiologic ranges. Polymyxin is effective against a number of important gram-negative bacilli including brucella, salmonella, *Haemophilus pertussis*, *Eberthella typhosa* and *Escherichia coli*. It is active in low concentrations more like those of penicillin rather than those of streptomycin within their respective fields. It is not active against gram-positive organisms, fungi or mycobacteria, and most strains of proteus are not inhibited. It is active in mice when given subcutaneously against infections with *Klebsiella pneumoniae*, *H. pertussis*, *Salmonella typhi*, *H. influenzae* and *Brucella bronchiseptica*, and it is also effective against fowl typhoid in chicks. It is not effective orally, but when given by this route, it results in replacement of sensitive by insensitive organisms in the feces.

Polymyxin is relatively nontoxic, but the hydrochloride may produce local irritation, and there is some evidence of a histamine-like contaminant

and possibly renal tubular damage from some preparations except possibly those that are highly purified. Resistant strains are not obtainable by the methods that readily produce streptomycin-resistant organisms, but resistance may be increased in vitro by serial passage, though much more slowly than with streptomycin. No morphologic changes result in the organisms. Polymyxin is equally effective against streptomycin-sensitive and streptomycin-resistant strains, and, contrariwise, streptomycin is equally active against strains made resistant to polymyxin as against their parent strains.

The action of the agent is apparently very rapid and is considered to be bactericidal at least when adequate concentrations are used. It is apparently well absorbed from parenteral routes but seems to have a high renal threshold.

Only one published report of the use of aerosporin in England is available.<sup>8</sup> The agent was used in the treatment of 10 cases of pertussis, and though the author appeared to be enthusiastic about the effects, the results as reported are difficult to interpret and are certainly far from convincing. There was some evidence of renal toxicity, and coexisting urinary-tract infections did not seem to be influenced favorably.\*

Obviously, more data are necessary before evaluation of this compound or of these agents, if they are different. The effectiveness and toxicity in further clinical trials of pure preparations are therefore being awaited. The only other intimation of beneficial effects in a number of infections in human beings is a brief mention of cases of infections due to *Pseudomonas aeruginosa*, *K. pneumoniae*, *H. pertussis* and *B. abortus* in which there was definite evidence of the therapeutic effectiveness of polymyxin.<sup>9</sup>

It is obvious that a better agent than streptomycin is needed in the treatment of infections due to the Friedländer bacillus, salmonella, brucella, pertussis and other gram-negative organisms. It will also be of interest, in view of preliminary indications of the high renal threshold, to know whether this agent is effective in the treatment of urinary-tract infections. The possibility of the development of resistant strains during treatment

\*A preparation called polymyxin B has recently been made available for clinical trials and is alleged by the manufacturer to be free of toxic effects on the kidneys.

# The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established 1828

Official Organ of

THE MASSACHUSETTS MEDICAL SOCIETY  
and  
THE NEW HAMPSHIRE MEDICAL SOCIETY

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND  
PUBLISHED WEEKLY UNDER THE JURISDICTION  
OF THE COMMITTEE ON PUBLICATIONS

Richard M. Smith, M.D., *Chairman*  
James P. O'Hare, M.D.      Conrad Wesselhoeft, M.D.  
Oliver Cope, M.D.      John Fallon, M.D.

Joseph Garland, M.D., *EDITOR*

*ASSOCIATE EDITORS*

Thomas H. Lanman, M.D.      Donald Munro, M.D.  
Henry Jackson Jr., M.D.

Clara D. Davies, *EXECUTIVE EDITOR*  
Robert O'Leary, *ASSISTANT EDITOR*

*EDITORIAL BOARD*

C. Guy Lane, M.D.	Maxwell Finland, M.D.
Henry R. Viets, M.D.	James M. Faulkner, M.D.
Robert M. Green, M.D.	Carroll B. Larson, M.D.
Dwight O'Hara, M.D.	Francis D. Moore, M.D.
Fletcher H. Colby, M.D.	C. Stuart Welch, M.D.
Robert L. Gondale, M.D.	Vernon P. Williams, M.D.
Chester M. Jones, M.D.	Benjamin Castleman, M.D.
Harvey R. Morrison, M.D.	Hugh R. Leavell, M.D.

**SUBSCRIPTION TERMS** \$7.00 per year in advance, postage paid, for the United States (medical students \$4.00 per year) Canada \$8.00 per year (Boston funds) \$9.50 per year for all foreign countries belonging to the Postal Union

**MATERIAL** should be received not later than noon on Thursday three weeks before date of publication

**THE JOURNAL** does not hold itself responsible for statements made by any contributor

**COMMUNICATIONS** should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15 Massachusetts Telephone KE 6 2094

**NEW ENGLAND ADVERTISING REPRESENTATIVE** Edwin B. Tyler, 89 State Street Boston Massachusetts Telephone LA 3-5516

## DOWN EAST DOCTOR

MARY ELLEN CHASE, professor of English at Smith College, is a coast of Maine New Englander, a product of the sturdy traditions and the independence of that particular rock-bound section of the country's shore line. That she should read the Aphorisms of Hippocrates in the original Greek or deliver the address at the annual dinner of the Massachusetts Medical Society is no more unusual than that she should have grown up and left the region of Penobscot Bay to teach English in a leading woman's college. Women of the Maine coast are accustomed to doing a day's work in fair weather or foul.

Professor Chase's recollections of the character and activities of a country doctor a generation

ago will stir nostalgic memories in many who read her address in this issue of the *Journal*, for it deals with a period and a place whose spirit is that of hardihood and self-reliance and personal independence. The smells of harness leather and the grain bin still linger in the nostrils of many of her countrymen who have not yet passed their active years, other ancillary facilities of transportation contributed to the "smell" of the doctor, as Miss Chase so nicely phrased it — the carriage lap robe, sun-cured hay and, at times, that Augean aroma that characterizes certain phases of the nitrogen cycle conspicuously identified with hooved animals. There are frontiers, too, where cold drawn castor oil and sweet spirits of niter are still in daily use, and the onion poultice has been professionally applied within the memory of living man.

The costs of medical care rarely constituted a problem in the country districts a generation ago, — Miss Chase's family spent \$105 for medical care over a period of sixteen years, — and pay was likely to be in "kind" — in labor or lobsters, a load of wood or a barrel of potatoes. The practice of medicine was not entirely a profession, it was a way of life, as farming once was, and a kindly one.

Miss Chase's reminiscences furnish something besides entertainment, they are more than a pleasant interlude in one of memory's lanes. They are a reminder that the medicine of today, if it is to be effective and economical, must be brought to the patient through the medium of one who is both counselor and friend. More and more, as life becomes increasingly complicated and the science of medicine more intricate and more costly it is apparent that the resourceful family doctor must remain as the backbone of the profession. Medicine in its relation to its public and in the service that it can economically deliver will be on firmer ground if the family doctor is encouraged to resume his former pastoral position.

The greater the complexities of medical science and the greater the need for specialization on that account, the greater also is the need of the patient for wise and kindly guidance. If the family practice of medicine should disappear, a great loss would be sustained. Such a loss would also mean that a type of life in which these values were appreciated had gone.

ens's London did not let their peg legs curtail their activities nor did the brilliant Confederate leader General Ewell reduce his mobility in the Shenandoah Valley on account of his. What a slap in the face for technocracy if all these modern prostheses dressed in new shoes and pants should languish behind the door except on state occasions! On thinking it all over, one finds it hard to escape the somewhat childish thought that a lot of waste motion could be saved simply by not blowing off peoples' arms and legs

### WHO RUNS MAY READ

THE *Lancet*\* comments philosophically on the replies made by twenty-five noted men and women when questioned on the subject What Life Has Taught Me. Each pupil learned a different lesson in this universal schoolroom, for, as Dean Inge pointed out, "life teaches us what we are capable of learning."

Tolerance for others in order to do a good job oneself is the lesson gleaned by one of these receptive students of life, respect for the individual is the text that another has acquired. Defined as a reluctance to inflict humiliation. Another finds logic in an immutable system of education that furnishes neither rewards nor punishments but only consequences.

The editor of *Punch* is pleased at finding that his countrymen value their sense of humor above wisdom, an eminent divine, deriving lessons from illness, "urges the invalid to be patient with doctors, who are amazingly nice when tamed." Still another student at life's bench deplores certain indications that the dweller in cities seems often to have no interest that warms life.

"The bravest of these commentators," the *Lancet* concludes, "have given us the best reading."

\*Annotations. Live to learn. *Lancet* 1 801 1948

### MASSACHUSETTS MEDICAL SOCIETY

#### DEATH

ROSMARIN — Ernest Rosmarin, M.D. of Boston, died on June 29. He was in his sixty-seventh year.

Dr. Rosmarin received his degree from Medizinische Fakultät der Universität, Vienna, in 1906.

A brother survives.

### A HUNDRED YEARS AGO

A bright morning sun on Wednesday last, gave promise of a pleasant meeting of the State Medical Society which was fully realized. Nearly four hundred medical gentlemen dined together at a spacious hall on Hudson Street, instead of Faneuil Hall as previously announced. The entertainment was elegant, and satisfactory we believe to all present. Last year the income to the treasury was \$1551.87 and the outgoes \$1038. About \$200 are now on hand. The permanent fund of the Society, securely invested in January next will amount to \$11,000. A large and respectable committee, consisting of one from each medical district in the State was raised to receive the delegates to the American Medical Association, who will assemble in Boston next year. A motion was made to authorize this committee to draw on the treasury for three hundred dollars. But this was voted down by an overwhelming majority, and a more lastingly mean act was never perpetrated by the Society. How is it possible to show the civilities of the Society or exhibit even a semblance of sincere attention, without the means of doing so? The plea was raised in extenuation that the Society was poor. Yet there is the sum of eleven thousand dollars at interest, which if sunk in Lake Superior Copper Stock, would not have been considered by some of the members so great a loss as that occasioned by this parsimonious act. A spirit of false economy saved the money while it disgraced the institution. Is it credible as was said, that the Massachusetts Medical Society never exhibited more vigor, enterprise and soundness of constitution, than at the present moment? — Through the influence and at the expense of a lodge of Odd Fellows in Boston, the community have been furnished with a printed lecture by Charles E. Buckingham, M.D., on *Circumstances affecting individual and public health*. If the Odd Fellows pass their evening conclaves in listening to instruction like this, it will be at once conceded that they are persons of excellent taste and judgment, who contemplate the sufferings of the afflicted with a view to administering to their relief. The spirited author has an independent manner of giving his opinion, which reminds us of the tense style of his father. Dr. B. is no friend to physic, unless it is positively indicated. After the simple manner of the prophet, he would have all men wash and be clean — breathe fresh air and be well. On the subject of sewerage, which is of immense importance in cities and appreciated in Boston more than in most other cities Dr. Buckingham is particularly emphatic. If the appropriate filth of sewers is suffered to run into the gutters of city streets working its sluggish way, and exhaling, as it goes, a pestiferous stench, the

must also be known before enthusiasm for this agent is engendered

### REFERENCES

- 1 Benedict, R. G. and Langlykke, A. F. Antibiotic activity of *Bacillus polymyxa* *J Bact* 54:24, 1947 (Abstr)
- 2 Stansly, P. G. Shepherd, R. G., and White, H. J. Polymyxin: new chemotherapeutic agent. *Bull. Johns Hopkins Hosp* 81:43-54, 1947
- 3 Ainsworth, G. C., Brown, A. M., and Brownlee, G. 'Aerosporin'—antibiotic produced by *Bacillus aerosporus* Greer. *Nature* 160:263, 1947
- 4 Stansly, P. G., and Schlosser, M. E. Studies on polymyxin: isolation and identification of *Bacillus polymyxa* and differentiation of polymyxin from certain known antibiotics. *J Bact* 54:549-556, 1947
- 5 *Idem*. Studies on polymyxin: agar diffusion method of assay. *J Bact* 54:585-597, 1947
- 6 Stansly, P. G., and Ananenko, N. H. Resistance of polymyxin to some proteolytic enzymes. *Arch. Biochem.* 15:473, 1947
- 7 Brownlee, G., and Bushby, S. R. M. Chemotherapy and pharmacology of aerosporin: selective gram-negative antibiotic. *Lancet* I:127-132, 1948
- 8 Swift, P. N. Treatment of pertussis with aerosporin. *Lancet* I:133-135, 1948
- 9 Schoenbach, E. B., Bryer, M. S., Bliss, E. A., and Long, P. H. Polymyxin: note on experimental and clinical investigations. *J A M A* 136:1096-1098, 1948

### NEW FASHIONS IN WOODEN LEGS

MAN's mechanical ingenuity is a strange and wonderful thing. Not content with devising ever better methods for blowing off human arms and legs, he ceaselessly toils to perfect artificial means of replacing them. When, in the sixteenth century, bombards and hand-cannon came into more effective use on the battlefield, it probably appeared to contemporary observers that scientific progress was entering a deplorable time of inhuman destructiveness. It then took a doctor to turn science into a more humanitarian channel. In 1564 Ambroise Paré published his first account of artificial limbs with joints that worked by springs and ratchets.

As the science of destruction continued to advance, so also did the science of replacing limbs, but to a more modest extent. Ravaton, White, Addison, Wilson, Brunninghausen, Ruhl, Miles, Serre and others did their best to keep Paré's crude inventions abreast of the times. The recent bound forward that civilization has taken in the development of land mines, blockbusters and atomic explosions is now placing an unprecedented strain on humanitarian inventiveness.

It is reassuring to know, however, that the race is not being abandoned. On May 13, 1948, the

armed forces, Veterans Administration and Committee on Artificial Limbs of the National Research Council held a demonstration of the newest prosthetic developments at the National Academy of Sciences in Washington, D. C. Not the least impressive feature of the Government's artificial-limb program is the list of high-powered names and agencies concerned. Though reminiscent of less immediately altruistic activities, such names as Vannevar Bush, Robert Patterson, Northrop Aircraft, Wright-Patterson and Naval Ordnance Laboratory assure at least the degree of scientific competence that was directed toward producing amputees on so large a scale.

The devices now ready for field testing prior to general production and distribution are as far ahead of Paré's as the atomic bomb is ahead of the bow and arrow. "Some involve rather radical principles of design," according to the official report. For example, a prosthesis for above-the-knee amputations incorporates "control of knee flexion by a hydraulic cylinder with unbalanced valve activated by muscle control." "Coordination of knee and ankle motion includes initial knee flexion on heel impact with partial knee extension during the load phase (due to a crossed linkage including the hydraulic cylinder) as well as toe pickup during the swing phase (due to a rod with hydraulic slip joint)." In another, "control of knee flexion is provided by a vane-type hydraulic snubber with valve closed by pressure on rear half of foot regardless of ankle position." Full advantage has been taken of flexible plastics to produce artificial hands of naturalistic appearance whose mechanism permits "fast fanning of fingers until they press the load against the thumb, then engagement of a force multiplier for increased grip" and an "automatic lock with anti-backlash device driven by the single control cable."

There can be no doubt about the technologic triumphs represented by these exhibits. How well they will all serve the needs of their recipients remains to be seen. Apparently, Paré had mental reservations concerning some of his own devices because he included the simple design of a peg leg, as he says, "for poor people." Certainly Long John Silver on Treasure Island and Silas Wegg in Dick-

# NOTICES (Concluded from page 316)

## SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING  
THURSDAY, AUGUST 26

FRIDAY AUGUST 27

\*10-00 a.m.-12-00 m Medical Staff Rounds Peter Bent Brigham Hospital

TUESDAY AUGUST 31

\*12 15-1 15 p.m. Clinico-röntgenological Conference Peter Bent Brigham Hospital

\*1 30-2 30 p.m. Pediatric Round Burnham Memorial Hospital for Children Massachusetts General Hospital

WEDNESDAY SEPTEMBER 1

\*12 00 m.-1 00 p.m. Clinical Conference (Children's Hospital) Amphitheater Peter Bent Brigham Hospital

\*Open to the medical profession

AUGUST 23-26 International Society of Hematology Page 419 issue of March 18

AUGUST 26-28 American Association of Blood Banks Page 420 issue of March 18

SEPTEMBER 7-11 American Congress of Physical Medicine Page 582 issue of April 15

SEPTEMBER 7-11 American Occupational Therapy Association Page xv issue of July 8

SEPTEMBER 9 Some of the Advances in Surgery Dr Frank H Lahey Pentucket Association of Physicians 8 30 p.m. Haverhill

SEPTEMBER 13-15 American Academy of Pediatrics Olympic Hotel Seattle Washington

SEPTEMBER 14 New England Society of Anesthesiologists Page 416

SEPTEMBER 16-18 Vermont State Medical Society Annual Meeting Burlington

SEPTEMBER 20-22 American Hospital Association Page 410 issue of February 26

SEPTEMBER 22 New England Conference of Industrial Physicians and Surgeons Page 244 issue of August 5

SEPTEMBER 29 Mississippi Valley Medical Editors Association Page 170 issue of January 29

OCTOBER 6-9 American Board of Ophthalmology Page 170 issue of January 29

OCTOBER 18-22 American College of Surgeons Page 34 issue of July 1

OCTOBER 27 New England Obstetrical and Gynecological Society Annual Meeting Hotel Somerset, Boston

NOVEMBER 1-3 American Clinical and Climatological Association. Page 582 issue of April 15

NOVEMBER 3 and 4 Annual Meeting of National Committee for Mental Hygiene, Inc. Page 282 issue of August 12

NOVEMBER 8-12 American Public Health Association Page 410 issue of March 18

NOVEMBER 10-13 Association of Military Surgeons of the United States Page 722 issue of May 13

NOVEMBER 20-23 American Academy of Pediatrics Annual Meeting Chalfonte Haddon Hall Hotel Atlantic City New Jersey

DECEMBER 7-9 Southern Surgical Association Annual Meeting Page 245 issue of April 8

DECEMBER 9 and 10 New York State Society of Anesthesiologists Page 34 issue of July 1

FEBRUARY 4 1949 American Board of Obstetrics and Gynecology Inc Page 244 issue of August 5

MARCH 28-APRIL 1 1949 American College of Physicians Page 155 issue of July 22

NOVEMBER 11-17 1949 Third Inter American Congress of Radiology Page 158 issue of July 22

## MEDICAL CORRESPONDENCE COLLEGE

19, WELBECK STREET, LONDON W1 ENGLAND

PROVIDES postal courses of instruction for medical students and practitioners for all medical and dental examinations, including all U.S.A. and Canadian examinations

Special courses for the higher examinations in surgery for the Fellowship examinations

Free guide to medical and dental examinations on application to the Secretary

Please state for which examination you desire preparation Address the Secretary, Medical Correspondence College, 19, Welbeck St. London W1, England

## Washingtonian Hospital

41-43 WALTHAM STREET, BOSTON, MASS

Incorporated 1859

Conditioned Reflex, Psychotherapy, Semi-Hospitalization For Rehabilitation of Male Alcoholics

Treatment of Acute Intoxication and Alcoholic Psychoses Included

Outpatient Clinic and Social-Service Department for Male and Female Patients

JOSEPH THIMANN, M.D., Medical Director

Visiting Psychiatric and Neurologic Staff

Consultants in Medicine, Surgery and the Other Specialties Telephone HA 6-1750

## Valleyhead Hospital

CONCORD, MASSACHUSETTS

For the treatment of psychoneuroses alcoholism, mild mental disorders and chronic diseases Pleasant pastoral setting near historic Concord Accepted modern therapies used Complete occupational and recreational facilities available including outdoor swimming pool and tennis court.

S GAGNON M.D.  
Superintendent

J BUTLER TOMPKINS M.D.  
Director of Clinical Psychiatry

J P THORNTON M.D.  
Consultant in Neuro-psychiatry

IRVING KAUFMAN, M.D.  
Psychiatrist

Post Office, Box 151 Concord Mass Tel Concord 1600

## DELINQUENT ACCOUNTS

COLLECTED

Ethically — Courteously — Efficiently

Experienced Over 15 Years

Monthly Report

Bonded

For particulars call or write

MEDICAL CLEARING BUREAU, Inc  
110 Tremont Street, Boston, Mass  
HU 2-5570

## TWO-WAY PROTECTION

Tablets FERROSATE (Kenmore)  
(Ferrous Sulfate gr 15)

are coated twice to provide a doubly protected Ferrous Sulfate offering these therapeutic advantages

- 1 Inner coating prevents premature oxidation in vivo
- 2 Outer coating increases palatability and aids in preventing tooth discoloration

Write Dept. NS for professional sample Kenmore Pharmacy, Inc.  
500 Commonwealth Ave Boston, Mass U.S.A.

health of no one can remain safe, within the reach of its baneful influence. A new impulse has been given to the great inquiry — how shall apartments be supplied with pure air? No wonder that the victims of pulmonary consumption are multiplied to a fearful extent in New England, where close sleeping apartments, air-tight stoves, and almost air-tight rooms, are considered necessary to everyday comfort. A profound sense of the destruction of life from these and kindred sources, is happily manifesting itself by the public generally, as well as by influential individuals, so that the hope of a better sanitary constitution of society may reasonably be indulged. While thanking Dr Buckingham for this strong argument in favor of reform, the lodge of Odd Fellows are entitled to the gratitude of all who are not odd, for their kind intentions in giving publicity to the discourse — A kind of ring mania is existing in New England. It is enough that a penny paper advertisement declares that Dr Cristy's Galvanic rings are a positive remedy for human maladies and many weak-minded people not only cover their fingers and neck, but their toes, with metallic hoops, which they imagine are charged with extraordinary medical powers. It is certain, however, that Dr Cristy has no right to claim the practice of this nonsense, as his own discovery. It seems that in 1812 *galvanic beads* were all the rage in Boston, promising to accomplish nearly the same blessed results expected to flow from the more recently devised galvanic rings — Another pamphlet on *The Ether Controversy* may soon be expected. Report says that Mr Bowditch, one of the trustees of the Massachusetts General Hospital, is the author. The contest is likely to be perpetuated while the several claimants to the honor of having discovered the value of ether inhalation continue able to write and publish — One of the anomalies of the present day, is the radicalism of practitioners of medicine. The community rings with the whims and caprices of those whose vocation is to interpret the language of nature, and medical schools are as much at variance with each other as individual practitioners. This creates confusion, engenders distrust in the public mind and lessens the confidence in those educated expressly to minister to human maladies. Indeed, there is an elevated class of citizens who countenance quackery in its thousand protean forms, because of the non-agreement of physicians, their radicalism and their want of confidence in the resources of medicine — Extract of dandelion is becoming a new article of domestic manufacture. The dandelion possesses a medicinal value far above the estimate often placed upon it. As a detergent and aperient, and especially as a diuretic, it might well take the place of some other articles in use — The approved modern treatment of acute gout has become well standardized. It should com-

mence with a purgative, which may be a smart one if the patient is robust and plethoric — from ten to twenty grains of jalap, and from three to eight of calomel, followed in from two to five hours with a draught, consisting of equal parts of the infusion of rhubarb and senna, containing a drachm of sulphate of potass, and a scruple of that alkali. After this, a diaphoretic tisane, consisting of one or two drachms of ipecacuanha wine and four drachms of the solution of acetate of ammonia, in a pint and a half of weak tea, is to form the patient's drink. The patient is to eat little or nothing for twenty-four hours. At night, a full dose of Dover's powder may be given. This will relieve pain, secure sleep, promote diaphoresis — each an important object. On the third day, the use of colchicum may be begun. It is efficacious when given simply in doses of from twenty to sixty drops of the wine in four or six ounces of distilled water, along with from five to ten grains of the nitrate of potass. To this, two drachms of the compound spirit of juniper, and a half a drachm of the spirit of nitric ether may be added. Few persons can bear or will require a dose of sixty drops of colchicum wine oftener than twice in the twenty-four hours. Many cannot endure a half or third of that quantity — Extracted from the *Boston Medical and Surgical Journal*, June-July, 1848

R. F.

## NOTICES

### NEW YORK POST-GRADUATE HOSPITAL RESEARCH FELLOWSHIPS IN MEDICINE

Two appointments for research fellows in medicine for studies in the field of metabolic and degenerative diseases are available in the New York Post-Graduate Hospital immediately. Opportunities for ward studies, postgraduate courses and outpatient clinics are included. The salary is \$3000 per annum.

Graduation from Grade A medical school and three years of approved hospital training in medicine and allied fields are required. Male and female applicants are acceptable. Applications should be addressed to Dr John D. Currence, New York Post-Graduate Medical School and Hospital, 303 East 20th Street, New York 3, New York.

### NEW ENGLAND SOCIETY OF ANESTHESIOLOGISTS

A meeting of the New England Society of Anesthesiologists will be held in the auditorium of Building A, Boston University School of Medicine, 80 East Concord Street, Boston, on Tuesday, September 14, at 8 p.m.

A scientific program will be presented by the Boston City Hospital Group.

#### PROGRAM

Symposium on Anesthesia for Thoracic Surgery  
 Variations in Induction for Intubation Dr Sidney C Wiggin  
 Management of Positive Pressure Dr Peter Saunders  
 As the Surgeon Sees Anesthesia for Thoracic Surgery Dr John W. Snieder  
 Control of Cardiac Arrhythmia and Ventricular Fibrillation Dr Dwight E. Harken  
 Physicians and medical students are invited to attend

(Notices concluded on page xiii)

# The New England Journal of Medicine

Copyright 1948 by the Massachusetts Medical Society

Volume 239

AUGUST 26, 1948

Number 9

## USE OF THE VAGINAL SMEAR AS A SCREENING TEST\*

HERBERT L. LOMBARD, M.D.,† MARGARET MIDDLETON, A.B.,‡ SHIELDS WARREN, M.D.,§ AND  
OLIVE GATES, M.D.¶

BOSTON

IN VIEW of the current interest in the vaginal smear and the optimistic hopes aroused by recent accounts of its usefulness, a preliminary report of a study being made by the Massachusetts Department of Public Health to evaluate the method may be helpful in clarifying its present status as a diagnostic test.

The technic for the detection of uterine cancer by means of vaginal secretions was first described by Papanicolaou<sup>1</sup> in 1928. In 1943 Papanicolaou and Traut<sup>2</sup> presented evidence of the value of this method for demonstrating carcinoma both in patients before symptoms had appeared and in those in whom clinical examination and biopsy had failed to reveal the presence of a carcinoma that was extensive enough to produce symptoms. At the same time Meigs and his co-workers<sup>3</sup> reported an original investigation along the same lines, with similar favorable results. In this publication the authors pointed out the possible usefulness of the smear as a routine diagnostic test and suggested that the diagnosis of vaginal smears should be available to all physicians through the Massachusetts Tumor Diagnosis Service.

In spite of general interest arising from these and a number of confirmatory reports by different workers during the past four years, the use of the method has been limited, owing in large part to difficulties of interpretation of smears and the time and training required for competence in diagnosis. The pressure of public demand resulting from recent publicity of the vaginal-smear technic has prematurely forced an answer to the question of its practicability both as a routine diagnostic method and as a screening test. The crux of the

problem rests on the facts that diagnosis of smears requires wide experience and much time and that only in exceptional cases does the smear give information unobtainable by clinical examination and biopsy.

It should not be supposed that an experienced pathologist or cytologist can successfully undertake the interpretation of smears without acquaintance with the manifold variations of the structure of exfoliated cells in cases of pelvic disease and neoplasia. Accuracy of interpretation depends primarily on a familiarity with the aberrations of cells in benign and malignant states. Fortunately, a medical or scientific background is not essential for acquiring this knowledge, which may be obtained by diligence and careful observation correlated with clinical information. It will take from four months to a year to gain proficiency in this type of diagnosis, depending on aptitude and richness of material available for study.

Despite the initial difficulties and expense involved in the diagnosis of smears the method appears to be peculiarly suited for large-scale use. The limiting factor at present is the availability of technical skill. The cost per specimen varies, according to the volume, from \$1.50 to \$5.00. Once the necessary training has been gained, a technician can read between twenty and forty smears a day. The specimen can be obtained by relatively unskilled personnel without discomfort or inconvenience to the patient. If symptomless cancer can be demonstrated in an appreciable number of cases, the vaginal smear is an economical and practical method for use in cancer-detection clinics.

With these considerations in mind, a long-range experimental study financed by the Commonwealth Fund was inaugurated in Massachusetts in January, 1945, by the Department of Public Health to determine whether this test is of sufficient value to warrant its use in the cancer clinics either as a screening test to detect symptomless carcinoma or as a routine diagnostic measure for all gynecologic cases and, secondly, whether it should be offered


\*From the Tumor Diagnosis Service, Massachusetts Department of Public Health.

†Assistant professor of hygiene and public health, Tufts College Dental School, director, Division of Cancer and Other Chronic Diseases and consultant in cancer control, United States Public Health Service.

‡Technician, New England Deaconess Hospital, technician, Tumor Diagnosis Service, Massachusetts Department of Public Health.

§Assistant professor of pathology, Harvard Medical School, pathologist, New England Deaconess and New England Baptist hospitals, director, Division of Biology and Medicine, Atomic Energy Commission.

¶Research associate in pathology, Harvard Medical School, assistant visiting pathologist, Pundville Hospital, pathologist, Tumor Diagnosis Service, Massachusetts Department of Public Health.



This baby's mother learned  
about Mead's Oleum Percomorphum from her physician, not from  
public advertising or displays

*"Servamus Fidem"*

## HOW much sun does the infant really get?

*Not very much* (1) When the baby is bundled to protect against weather or (2) when shaded to protect against glare or (3) when the sun does not shine for days at a time Mead's Oleum Percomorphum is a prophylactic against rickets available 365 $\frac{1}{4}$  days in the year, in measurable potency and in controllable dosage *Use the sun, too*

Mead Johnson & Co , Evansville, Ind., U S A

tory of such symptoms. These 1512 symptomless patients should be representative of apparently well women so far as gynecologic conditions are concerned, and the percentage of positive smears may be considered indicative of what might be expected among such women, barring chance errors.

TABLE 1 *Participation of Different Clinics during Successive Six-Month Periods of Study*

PERIOD	WESTFIELD	PONDVILLE	FALL RIVER	SPRINGFIELD	BOSTON DISPENSARY	LOWELL	BEVERLY	OTHERS*	TOTALS
	NO OF SPECIMENS	NO OF SPECIMENS	NO OF SPECIMENS	NO OF SPECIMENS	NO OF SPECIMENS	NO OF SPECIMENS	NO OF SPECIMENS	NO OF SPECIMENS	
February-June 1945	162	52	72	22	0	2	0	37	347
July-December 1945	370	110	76	72	3	15	24	80	748
January-June 1946	306	327	40	51	50	29	46	99	948
July-December 1946	311	312	44	30	25	21	4	64	809
January-June, 1947	275	254	74	26	21	20	2	64	754
Totals	1422	1055	306	201	97	85	76	344	3586

\*Including specimens from clinics that did not submit thirty smears in any of the five periods

Eight positive smears were found, or 1 positive smear in 189 women without gynecologic symptoms. Of the 8 positive smears 5 were not confirmed by biopsy, although there is a possibility that some or even all of these patients had carcinoma in situ that will be confirmed at a later period. The true picture will probably lie somewhere between 1 in 189 and 1 in 500. Papanicolaou<sup>4</sup> has reported 2 symptomless cases of uterine cancer discovered by means of the vaginal smear among 500 women without gynecologic symptoms. Jones et al.<sup>5</sup> reported 3 cases of carcinoma discovered by the smear in patients without symp-

tom of carcinoma but no biopsies, and 27 furnished no evidence of uterine cancer. If only the patients with positive biopsies are considered, there would be 1 uterine cancer for every 16 women with gynecologic symptoms. The 27 smears diagnosed as positive but unconfirmed from the group of 1364

women with gynecologic symptoms combined with the 5 positive smears from those without a history or symptoms of gynecologic disorders make a total of 32 persons showing positive smears with no apparent uterine cancer at the time of the original smear.

A more detailed account of the smear diagnoses is presented in Table 2. The classifications are based on the diagnoses made on biopsy either at the time of smear or within a few days. On follow-up study it is probable that the classifications will be altered. The time required for final evaluation

TABLE 2 *Preliminary Results of the Cytologic Test for Uterine Cancer (January 1, 1945, to July 1, 1947) \**

EVALUATION OF CASE	POSITIVE SMEARS†		QUESTIONABLE SMEARS		NEGATIVE SMEARS		TOTALS
	NO	PERCENTAGE	NO	PERCENTAGE	NO	PERCENTAGE	
No history or symptoms of gynecologic disorder							
Evidence of uterine cancer (positive biopsy at time of smear)	5	75.0	1	25.0	0	—	4
No evidence of uterine cancer	5	0.5	49	3	1454	96.4	1508
Totals	8		50		1454		1512
Symptoms of gynecologic disorder but no known uterine cancer							
Evidence of uterine cancer (positive biopsy at time of smear)	89	59.5	39	26.0	22	14.7	150
Evidence of uterine cancer (clinical diagnosis at time of smear)	17	50.0	7	20.6	10	29.4	34
No evidence of uterine cancer	27	2.5	104	8.8	1049	88.9	1180
Totals	133		150		1081		1364
Grand total							2876

\*Of the total of 3586 records collected 2876 were used, the remainder consisting of 454 specimens from patients with a history of uterine cancer, 153 specimens that were unsatisfactory and 123 specimens from patients with cancer of organs adjacent to the uterus which might have given false-positive smears.

†The proportions of positive smears were 1/189 in the total 1512 patients with no history or symptoms of gynecologic disorders (1/504 in the group in which the diagnosis was confirmed by biopsy) and 1/103 in the total 1364 patients with symptoms of gynecologic disorders (1/15.5 in the group in which the diagnosis was confirmed by biopsy). Many of these percentages are based on too small numbers to be significant.

toms suggestive of carcinoma from 182 patients examined in a gynecologic endocrine clinic.

Among the 1364 persons who presented gynecologic symptoms at the time of the smear 133 positive smears were obtained — an incidence of 1/10, 89 of these positive smears were confirmed by positive biopsies, 17 had clinical diagnoses of ques-

tion of carcinoma but no biopsies, and 27 furnished no evidence of uterine cancer. If only the patients with positive biopsies are considered, there would be 1 uterine cancer for every 16 women with gynecologic symptoms. The 27 smears diagnosed as positive but unconfirmed from the group of 1364

of a case will vary from a few days to three years. For example, a positive biopsy would confirm a positive smear, but in cases of carcinoma in situ, some time might elapse before a positive biopsy could be obtained to confirm a positive smear. Persons with negative smears, regardless of whether or not symptoms are present, are to be followed for

to all physicians in Massachusetts as another form of tumor diagnostic service. An advisory committee consisting of physicians particularly interested in this diagnostic technic was appointed to assist in planning the project. This committee consisted of Dr Thomas Almy,\* Dr John Fallon, Dr Reginald Fitz, Dr Joe V Meigs, Dr Maurice Fremont-Smith, Dr Edward G Huber,\* Dr Herbert L Lombard and Dr Shields Warren.

The following is an account of the procedure of this investigation and the initial results of two and a half years of study. Although the evaluation will not be completed for at least three years, the data at hand give some indication of what may be expected from the final analysis.

The collection and examination of the smears and the follow-up study of the patients were a joint undertaking of the Massachusetts Department of Public Health, the Tumor Diagnosis Laboratory and the state cancer clinics. All the eighteen Massachusetts cancer clinics took part in the program. Although the majority of the cases examined were from the two state cancer hospitals, Pondville Hospital and Westfield Sanatorium, several of the smaller clinics submitted smears from as high or even a higher proportion of their cases. At the time work began on this study, the vaginal smear was just beginning to be generally known, and it was therefore necessary to acquaint the staffs of the clinics with the method of obtaining secretions and preparation of the smears as well as with the purpose of the study. A prospectus of the study was sent to the physician in charge of each clinic. Personnel from the Tumor Diagnosis Laboratory studied the technic with Dr Papanicolaou and later, on request of the chief of each clinic, gave instructions regarding the making of smears. At the end of the first six months the test had been introduced in all but three of the eighteen state cancer clinics.

The necessary paraphernalia and record forms were supplied by the Tumor Diagnosis Laboratory and the Division of Cancer and Other Chronic Diseases. Pipettes were made at the laboratory and sold at cost to the clinics. Solution bottles for fixation of smears, mailing containers and requisition cards were supplied without charge. Forms for complete data on each case were sent to the follow-up workers of the clinics, who were responsible for filling them out. Each patient examined was given a card explaining that a new test had been performed and that she would be asked to return to the clinic later. A report on each smear was sent out from the laboratory to the clinic within two or three days of receipt of the smears.

The plan of study, which is still in progress, is as follows: obtaining a single smear from each person who attended the cancer clinics between January 1, 1945, and June 30, 1947, obtaining a follow-

up history and, whenever possible, a pelvic examination and a repeat smear at the end of three years after the original smear, and following for a longer period persons with unconfirmed positive smears. In a two-and-a-half-year period a single smear has been examined from each of 3586 women.

The smears were read by one technician. During the first part of the study each smear was examined for twenty minutes unless obvious carcinoma was found in a shorter time. As the number of smears increased, this rule could not be followed. No smear was examined for more than twenty minutes, but it was found that many smears could be adequately surveyed in much less time. Three forms of diagnoses were used: negative, biopsy and curettage indicated, and carcinoma, biopsy and curettage indicated. The smears with atypical, possibly malignant cells as well as many of the positive smears were reviewed by the pathologist. At the outset the pathologist and technician had had rather limited experience, but this lack was compensated for by the unfailing generosity of Dr G N Papanicolaou, who gave freely of his time on several occasions and so resolved many of the difficulties that would otherwise have been a serious hindrance. Also important was the help and encouragement derived from the monthly conferences with Dr Maurice Fremont-Smith, Mrs Ruth Graham and their co-workers at the Vincent Memorial Laboratory, Massachusetts General Hospital. We wish also to acknowledge our indebtedness to Dr J V Meigs, by whom we were first introduced to the method.

To determine how far the interest, familiarity with the method on the part of the staff of the clinics, and skill gained in diagnosis of smears would influence the study, the material is tabulated according to successive six-month periods during the two and a half years of study. The quality of the smears regarding proper spreading, fixation and so forth varied a good deal, especially in the first year. A definite improvement was seen in their preparation as time went on. Only smears that were entirely unreadable were classed as unsatisfactory. Table 1 shows a steady increase in the total number of specimens received during the first year and a half, and a gradual decrease during the second year. All the clinics alike showed the same trend.

Analysis of the records of the 3586 women examined gives the following information. There were 153 smears that were unsatisfactory for diagnosis, 434 from patients known to have a history of a uterine cancer, and 123 from patients with cancers of organs adjacent to the uterus. Among this last group positive smears might be present from extra-uterine sources. Omission of these three groups leaves records of 2876 patients available for study, of whom 1364 reported symptoms suggestive of gynecologic disorders, whereas 1512 gave no his-

\*Deceased

as a screening test, although more economical than other procedures available for detection of the earliest stages of cancer among large groups of apparently well persons, is not likely to bring to light many cases

The rather startling results obtained by the use of the vaginal smear in certain cases must be considered in relation to other factors such as the proved efficiency of the biopsy in disclosing early lesions and the possibility of curing lesions that, though still early, have given rise to symptoms. The early carcinomas with symptoms far outnumber the symptomless cases discovered (Table 4). Among 6265 patients examined by the vaginal smear only 8 symptomless carcinomas were found, but there were an estimated 39 "early" carcinomas that produced symptoms and were diagnosed by a positive biopsy as well as a positive smear. In only 5 cases of carcinoma was the initial biopsy negative while the smear was positive. The recent reports of carcinoma in situ by Fremont-Smith et al<sup>8</sup> and Isbell and his co-workers<sup>9</sup> indicate that most cases of carcinoma in situ present symptoms, although they are not always recognized as suggestive of cancer.

One of the important things the vaginal-smear technic has done has been to enlarge our understanding of symptoms and signs that should be considered as possible evidence of early carcinoma. It is not, we believe, generally appreciated what an impetus to the interest in early carcinoma has resulted from the studies on the application of the vaginal smear carried out by Dr Papanicolaou, Dr Meigs, Dr Fremont-Smith and their associates. In broadening the concept of the medical profession regarding early manifestations of carcinoma, these

workers have performed an unusual service in the field of education.

The technic is more likely to lower cancer mortality because it has made a large number of physicians aware of the insignificance of the signs and symptoms that may be associated with early carcinoma of the uterus than because of the number of early cases it discloses.

### SUMMARY

The present findings indicate that by the cytologic test for cancer it may be possible to find 1 case of uterine cancer among 200 to 500 women free from symptoms. The final evaluation of the technic as a screening test cannot be made until the results of the follow-up study are known three years hence.

Submitted for publication on February 9, 1948

### REFERENCES

- 1 Papanicolaou G N. New cancer diagnosis. In *Proceedings of the Third Race Betterment Conference January 2-6 1925*. 748 pp. Battle Creek, Mich. Race Betterment Foundation 1948. Pp 528-534.
- 2 Papanicolaou G N and Trant, H F. *Diagnosis of Uterine Cancer by the Vaginal Smear*. 47 pp. New York: Commonwealth Fund, 1945.
- 3 Meigs J V, Graham, R. M., Fremont-Smith, M., Kapnick, I., and Rawson R. W. Value of vaginal smear in diagnosis of uterine cancer. *Surg Gynec & Obst* 77:449-461 1947.
- 4 Papanicolaou G N. Vaginal and endometrial smear as diagnostic procedure in cancer of uterus. *New York State J Med* 45:1336-1338 1945.
- 5 Jones C. A., Neustaedter T. and Mackenzie L. L. Value of vaginal smears in diagnosis of early malignancy: preliminary report. *Am J Obst & Gynec* 49:159-168 1945.
- 6 Gates O., and Warren S. *A Handbook for the Diagnosis of Cancer of the Uterus by the Use of Vaginal Smears*. 182 pp. Cambridge, Mass. Harvard University Press 1947.
- 7 Meigs J V, Graham, R. M., Fremont-Smith M., Janzen L. T., and Nelson C. B. Value of vaginal smear in diagnosis of uterine cancer. *Surg., Gynec & Obst* 81:337-345 1945.
- 8 Fremont-Smith M., Graham, R. M. and Meigs J V. Vaginal smears as aid in diagnosis of early carcinoma of cervix. *New Eng J Med* 237:502-504 1947.
- 9 Isbell N. P., Jewett J. F., Allan M. S. and Hertig A. T. Correlation between vaginal smear and tissue diagnosis in 1045 operated gynecologic cases. *Am J Obst & Gynec* 54:576-583 1947.

three years Those with positive smears, not confirmed by biopsy, are to be followed for a longer period

The accuracy of the test depends on two factors, both of which elude strict analysis the adequacy of the smear in representing the state of the genital tract, and the accuracy of interpretation of cells The representative character of the smear has been

suggests that the false-negative diagnosis, or error among cases of cancer, is from five to twenty times more frequent than the false-positive diagnosis, or error among patients without cancer

The smears that were misinterpreted have been reviewed, and almost without exception the error was at once obvious It is undoubtedly true that false-positive diagnoses may be avoided provided

TABLE 3 Comparison of Results in Large Series of Cases Examined by Vaginal Smear

SOURCE	NO. OF CASES	NO. OF SMEARS	PROVED CASES OF CANCER	FALSE POSITIVE DIAGNOSIS		FALSE NEGATIVE DIAGNOSIS		TOTAL ERROR	
				CASES	SMEARS %	CASES	SMEARS %	CASES	SMEARS %
Papanicolaou and Traut <sup>2</sup> (random cases)	3 014	7 000	194	—	—	11	6 0	11	0 3
Meigs et al. <sup>7</sup>	1 015	10 000	154	25	2 9	16	10 3	41	4 0
Gates and Warren <sup>8</sup>	1 300	1 300	81	16	1 3	19	23 0	35	2 5

found by different observers to be reliable in from 80 to 94 per cent of cases <sup>6</sup> The wide range of these findings probably depends on whether a single examination or multiple examinations were used for judging the accuracy of the smear method in the individual case The over-all error of interpretation has been reported as between 0 3 and 4 0 per cent in large series of cases (Table 3)

The method of computation of the percentage of error in general use has been to divide the number of mistakes by the total number of positive or negative cases to determine the false-positive or false-negative error For example, in Table 3 the 23 0 per cent false-negative smears means that among known cancer cases the smear diagnosis was correct in 77 and wrong in 23 per cent It

that only the smear with typical numerous tumor cells is accepted as evidence of carcinoma If this rule is followed, a positive diagnosis will not often be made, and one must rely on suggestive or descriptive reports

In this study smears that showed atypical but not distinctly malignant cells were reported under the heading of biopsy and curettage indicated The smears in this category, 261 in number, included those in which the evidence of a few cells was strongly in favor of carcinoma, and those in which the atypical forms present were not definitely suggestive of cancer but were yet unaccountable This is the most interesting group of the whole series inasmuch as early and premalignant lesions might be expected here if anywhere The answer to the

TABLE 4 The Vaginal Smear as an Ancillary Method for the Demonstration of Early and Obscure Cases of Carcinoma \*

SOURCE	TOTAL CASES	CANCER OF UTERUS	SYMPTOM LESS CASES	POSITIVE SMEAR WITH NEGATIVE BIOPSY	EARLY CANCER OTHER THAN IN SITU	CANCER IN SITU
Papanicolaou and Traut <sup>2</sup>	3 014	180	2	3	9	7
Meigs et al. <sup>7</sup>	1 015	148	—	—	16	3
Papanicolaou <sup>6</sup>	500	2	2	—	—	—
Jones et al. <sup>11</sup>	182	3	3	—	—	—
Gates and Warren <sup>8</sup>	1 554	142	1	2	2	1
Totals	6 265	475	8	5	27	11

\*The total number of cases in which the vaginal smear was of special value cannot be determined inasmuch as it is not certain from the reports which cases were placed in more than one of the categories listed

†These figures do not represent the total cases reported by these authors but only the group among which the unsuspected cases were found

would probably be better to substitute for "false negative" the words "errors in diagnosis among cancer cases," since the present terminology is confusing and may give an erroneous impression Examination of the data in Table 3, in which the results for the first thirteen months of this study are presented along with the large series reported by Papanicolaou and Traut<sup>2</sup> and by Meigs et al.,<sup>3</sup>

question of the practicability of the vaginal smear as a screening test may be decided by the evidence that the follow-up on these cases will bring forward

### DISCUSSION

There is no indication for using the vaginal smear as an adjunct to biopsy in the ordinary case of pelvic disease, and the application of the method

ters" in 3, four diopters in 1, three diopters in 2, two diopters in 1, one or two diopters in 1, and one diopter in 2 Of the eleven patients with brain tumor and choked disk, the elevation was four diopters in 4, three diopters in 2, two diopters in 2, and one diopter in 3

Marked vasoconstriction is the prime characteristic of hypertension with papilledema and might

sol curve, rises in the midzone were quite common both in patients with brain tumor and in those with severe hypertension and papilledema, whereas in patients with severe hypertension without papilledema slight alterations in the midzone occurred but were less notable

One is forced to the conclusion that an intracranial tumor often must be ruled out when severe

TABLE 1 Examination of the Fundi

DIAGNOSIS	NO OF CASES	CASES WITH NO EDEMA OF DISKS	CASES WITH PAPILLEDEMA*	CASES WITH CHOKED DISK†	CASES WITH HEMORRHAGE	CASES WITH EXUDATE
Grade IV (malignant or severe hypertension with papilledema)	30	0	20	10	24	26
Brain tumor	25	8	6	11	6	1
Grade III (severe hypertension without papilledema)	15	15	0	0	3	6

\*Less than 1 diopter  
†1 diopter or more.

be a differential point except that it may also occur with incidental hypertension in patients who have brain tumor Judgment of the degree of arteriolar constriction may be an important factor, since ordinarily the most marked degree of vasoconstriction is found in severe hypertension with neuroretinitis

The findings from lumbar puncture offer guidance but not positive differentiation (Table 2) Increased spinal-fluid pressure may occur in severe hypertension either with or without papilledema The maximum elevation of cerebrospinal-fluid pressure (500 to 700 mm of water) occurred in the patients with brain tumor In the patients with malignant hypertension and papilledema the pressure never exceeded 450 mm of water It is evident that elevation of the cerebrospinal-fluid pressure is not a differential criterion The same statement may be made of the spinal-fluid protein, though from a comparison of these three groups of patients, the higher the spinal-

hypertension with papilledema (Grade IV, "malignant" hypertension) is encountered and that data from lumbar puncture alone, although helpful, are not positively diagnostic Since coincidence of

TABLE 2 Spinal-Fluid Examination

DIAGNOSIS	NO OF CASES	INITIAL PRESSURE		
		300 or more	200-300	100 or less
Grade IV (malignant or severe hypertension with papilledema)	30	11	14	5
Brain tumor	25	18	3	4
Grade III (severe hypertension without papilledema)	15	2	5	8

hypertension and brain tumor may be anticipated statistically, it will be dangerous to ascribe to hypertension abnormalities in fundi or in the cerebrospinal fluid that could be caused by brain tumor

TABLE 3 Total Protein on Spinal-Fluid Examination

DIAGNOSIS	TOTAL PROTEIN			
	100 mg / 100 cc or more	75 to 99 mg / 100 cc	50 to 74 mg / 100 cc	40 mg / 100 cc or less
Grade IV (malignant or severe hypertension with papilledema)	5	4	7	16
Brain tumor	8	7	3	7
Grade III (severe hypertension without papilledema)	1	2	2	10

fluid protein the more likely is brain tumor (Table 3) The patients with hypertension may have a high protein, but it is more likely to be normal than that in patients with brain tumor A slightly elevated protein is occasionally encountered in severe hypertension without papilledema In only 2 of the patients with hypertension and choked disk (more than one diopter) was the nonprotein nitrogen over 40 mg per 100 cc initially In several cases the nonprotein nitrogen rose terminally As for the gold-

Study is not complete without a competent neurologic examination, skull plates, an electroencephalogram and sometimes air-injection studies

CASE REPORTS

CASE 1 In 1935 a 57-year-old woman entered the hospital with a history of known hypertension and exertional angina pectoris of 10 years' duration Failing memory had been noted for 5 months, and she had complained of severe frontal and left-sided headaches and had been stuporous for 9 days For the 12 hours prior to entry there had been vomiting and coma The blood pressure at entry was 180/100 Examination

## SEVERE HYPERTENSION WITH PAPILLEDEMA SIMULATING BRAIN TUMOR\*

## Differential Diagnosis and Treatment

ROBERT STERLING PALMER, M D,† ALBERT F NYSSENS, M D,‡ AND JAMES C WHITE, M D§

BOSTON

ESSENTIAL hypertension is a very common condition, and expanding intracranial lesions are common enough so that coexistence of the two may be anticipated. The symptoms (impairment of vision, headache, nausea, vomiting, convulsions, stupor, unconsciousness and coma), physical findings (papilledema and localizing signs) and spinal-fluid alterations (increased pressure and elevated protein) may occur both in severe hypertension and in brain tumor. Increased intracranial pressure associated with a slowly expanding intracranial lesion is not accompanied by a significant increase in the blood pressure. The presence of an acutely expanding intracranial lesion (from trauma or hemorrhage), which may cause an elevation of the blood pressure, is usually apparent. The differential diagnosis, therefore, is not a mutually exclusive one. The choice is between the severe form of hypertension with papilledema (Grade IV or malignant hypertension) and brain tumor with coexisting hypertension. Actually, in our experience the presence of brain tumor often requires consideration in patients with severe hypertension. Sometimes the suspicion of brain tumor remains in such patients, the possibility persisting in spite of appropriate and detailed investigation. Rarely, brain tumor in association with hypertension has mistakenly been considered severe hypertension with papilledema, and conversely exploratory craniotomy has sometimes been performed because an expanding intracranial lesion could not be excluded positively.

Because of the similarity in symptoms and signs between these two conditions and because patients have been encountered in whom essential hypertension and brain tumor coexisted, we have compared the symptoms, signs and spinal-fluid findings in 30 patients with severe hypertension and papilledema, in 25 patients with proved brain tumor and in 15 patients with severe hypertension but without papilledema. We wish to clarify this important problem.

## DIFFERENTIAL DIAGNOSIS

From a review of our data, striking similarities are apparent. In differentiating severe hypertension

with papilledema and expanding intracranial lesions with coexisting hypertension, the following observations are pertinent.

Severe hypertension with papilledema (Grade IV or "malignant") is most frequent under the age of fifty. Brain tumor is widely distributed at all ages. Severe hypertension without papilledema (Grade III) occurs most frequently at middle life and after, and is a little more common in women than in men. Grade IV or malignant hypertension is more common in men.

Headache appears to be actually more frequent and possibly more severe in the hypertensive cases. Symptoms referable to the heart are naturally more common in patients with hypertension, but would be expected equally in patients with brain tumor and coexisting hypertension. Cerebrovascular accidents are likely to be sudden and progress rapidly either toward improvement or to death, whereas the neurologic changes associated with brain tumor are more likely to be slowly and steadily progressive with or without episodic exacerbations. (*This difference in the course of the symptoms is, as a rule, one of the most important differential points*.) Our patients with hypertension and papilledema were taken for study as they appeared and were not selected because of hypertensive crises or hypertensive encephalopathy. It so happens that only 1 of this series of 30 patients had convulsions and unconsciousness. When hypertensive encephalopathy occurs there may be coma or stupor, with or without convulsions that may be general or unilateral, and with or without paresis. These crises may result in death or in recovery without residual symptoms. In brain tumor the neurologic changes are persistent and progressive. In the 25 patients with brain tumor convulsions occurred in 9, and unconsciousness in 12.

In the appearance of the fundi the character and degree of papilledema, the presence of atrophy and the finding of hemorrhages are not positively differential (Table 1). In one patient with brain tumor and without coexisting hypertension, exudate was found by a competent ophthalmologist. On the other hand, papilledema alone without hemorrhage or exudate occurred in 4 of the patients with hypertension. Unilateral choking with optic atrophy on the opposite side was found in 1 case of malignant hypertension, brain tumor being excluded by autopsy.

Of the 10 patients with hypertension and choked disks, the elevation was recorded as "several diop-

\*From the Medical and Surgical Services and the Committee on Research in Diseases of the Autonomic Nervous System, Massachusetts General Hospital.

This study was supported in part by a grant from the Life Insurance Fund of America and another medical foundation which wishes to remain anonymous.

†Associate physician, Massachusetts General Hospital.

‡Fellow for Commission for Relief in Belgium, Antwerp, Belgium, formerly clinical fellow in medicine, Massachusetts General Hospital.

§Assistant professor of surgery, Harvard Medical School, chief Neurosurgical Service, Massachusetts General Hospital.

evidence of intracranial pressure appeared positive enough to warrant exploration. Craniotomy was done in 2 cases, and the author refers to similar experiences of others. The French school stress this similarity between severe hypertension with papilledema and space-taking intracranial lesions by referring to it as pseudotumoral hypertension<sup>4-8</sup>. From the cases cited the need for combined medical and neurologic study of these problems is obvious. With increasing use of air studies in the preoperative workup of cases in which brain tumor is suspected, which today is the custom in most clinics, errors of the sort reported are not likely to occur. We believe that this procedure should be routine in doubtful cases, especially when convulsive seizures or localizing neurologic signs are present.

#### PROGNOSIS, MORTALITY AND EFFICACY OF SYMPATHECTOMY

The outcome in these 30 cases of the severe form of hypertension justifies the ominous significance usually ascribed to the combination of hypertension and papilledema. The status of 2 patients is not known. Of the remaining 28 patients 3 are known to be alive nine to ten years after hospital study. Of the others 1 survived seven years, and 5 others survived between one and two years after hospital observation. The rest were dead in less than a year.

Four were postoperative deaths: 3 after dorsal sympathectomy and 1 after right nephrectomy for pyonephrosis, actually from bilateral adrenal hemorrhage. Three patients died with cerebral accidents. Congestive heart failure was the chief cause of death in 1 case, a contributory cause of death with uremia in 2 and was associated with cerebral accident in another. Uremia was a cause of death in 8 patients. One patient with adrenal paraganglioma died in a paroxysm of hypertension. One died a respiratory death evidently from a pressure cone, spinal puncture had not been done within two months. Seven patients died away from the hospital, the precise cause being undetermined.

Nine of the patients who died were autopsied, and in 7 of these the brain was examined. Aside from varying degrees of arterial and arteriolar disease, hemorrhage was present in 1 case, infarction in 3, a definite pressure cone in 2 and a questionable pressure cone in a third. In 1 the ventricles of the brain were enlarged to one and a half times their normal size. Hypertrophy of the heart was found in 8 cases, but the heart of the patient who died in a paroxysm of hypertension due to a paraganglioma was not enlarged. Malignant vascular nephritis was diagnosed pathologically in 3 cases and was questioned in 1. Chronic vascular nephritis was diagnosed in 3 cases. Only slight intimal thickening of the renal arterioles was found in the remaining kidney of the patient who died after nephrectomy. The kidneys of the patient with the adrenal paraganglioma were normal.

In this series of 30 patients with hypertension and papilledema, dorsal sympathectomy was performed in 15, and dorsolumbar sympathectomy in 1. Two of these died soon after operation. These deaths were ascribed to the advanced stage of the disease when the patients were operated upon. The third operative death was due to bilateral pneumothorax. Of the remaining 12 in whom dorsal sympathectomy was performed, 6 patients died within a year, and 3 within two years. One survived seven years after operation. Two patients are living ten years after dorsal sympathectomy. In 1 of these the blood pressure was unchanged, but the papilledema of two or three diopters entirely cleared up. In the other, eye grounds and vision became almost normal, but extensive peripheral vascular disease had developed. Another patient, one of the first to have dorsolumbar sympathectomy, is alive nine years after operation, but her precise condition is unknown.

#### DISCUSSION

Is papilledema of whatever degree, even though of less than measurable elevation, an infallible sign of the severe rapidly progressive form of hypertension? The uniformly fatal outcome in this group, except for 4 cases in which sympathectomy was performed, whether the papilledema was more or less than one diopter, certainly suggests that these patients have something in common that is of ominous significance. The foremost sign of this we believe, is edema of the optic disks. When we refer to malignant hypertension clinically, we mean the patients usually under fifty years of age who, with or without a previous known hypertension of milder degree, present severe symptoms of recent onset, commonly with intractable headache and failure of vision, who have a very high diastolic blood pressure and papilledema, and most of whom pursue a rapidly progressive clinical course to death within two years. This does not mean that in every case a pathological diagnosis of malignant nephrosclerosis (necrotizing arteriolitis) will be made at autopsy.

The possibility remains that all the patients with the diagnosis of malignant hypertension do not necessarily have an extremely poor prognosis. Mistakes may be made in patients with severe arteriolar sclerosis with extensive hemorrhages and exudate and in certain patients with marked vasospasm when the accompanying edema may not be so serious. In 1 of the patients surviving ten years after dorsal sympathectomy the presence of pathologic blurring or edema of the disks was somewhat questionable and, if present, may have been due to extensive vasoconstriction, hemorrhages and exudates. The acute onset, severity and apparent rapid progression of his disease indicated malignant hypertension. Individual cases of remission<sup>9</sup> and even prolonged survival<sup>10</sup> after a clinical diagnosis of malignant hypertension are on record, but these are considered exceedingly rare. The correctness

of the fundi showed papilledema of 3 or 4 diopters bilaterally, narrowing and tortuosity of the arterioles, hemorrhages but no exudate. There were no localizing neurologic signs, though the family thought the patient's actions had been peculiar, talk had been senseless, and there may have been drooping of the left eyelid. No difference in the size of the pupils was noted. An attack of severe substernal pain had occurred on the day of admission. Lumbar puncture showed an initial pressure equivalent to 350 mm of water and a total protein of 34 mg per 100 cc. The nonprotein nitrogen was 41 mg per 100 cc. The diagnoses were severe hypertension, with hypertensive encephalopathy and neuroretinitis, and hypertensive and arteriosclerotic heart disease with angina pectoris. Lumbar puncture was performed twice, with apparent improvement in the clinical condition. In the course of a few days rales appeared at the bases. The temperature rose to 104°F, the patient died. At autopsy, an unsuspected glioblastoma multiforme in the left frontal lobe was found, with signs of increased intracranial pressure (flattening of the convolutions), wet lungs, a slightly enlarged heart and coronary sclerosis with healed myocardial infarction.

This patient was rather old to be typical of severe hypertension with neuroretinitis. Her blood pressure, especially the diastolic, was too low to be typical. Concentration on the obvious and severe vascular disease, including disease of the retinal arterioles and the hypertension, and failure to evaluate properly the history and clinical findings misled the observers in this case. Known antecedent severe vascular disease and the recent cerebral symptoms were wrongly taken to be cause and effect. Lumbar puncture was a hazardous and ill considered procedure. This maneuver should not be done in patients with increased intracranial pressure before the needed information to be obtained has been balanced against the risk of inducing a pressure cone.

**CASE 2** A 63-year-old housewife had had variable hypertension for 1 year and 7 months and complained of unsteadiness and of soreness in the neck since a fall 6 months before admission. She stated that her eyes did not respond to her wishes. She was troubled by weakness of the arms and finally by numbness of the right side of the face and tongue with increasing deafness and tinnitus on the right. Blurring of the optic disks was found. Her blood pressure was as high as 200/125 when she was ambulatory and as low as 130/78 at rest. Lumbar puncture revealed an initial pressure equivalent to 150 mm of water, a total protein of 80 mg per 100 cc and a negative spinal-fluid Wassermann test. On exploratory craniotomy an acoustic neuroma in the right cerebellar pontine angle was found and removed. A year later she was known to be alive though still having some difficulty in walking.

The variable though at times very high blood pressure was incidental to the brain tumor, which, in this case, was obvious from the typical history of steadily progressive neurologic change.

**CASE 3** A 45-year-old woman had had hypertension (a blood pressure of 190/130) for 1 year and 3 months and constant headaches of 10 years' duration. On entry to the hospital in 1938 she complained of poor vision in the left eye and intermittent diplopia of 9 months' duration. A few days before admission there had been transient numbness of the lower lip and tongue and left lower arm. Her father and one brother had died suddenly at 65 and 47 years of age respectively. Bilateral choked disks were found (4 diopters on the left and 1 diopter on the right). The retinal arterioles were markedly attenuated. There were no exudates or hemorrhages. Examination of the urine was negative. Renal function was normal. On lumbar puncture the initial pressure was equivalent to 330 mm of water. The spinal-fluid protein was

29 mg per 100 cc. The spinal-fluid Wassermann reaction was negative, as were blood Wassermann and Hinton tests. X-ray films of the skull showed a grossly abnormal sella. A ventriculogram demonstrated both lateral and third ventricles to be displaced to the right. A left temporoparietal craniotomy revealed the brain under moderately increased pressure. The tumor proved to be an aneurysm of the internal carotid artery. Nothing could be done, and the wound was closed.

The gradually enlarging aneurysm in this case may have been primarily responsible for the recent symptoms and the increased intracranial pressure. Nevertheless, it was not possible to exclude with certainty the severe form of hypertension with papilledema. In support of this diagnosis were the headaches and poor vision since the age of thirteen, a known duration of hypertension of one year and three months with a very high diastolic pressure, marked attenuation of the fundus arterioles and age well within the usual range of severe hypertension with papilledema. In favor of a slowly developing intracranial tumor were the constant left-sided headache for several years, progressive failure of vision more marked on the left for several weeks, deformity of the sella and displacement of the lateral and third ventricles to the right.

With the recent increase in interest in and knowledge of intracranial aneurysm the disturbances in ocular movement and trigeminal hypesthesia, together with deformity of the sella, should have suggested the correct diagnosis. Precise interpretation is difficult, but we suspect that this patient may be an example of the coexistence of the severe form of hypertension with papilledema and an expanding intracranial lesion. It is reasonable to suppose that the very severe hypertension hastened the expansion of the aneurysm of the internal carotid artery.

Other observers have found this differential diagnosis interesting and at times difficult, as Cushing and Bordley<sup>1</sup> did forty years ago. Abbott et al.<sup>2</sup> report the case of a female patient aged forty-eight, who had hypertension and complained of weakness of the left hand for several years and who for two years had experienced convulsive seizures with residual paresis of the left arm and leg. In this case there was no papilledema, but the persistent localizing signs and the seizures should have suggested neoplasm with coexisting hypertension. Nevertheless, the patient was treated for the hypertension for over a year. The treatment included bilateral partial adrenalectomy after which there was apparent improvement in the blood-pressure level. Continued convulsive seizures and the persistent localizing signs finally led to skull plates, which showed bony change in the central region. At craniotomy a 150-gm meningioma was removed.

Grant<sup>3</sup> reports 5 cases seen in the course of two years diagnosed as suspected brain tumor because of choked disks, headache and suggestive neurologic signs. Before renal vascular disease was conclusively demonstrated, the neurologic symptoms and

that in certain selected cases in the hands of a competent surgeon, cerebral decompression may be justified in the presence of advanced visual failure. Dereux<sup>17</sup> advocates this procedure in the face of positive evidence of increased cerebrospinal-fluid pressure, progressive symptoms and ineffectiveness of medical measures.

On review of our own experience in the treatment of the hypertensive syndrome of increased intracranial pressure, both medical and surgical, and some of the reported surgical experiences of others, we conclude that cerebral decompression alone is rarely justified. Our reasons are as follows:

Craniotomy is a radical and dangerous procedure that by itself as a rule offers only doubtful and temporary relief in the rapidly progressive course of an almost always rapidly fatal disease.

Venesection drainage of the spinal fluid by lumbar puncture (with caution and only when an intracranial neoplasm has been excluded), hypertonic intravenous infusions and free use of intramuscular or intravenous magnesium sulfate are as often followed by as much relief, or recovery occurs spontaneously.

If improvement does not follow medical treatment, we think that irreversible pathologic change, thrombosis with infarction or hemorrhage of greater or lesser degree — or a combination of all three — is very likely. Craniotomy in this situation in the present state of knowledge and technic is not justified.

Kempner<sup>18</sup> has reported 33 patients "with papilledema, hemorrhage or exudate" who followed the rice diet for a period of at least eight weeks. In 21 cases "the retinopathy improved greatly or even cleared up entirely under the rice regime." The retinal photographs taken before and after treatment leave no doubt about the extraordinary improvement. The Selyes<sup>19</sup> are encouraged by the favorable results in malignant hypertension that follow the long-continued use of a low-sodium, low-protein, low-fat diet with high carbohydrate and large doses of ammonium chloride. Our experience with these regimes is not yet extensive enough for us to comment authoritatively. To date, the only patients with severe hypertension and papilledema whom we have seen definitely helped for considerable periods have been those submitted to sympathectomy. Final judgment of efficacy between the various surgical technics and medical regimes will depend upon the survival time of patients who conform to the clinical criteria for the diagnosis of malignant or Grade IV hypertension.

## SUMMARY

The similarity in symptoms, physical signs and spinal-fluid findings between severe hypertension with papilledema and expanding intracranial lesions is pointed out. A comparison is made of observations in 30 patients with severe hypertension and papilledema, in 25 patients with expanding intracranial lesions and in 15 patients with severe hypertension without papilledema.

The differential diagnosis between severe hypertension with papilledema and an expanding intracranial lesion with coincident hypertension is discussed and illustrated by a report of 3 cases. The most important differential characteristic is the slow, steady progression of neurologic localizing signs in brain tumor. Proper evaluation depends upon expert neurologic examination and sometimes upon supplementary pneumograms.

In our hands extensive sympathectomy has thus far been the measure that has relieved symptoms, reduced the papilledema and stayed the rapid progress to a fatal outcome that is almost uniform in patients with malignant hypertension. It is suggested that denervation of the splanchnic bed abolishes or minimizes the orthostatic pressor responses and thus protects the cerebral circulation.

## REFERENCES

1. Cushing H., and Borden J., Jr. Subtemporal decompression in case of chronic nephritis with uremia with special consideration of neuroretinal lesion. *Am. J. M. Sc.* 136:484-704 1908.
2. Abbott, W. D., Anderson E. W., Van Epps C., and Walker A. E. Hypertension and brain tumor: case report. *Iowa State M. Soc.* 26:303-7, 1916.
3. Grant, F. C. Differential diagnosis of tumor of brain: importance of considering renal hypertension with choked disk. *Arch. Neurol. & Psychiat.* 27:816-827 1932.
4. Moniqueand, G., Savoye J., and Roget, J. Néphrite hypertensive chez un enfant de dix ans avec signes cérébraux pseudo-neoplasiques. *Rev. méd.* 158:327-331 1916.
5. Charvay J. A. Manifestations cérébro-oculaires de l'hypertension artérielle simulant la tumeur cérébrale. *Presse méd.* 44:198 1916.
6. Dereux, J. Sur une forme clinique d'hypertension artérielle: l'hypertension pseudo-tumorale. *Presse méd.* 45:1509-1511 1917.
7. *Idem.* Sur une variété particulière d'hypertension artérielle: la forme de la forme clinique isolée par Puech. *Rev. neurol.* 67:735-740 1917.
8. Riser J., Planques and Barbier P. L'hypertension crânienne chez les hypertendus artériels. *Presse méd.* 47:649-652 1919.
9. Keith N. M., and Wagener H. P. Acute vasospastic hypertension: case with signs of cerebral irritation and severe retinitis with remission. *Am. J. M. Sc.* 190:454-459 1935.
10. Fishberg A. M. *Hypertension and Nephritis*. Fourth edition 779 pp. Philadelphia: Lea & Febiger 1939. P. 515.
11. Keith, N. M., Wagener H. P., and Barker N. W. Some different types of essential hypertension: their course and prognosis. *Am. J. M. Sc.* 197:332-345 1939.
12. Rogers W. F. and Palmer R. S. Essential hypertension: prognosis and comparison of medical and surgical treatments. *Am. Practitioner* 1:459-465 1947.
13. Peet, M. M., and Isberg E. M. Surgical treatment of essential hypertension. *J. A. M. A.* 170:467-473 1946.
14. Palmer R. S. Medical evaluation of surgical treatment of hypertension. *J. A. M. A.* 134:914 1947.
15. Hammarstrom S. Arterial hypertension. *Acta med. Scandinavica* Suppl. 192:1-501 1947.
16. Shelburne, S. A., Blaine D., and O'Hare, J. P. Spinal fluid in hypertension. *J. Clin. Investigation* 11:489-496 1932.
17. Dereux, J. Le traitement chirurgical de l'hypertension artérielle pseudo-tumorale. *Presse méd.* 35:466, 1945.
18. Kempner W. Compensation of renal metabolic dysfunction: treatment of kidney disease and hypertensive vascular disease with diet. *North Carolina M. J.* 6:61-72 and 117 1945.
19. Selye, H., and Selye F. L. Personal communication.

of diagnosis and prognosis is indicated by the fatal outcome in 90 per cent of cases so diagnosed in two years. The efficacy of sympathectomy may be judged by the survival time of patients in whom malignant hypertension was diagnosed clinically who have been sympathectomized, as compared with those not so treated.

Keith, Wagener and Barker<sup>11</sup> reported 146 cases of malignant or Grade VI hypertension, of whom 79 per cent were dead in one year, 88 per cent in two years, 94 per cent in three years, 98 per cent in four years, and 99 per cent in five years. Our experience to date with the medical management of malignant hypertension is in accord.<sup>12</sup> The survival for seven to ten years of 3 out of 15 of our patients in whom dorsal sympathectomy was performed has been noted. Peet and Isberg<sup>13</sup> reported 21 patients (19 per cent) of 112 with malignant hypertension alive five to eleven years after dorsal sympathectomy. It was noted above that 1 of the first patients to have dorsolumbar sympathectomy is living nine years after operation, and it has been reported elsewhere that 5 of 11 patients with malignant hypertension were living three to five years after dorsolumbar sympathectomy.<sup>14</sup> Hammarström,<sup>15</sup> in reporting his experience with 101 hypertensive patients sympathectomized in the past five and a half years, states that of 17 patients with malignant hypertension sympathectomized, the median and mean length of life is definitely greater than that in the control material of Keith and Wagener.<sup>9</sup>

It is admitted that an exceptional case in which sympathectomy was performed may have erroneously been diagnosed as malignant hypertension, and that the patient may therefore have survived longer. It is also possible that the severity of the disease varies in patients who exhibit the clinical features of malignant hypertension, those with less severe disease surviving longer whether or not sympathectomized. Nevertheless, the mortality bears out the diagnosis and prognosis uniformly in the unoperated cases, and the operated cases exhibit the same clinical features. The important fact is that these clinical features are changed in a number of the operated patients. When successful, operation relieves the intractable headache, the papilledema disappears, and the rapid, intense course of the disease is slowed.

That the changes in advanced malignant hypertension may be reversed by sympathectomy is illustrated by the following case report.

A 35-year-old Navy officer, who had been working in the Radiation Laboratory at Massachusetts Institute of Technology, had complained of unusual fatigue for 6 months and headaches for 3 months, followed by blurring of vision and nocturia of 1 month's duration. Ten days prior to admission to the United States Naval Hospital in Chelsea he had suffered a series of convulsions, with amnesia, and had fallen out of bed injuring his forehead. On May 31, 1943, his fundi showed severe papilledema (5 diopters), with much exudate and scars of old hemorrhage. His heart was of normal size, but an electrocardiogram showed hypertensive changes. Neurologic

examination was negative. The urine gave a + test for albumin and contained a maximal concentration to a specific gravity of 1.021, the nonprotein nitrogen was 34.5 mg per 100 cc. An intravenous pyelogram was normal, and phenol sulfonephthalein excretion was satisfactory. Events are best recorded in chronologic order, as follows.

On May 19 the patient had convulsions. The cerebrospinal-fluid pressure was equivalent to 390 mm of water, and the protein was 20 mg per 100 cc.

Two days later the blood-pressure readings were 200/130 (recumbent), 190/140 (sitting) and 200/150 (standing). When the arm was immersed in ice water the blood pressure rose to 300/180.

On June 4, when the patient had had recurrent convulsions for the past 2 days, the fundi showed many recent hemorrhages.

On June 7, thoracolumbar sympathectomy (ninth thoracic to first lumbar segment) was performed by one of us (J.C.W.).

On June 15 the patient complained of more blurring of vision. Vertigo and headache were so intense that he could not get up. The blood pressure was 200/120.

On June 22 left thoracolumbar sympathectomy (eighth thoracic to second lumbar segment) was performed by one of us (J.C.W.). The blood pressure fell to 78/40.

On July 2 the blood pressure was 150/90. The patient noted improvement of vision. His headaches had disappeared, and he was no longer dizzy. He was out of bed and comfortable.

On July 8 the blood-pressure readings were 146/90 (recumbent), 136/90 (sitting) and 130/80 (standing). The cerebrospinal-fluid pressure was equivalent to 220 mm of water.

On August 14 there was remarkable improvement. The patient felt well and was swimming and skipping rope. He was discharged from the hospital on sick leave.

On December 21 the papilledema was gone, and the retinal exudates and hemorrhages had cleared. Vision had returned to normal, but the patient still tired easily and complained of occasional headaches. He had returned to work, and gave the interesting story of how, prior to his cerebral crisis, he had been working on an important problem in radar electronics. He had entirely lost track of this work, but after returning to his desk had soon picked up these ideas from his previous notes.

On August 1, 1944, he was working hard but tired easily. The blood pressure was 168/118, the heart was not enlarged. The urine was normal and the nonprotein nitrogen was 36 mg per 100 cc. The fundi were normal except for narrowed arteries with arteriovenous nicking.

On May 6, 1947 (4 years after sympathectomy), the patient was reviewed by Dr. K. A. Evelyn at the Hypertension Laboratory of the Massachusetts General Hospital. He was then an insurance salesman and doing regular work with only the complaints of slight fatigability and occasional mild headaches. Examination of the fundi revealed normal disks and a few residual scars of the old hemorrhages. There were moderate changes in the caliber of the retinal arteries, slight arteriovenous compression and barely noticeable broadening of the light reflex. An electrocardiogram showed only minimal hypertensive changes. The blood-pressure readings were 170/120 (recumbent), 160/110 (sitting) and 150/115 (standing). The rise on cold-pressor test was to 200/140 as against the preoperative rise to 300/180.

It is evident that the severe cerebral and retinal changes in this case of malignant hypertension were reversed and have remained controlled for four years. Although the patient has had a partial re-elevation of blood pressure to a more moderate hypertensive level and has mild residual symptoms, he has been able to lead a moderately active life and to earn his living.

Direct surgical relief of the hypertensive syndrome of increased intracranial pressure by decompression was suggested by Cushing and Bordley<sup>1</sup> in 1908. Grant<sup>3</sup> performed cerebral decompression in 2 patients and referred to similar experiences of others. Shelburne, Blaine and O'Hare<sup>16</sup> suggested

week. After discharge she attended irregularly for injections, and hence received an average of only one each month for the next year. Because of failure to reach normal blood values she was started on 50 mg of folic acid orally daily on September 9, 1947, and she continued to take this amount until the end of the year. At about Christmas time she developed some numbness and stiffness of the hands, together with difficulty in their use for finer motions. This lasted 4 or 5 weeks and then disappeared completely. From this time she took folic acid irregularly, sometimes averaging one dose of 50 mg every other day, but at other times omitting therapy for periods up to 1 week when her supply of medicine ran out.

Apart from some throbbing in the upper part of the chest she felt well until 1 week before entering the hospital. At that time, while walking in the street, she suddenly experienced a sensation of pressure about the upper abdomen as if she were wearing an elastic girdle, and at the same time her gait became unsteady. These symptoms persisted with some fluctuation in severity. Her legs felt numb from the knees down, and she had to be helped to the hospital by two friends because of the difficulty in walking.

Physical examination showed a pale, well nourished woman with normal findings except on neurologic examination, which revealed gross ataxia with positive Romberg's sign and defective position sense and pinprick perception in the toes. There was absence of vibratory sensation in the lower extremities.

Movements of the ankle, the knees and the fingers. Vibration sense, as tested with a heavy tuning fork (128 double vibrations), was slightly diminished in the middle and index fingers of both hands, absent over the sacrum and spinous processes below the second lumbar segment and only faintly perceived with maximum vibration applied to the iliac crests. Maximum vibration was not perceived in the patellas, tibias, ankles or feet.

On the 3rd hospital day, as a test of sensitivity, the patient was given a single intradermal injection of 0.01 cc. (0.15 U S P units injectable) of a pork liver extract in one forearm. This led to a severe and massive local reaction involving the entire volar aspect of the forearm and lasting 4 or 5 days. There was also a systemic reaction in the form of wheals on the opposite forearm and a choking sensation, relieved by 0.5 cc. of 1:1000 solution of adrenaline hydrochloride.

On the fifth hospital day treatment was started with injections of vitamin B<sub>12</sub>\* in doses of 5 microgm daily for a total of eight injections, the first being given intradermally and the subsequent ones intramuscularly. The intradermal injection was given in 0.2 cc of physiologic saline solution, producing a wheal that reached a maximum size of 2 cm in 30 minutes and subsided entirely in a few hours. No systemic symptoms followed the intradermal or the subsequent intramuscular injections of vitamin B<sub>12</sub>, each of which contained 5 microgm, an amount approximately forty-five times as

TABLE 1 (Continued)

DAY OF THERAPY	POSITION SENSE	PLANTAR REFLEXES		TENDON REFLEXES	NUMBNESS	
		RIGHT	LEFT		HANDS	FEET
1	Absent in toes	Extensor from outer border of foot	Poor flexor (equivocal) from outer border	Greatly increased	Present	Distal to both ankles
6	Absent in toes	Extensor	Flexor	Increased	Absent	Distal to both ankles
10	Absent in toes	Flexor	Flexor	Normal	None	In toes
13	Inaccurate for slight movements of toes only	Flexor	Flexor	Normal	None	In toes
19	Inaccurate for moderate and slight movements of toes	Flexor	Flexor	Increased	None	In toes
23	Inaccurate for very slight movements of toes only	Flexor	Flexor	Normal	None	In great toes only
60	Inaccurate for very slight movements of toes only	Flexor	Flexor	Normal	None	Very slight in right great toe only

The plantar responses were of flexor type. The day after entering the hospital she noticed numbness of the tips of the index and middle fingers, and examination demonstrated hypalgesia at these sites.

Examination of the blood disclosed a red-cell count of 1,920,000, with a hemoglobin of 6.5 gm per 100 cc. (42 per cent), a mean corpuscular volume of 104 cubic microns, a mean corpuscular hemoglobin concentration of 32 per cent and a mean corpuscular hemoglobin of 33 micromicrogm. The reticulocytes were 0.6 per cent, and the white-cell count was 2200.

The patient was placed on a diet free of meat, fish and eggs. Folic acid was discontinued, and no antianemic therapy was given for the first 4 days. On the 4th hospital day she was grossly ataxic in walking, requiring continued support and assistance. When she stood with the eyes open she swayed, and when the eyes were closed she fell backward within 10 seconds. There was no affection of vision, and the optic disks were normal. The hands were used clumsily, but there was no weakness. The tendon jerks in the upper limbs were all very brisk — the right more than the left. The lower limbs were ataxic in heel-shin tests but were not weak. The knee and ankle jerks were very brisk, and the left ankle jerk was more increased than the right. The right plantar response was extensor from the outer border of the foot, and flexor from the inner. Sensation to pinprick was diminished over the two distal phalanges of the fingers of both hands and distal to both ankles. No loss of sensation to cotton wool could be found in any part. The muscles were not tender. Sensation of position was absent in both great toes, but was present for gross

great as that contained in the 0.01 cc. of liver extract tested.

The reticulocytes began to rise on the 4th day of treatment and reached a peak of 16.0 per cent on the 6th day. By this time the patient felt well and displayed an excellent appetite. After 10 days of vitamin B<sub>12</sub> therapy the red-cell count and the hemoglobin had risen to 2,840,000 and 9.0 gm per 100 cc. (58 per cent), respectively.

Remarkable changes in the neurologic disorder were already evident by the 10th day of treatment. The recent numbness of the fingers and clumsiness in using them had vanished by the 4th day. On and after the 6th day of treatment an extensor plantar response was rarely obtained. By the 10th day the patient could walk without support, with only occasional unsteadiness, the tendon reflexes were of normal amplitude, and the plantar responses were both clearly flexor. By the 13th day mild vibration was appreciated in the right patella, and maximum vibration was perceived in the right tibia and left patella.

Beginning on the 9th day after the start of therapy, treatment with vitamin B<sub>12</sub> was discontinued for 7 days because of delay in obtaining a further supply of the material. After the 13th day there was a slight setback in the neurologic improvement, so that by the 19th day there was a reversion of neurologic signs to their status of the 6th and 10th days. This finding was reported by the neurologist without his knowledge of the lapse in treatment.

Treatment was reinstituted on the 16th day in doses of 5 microgm of vitamin B<sub>12</sub> intramuscularly three times a

\*Kindly supplied by Dr. Augustus Gibson of Merck and Company Rahway, New Jersey.

EFFECTIVENESS OF VITAMIN B<sub>12</sub> IN COMBINED SYSTEM DISEASE\*

## Rapid Regression of Neurologic Manifestations and Absence of Allergic Reactions in a Patient Sensitive to Injectable Liver Extracts

LIONEL BERK, M D , P H D ,† DEREK DENNY-BROWN, M D ,‡ MAXWELL FINLAND, M D ,§ AND WILLIAM B CASTLE, M D ¶

BOSTON

IT IS well known that in patients with pernicious anemia, adequate therapy with desiccated stomach, whole liver and liver extracts for oral use, or with crude or refined liver extracts given by injection, will arrest the progress of combined system disease and may bring about a variable amount of recovery of nervous function, depending on the duration and severity of the process.<sup>1</sup> Since in many

A crystalline substance, vitamin B<sub>12</sub>, has recently been isolated from liver extracts<sup>2</sup> and found to produce hematologic remissions in pernicious anemia.<sup>3</sup> An unusual opportunity for testing the effectiveness of vitamin B<sub>12</sub> upon the neurologic disturbance of pernicious anemia presented itself in a patient who had developed acute combined system disease while receiving hemopoietically inadequate doses of

TABLE 1 Results of Vitamin B<sub>12</sub> Therapy\* in a Patient with Combined System Disease and Pernicious Anemia

DAY OF THERAPY	PINPRICK SENSATION		VIBRATION PERCEPTION	ATAXIA	ROMBERG'S SIGN
	FINGERS	FEET			
1	Impaired index and middle fingers	Impaired distal to ankles	Absent at toes ankles tibias patellas and below 2nd lumbar segment	+++	++
6	Normal	Impaired distal to ankles	Absent at toes ankles tibias patellas and below 2nd lumbar segment	+++	++
10	Normal	Impaired in toes	Present in right patella	+	+
13	Normal	Slightly impaired in toes	Present in 3rd lumbar segment, both patellas and right tibia	±	+
19	Normal	Impaired in toes	Absent in left patella both tibias and feet	±	+
23	Normal	Slightly impaired in great toes only	Present in both patellas and both tibias	±	+
60	Normal	Normal	Present in right internal malleolus	None	Negative

\*Therapy consisted of 5 microgm intramuscularly each day for eight days. Treatment was omitted from the ninth through the fifteenth day and resumed (in doses of 5 microgm three times a week) from the sixteenth day onward.

patients the neurologic and hematologic manifestations of pernicious anemia differ strikingly in degree, the possibility exists that these abnormalities are due to deficiency of two different substances, both of which are contained in the therapeutic agents listed above. The frequent development or relapse of neurologic lesions in spite of favorable hematologic response or maintained normal hematologic status in patients with pernicious anemia under treatment with synthetic pteroylglutamic acid,<sup>2</sup> presumably a single pure substance, lends additional support to the possibility that the neurologic and hematologic disorders arise from different deficiencies.

synthetic pteroylglutamic acid. The patient also had an acquired allergic sensitivity to injected liver extracts. It was of additional interest, therefore, to determine the relation of vitamin B<sub>12</sub> to this sensitivity.

## CASE REPORT

A 41-year-old mulatto woman entered the hospital on May 26, 1948, because of ataxia. She had been admitted to the hospital because of anemia 6, 4 and 2 years previously. Histamine-fast achlorhydria was demonstrated repeatedly, and at the first two admissions she showed adequate hematologic and clinical response to the injection of purified liver extracts. After she had received injections of liver extracts derived from pork for 9 months without discomfort, she experienced generalized urticaria and itching after each of two such injections. Relief followed a change of therapy to beef-liver extract. After receiving the latter for 10 months the patient began to react to this substance also. Positive skin tests to both pork and beef extracts were demonstrated, nine different commercial liver preparations being used. Consequently, on the third admission in September, 1946, she was treated intramuscularly with synthetic pteroylglutamic acid (folic acid) in doses of 10 mg daily for 10 days, again with typical hematologic and clinical responses. No neurologic changes were demonstrable at any of the three admissions. Before discharge from the hospital she received four doses of folic acid, 75 mg each intramuscularly at intervals of a

\*From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard) and the Neurological Service, Boston City Hospital and the Departments of Medicine and Neurology, Harvard Medical School.

†Research fellow in medicine, Harvard Medical School and Thorndike Memorial Laboratory.

‡James Jackson Putnam Professor of Neurology, Harvard Medical School, director, Neurological Unit, and neurologist in chief, Neurological Service, Boston City Hospital.

§Associate professor of medicine, Harvard Medical School, chief, Fourth Medical Service and associate physician, Thorndike Memorial Laboratory, Boston City Hospital.

¶Professor of medicine, Harvard Medical School, director, Second and Fourth Medical Services and director, Thorndike Memorial Laboratory, Boston City Hospital.

## CONDITIONED-REFLEX TREATMENT OF CHRONIC ALCOHOLISM

### Results Obtained in 2323 Net Cases from 3125 Admissions Over a Period of Ten and a Half Years

PAUL O'HOLLAREN, M D,\* AND FREDERICK LEMERE, M D†

SEATTLE, WASHINGTON

THE conditioned-reflex treatment of chronic alcoholism, as employed at the Shadel Sanitarium, consists of establishing an aversion to the sight, taste, smell and thought of all types of alcoholic beverages. This is accomplished by repeated conditioning seances, which may number four to eight before the desired aversion is established.

An individual seance consists of the administration of a nauseant drug, emetine, which, acting as the unconditioned stimulus, elicits an unconditioned reflex. Immediately before the onset of nausea a patient is given various types of alcoholic beverages (the conditioned stimulus). After the repetition of several such seances a conditioned-reflex aversion against all types of alcoholic beverages is developed, and the patient has a deep and lasting aversion to the sight, taste and smell of each. Details of technique have been published elsewhere.<sup>1-4</sup>

From the middle of 1935 to the end of 1945 there were 3125 admissions for the treatment of chronic alcoholism. These were unselected cases. No patient was refused treatment except for physical incapacity, psychotic tendencies or obvious insincerity. Patients treated subsequent to 1940 were offered a year's reinforcement program<sup>5</sup>—that is, the initial conditioned reflex was reinforced by periodic single conditioning seances for a year after treatment.

These 3125 cases represented people from all walks of life. Social status ranged from the very rich to the very poor—from the highly trained professional man to the former inmates of state institutions. Practically every type of labor, trade and profession was represented, indicating that alcoholism is no respecter of person, class or intelligence. The ages ranged from twenty to seventy-eight years. The vast majority of the patients, however, fell into the age group from thirty-five to fifty-five. Ninety-three per cent of the patients were men. Indications are, however, that the percentage of women will be higher in the future series. Types of personalities varied from the well adjusted business or professional man to the more severe type of psychoneurotic.

The treatment is a safe procedure if administered by properly trained personnel. There were only 3 deaths that might be associated with the treatment. Of these, one resulted from congestive heart failure, and 2 from coronary occlusion. Its wide applica-

bility is seen in the fact that only 32 patients, or approximately 1.100, were believed unfit physically to take the treatment. The only intellectual requirement was that the patient not be psychotic and that he be sincere in wanting to overcome his problem.

#### ESTABLISHMENT OF NET CASES

Of the 3125 patients admitted during this period, 304 did not complete treatment. Of these 135 refused to accept treatment after sobriety was established, 32 were refused treatment because of physical disabilities such as severe heart disease, advanced arteriosclerosis and perforating ulcer, 31 refused to complete treatment after it was begun, and 13 were refused treatment because of psychotic symptoms or obvious insincerity. The reason for not giving treatment to 86 patients was not shown on the hospital records. There were 7 deaths in this group, 4 were secondary to delirium tremens, and 3 were considered secondary to the treatment. Patients who could not be traced numbered 448. In 50 patients who died before the closing of this survey the cause of death was also classified as "unknown" even though they were sober at the time of death. This was necessary for statistical purposes because it could not be said that they would have remained sober until the close of the survey. There were, therefore, 2323 patients who were treated and whose status was definitely known at the closing date of the survey.

#### RESULTS

The tabulated data showing the percentage of abstinence among the net cases are presented in Figure 1. Continuous and complete abstinence from alcohol in any form, from the time of treatment until the closing date of the survey, was necessary for the patient to be classified as abstinent. Of the 2323 patients treated over the previous ten and a half years 1042, or 44.8 per cent, were found to be abstinent at the close of the survey in 1945. An additional 92 patients were retreated a short time after relapse and remained abstinent, giving an over-all figure of 48.8 per cent for the entire series.

A better understanding of the effects of time on the abstinence ratio can be had if the ten and a half years are divided into twenty-one periods of six months each as shown in Figure 1. From this it can be seen that about 85 per cent will remain abstinent for six months, about 70 per cent will remain abstinent for a year, 60 per cent will remain abstinent for

\*Assistant chief of staff, Shadel Sanitarium.

†Staff psychiatrist, Shadel Sanitarium.

week. By the 21st day further improvement was already appreciable. Vibration sense had been regained in both tibias, as well as in both patellas, and the tendon reflexes had returned to normal. By this time also hypalgesia had become difficult to demonstrate, position sense was remarkably accurate and the gait showed only a slight falter. From then on progress was slower. Sixty days after the beginning of treatment, the patient's gait was natural and she was able to stand with eyes closed without swaying. There was still slight numbness of the right great toe, but not elsewhere. The plantar responses were both clearly flexor, the tendon jerks were of normal amplitude, and there was doubt, if any, disorder of sensation to touch or pinprick. Sense of position was acute in all extremities except for appreciation of very small movements in the right great toe and small movements in the left great toe. Vibration was just appreciated over the internal malleolus on the right side and was readily perceived over both tibias and patellas. The neurologic findings are summarized in Table 1.

On the 24th day the red-cell count had reached 3,380,000, and the hemoglobin 10.2 gm per 100 cc (65 per cent).

### DISCUSSION

In view of the fact that marked anemia was present at the time of the development of the neurologic symptoms, it is difficult to decide whether the neurologic disturbance occurred as a natural event in the history of the disease or whether its development can be attributed to the previous synthetic pteroylglutamic acid therapy. Although the neurologic findings were entirely consistent with the presence of combined system disease, it is possible that the improvement may have been due simply to the cessation of folic acid therapy at the time of entry. Against such an explanation is the progression of the neurologic lesion during the first four days under observation and the rapid and extensive improvement following the initiation of vitamin B<sub>12</sub> therapy on the fifth hospital day. Especially significant is the slight setback during interruption of vitamin B<sub>12</sub> therapy with further recovery after its resumption.

These findings indicate that, as with previous stages in the purification of liver extract, the achievement of a crystalline derivative with intense hemopoietic activity has not diminished the ability of the material to arrest and in part to reverse recent neurologic manifestations of pernicious anemia.<sup>1,5</sup> The dramatic changes in this patient strongly suggest that a deficiency of vitamin B<sub>12</sub> is closely related to the natural origin of both the blood and the nervous changes. They should not be interpreted to

mean that vitamin B<sub>12</sub> was more effective than treatment with liver extract would have been.

It is evident that the neurologic lesion in this patient was in great part reversible, exemplifying the stage of "biochemical lesion" that precedes the structural degeneration of the spinal cord. The experience recorded above emphasizes the well known fact that spinal-cord symptoms of combined system disease constitute a medical emergency. The longer the lesion has existed, the more difficult it is to reverse.

The findings in this case also suggest that allergic sensitivity to liver extract is due not to sensitivity to the active principle itself but to other material in liver extracts, with species specificity, as demonstrated by Bauer and his co-workers.<sup>6</sup>

### SUMMARY AND CONCLUSIONS

In a patient with pernicious anemia in relapse and acute combined system disease that developed during irregular treatment with synthetic pteroylglutamic acid, a hematologic remission and rapid and marked improvement in the neurologic picture followed treatment with crystalline vitamin B<sub>12</sub>. The patient showed severe local and systemic sensitivity reactions to purified liver extracts derived from both pork and beef, but not to vitamin B<sub>12</sub>.

The findings in this patient suggest that vitamin B<sub>12</sub>, like the presently available injectable liver extracts, should prove effective against the neurologic as well as the hematologic manifestations of pernicious anemia. They also suggest that vitamin B<sub>12</sub> is not responsible for sensitivity reactions to liver extracts.

### REFERENCES

1. Bethell F. H. and Sturgis C. C. Relation of therapy in pernicious anemia to changes in nervous system, early, and late results in series of cases observed for periods of not less than ten years and early results of treatment with folic acid. *Blood* 3: 57-67 1948.
2. Ross J. F., Belding H. and Paegel B. L. Development and progression of subacute combined degeneration of spinal cord in patients with pernicious anemia treated with synthetic pteroylglutamic (folic) acid. *Blood* 3: 68-90 1948.
3. Rickes E. L., Brink N. G., Koninszky, F. R., Wood T. R. and Folkers K. Crystalline vitamin B<sub>12</sub>. *Science* 107: 396 1948.
4. West, R. Activity of vitamin B<sub>12</sub> in Addisonian pernicious anemia. *Science* 107: 398 1948.
5. Smith E. L. Purification of anti pernicious anaemia factors from liver. *Nature* 161: 638 1948.
6. Bauer J. L., Watson R. J., Chambliss J. R. and Davidson C. S. Sensitivity to pork liver extract in pernicious anemia: clinical observations on fourteen patients. *New Eng J Med* 236: 622-625 1947.

about 55 per cent will remain abstinent for three years, 40 per cent will remain abstinent for four years, 30 per cent will remain abstinent for seven years, and 25 per cent will remain abstinent up to ten and a half years or longer.

The treatment is of definite benefit both economically and from a social standpoint, even for patients who have relapsed. The relapsed patients remained abstinent for an average of slightly more than eleven months before resuming drinking.

The results obtained prove, beyond all reasonable doubt, the inherent value of this treatment. Adjunct forms of therapy have been used more extensively since this survey has ended. Their ultimate value, however, has as yet not been fully determined.

Factors such as age, occupational stability, marital unhappiness, nervousness, history of recurrent delirium tremens and financial indolence have a definite effect upon the prognosis, either favorable or unfavorable. Further studies of these influences may prove of value in determining the type and extent of treatment necessary in the individual case.

These patients closely represented a cross section of humanity from an occupational and social standard as well as personality types. The wealthy, the middle class, the poor and the gamut of all classifications of character types were amply represented.

It is hoped that the conditioned-reflex will be utilized more widely and combined with other forms of therapy in selected cases since it assists therapists by helping the patient remain abstinent while a program of personality and environmental adjustment is carried out.

#### REFERENCES

- 1 Voegtlin W L. Treatment of alcoholism by establishing conditioned reflex. *Am J M Sc* 199 802-810 1940
- 2 Lemere F and Voegtlin W L. Conditioned reflex therapy of alcoholic addiction: specificity of conditioning against chronic alcoholism. *California & West Med* 53 268 1940
- 3 Lemere F Voegtlin W L. Broz, W R. O'Hollaren P and Tupper W E. Conditioned reflex treatment of chronic alcoholism. VII. Technique. *Dis Nerv System* 3 243-247 1942
- 4 *Idem*. Conditioned reflex treatment of chronic alcoholism. VIII. Review of six years' experience with this treatment of 1526 patients. *J A M A* 120 269 271 1942
- 5 Voegtlin W L. Lemere F. Broz W R. and O'Hollaren P. Conditioned reflex therapy of chronic alcoholism. IV. Preliminary report on value of reinforcement. *Quart J Stud on Alcohol* 2 505 511 1941
- 6 Voegtlin W L. and Broz, W R. Unpublished data
- 7 O'Hollaren P. Pentothal interview in treatment of chronic alcoholism. *California Med* 67 382-385 1947

## MEDICAL PROGRESS

### PREGNANCY TESTS\*

STANLEY L. ROBBINS, M D †

BOSTON

IT IS remarkable that a condition so essentially benign and self-limited as pregnancy, which must inevitably become obvious in the due course of time, has evoked so much interest in its early diagnosis. Despite the fact that in all but possible ectopic pregnancies no great need for speed in diagnosis truly exists, constant emphasis has been attached to the time required for the performance of a pregnancy test. As a result, although the first modern pregnancy test, the Aschheim-Zondek, which was described approximately twenty years ago, has never been surpassed for accuracy, new procedures have appeared each year, designed essentially to cut down the time required for a diagnosis. In addition, the practice of attaching the name of the investigator to each modification of an established test has created so many new tests that intimate knowledge of each is now virtually impossible for any one person. In general, however, the great variety of procedures fall either into one

of several well defined categories, such as biologic assays, chemical assays and skin tests, or into a heterogeneous group, which is composed of such procedures as white-cell counts, biopsy technics and others.

It is the purpose of this paper to review critically the historical development of present-day pregnancy tests and to discuss briefly tests that have gained acceptance by clinical trial as well as those that bear promise for the future. Accepted or new technics now in current use are discussed individually, their *modus operandi* being emphasized. It is perhaps well to state at the outset that no perfect pregnancy test exists and that it is certainly impossible to select any one of the existent procedures described below as best. However, in considering the advantages and disadvantages of each, it is hoped that the specific value of each technic will be better appreciated and its place in pregnancy diagnosis more clearly defined.

#### HISTORICAL REVIEW

From existing translations of Egyptian papyrus it is evident that tests for pregnancy were per-

\*From the Mallory Institute of Pathology, Boston City Hospital.

†Assistant professor of pathology, Boston University School of Medicine; instructor in pathology, Tufts College Medical School; instructor in pathology, Harvard Medical School; assistant pathologist, Mallory Institute of Pathology, Boston City Hospital.

two years, about 55 per cent will remain abstinent for three years, about 40 per cent will remain abstinent for four years, over 30 per cent will remain abstinent up to seven years, and about 25 per cent will remain abstinent up to ten and a half years or longer

While the data pertaining to the results obtained were being compiled a more comprehensive analysis

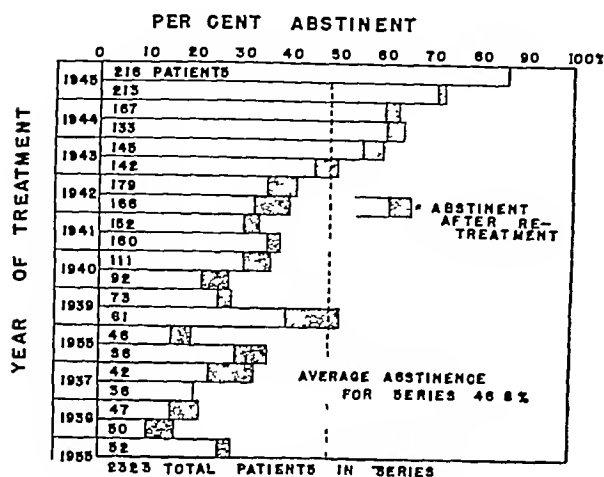


FIGURE 1. *Abstinence (Percentage) for Each Six-Month Period from the Middle of 1935 to the End of 1945*

The number of patients in each group is also shown. The stippled area represents an additional percentage obtained from 92 patients who remained abstinent as a result of retreatment shortly after relapse

of the patients in this series was carried out. A full analysis of these findings will be reported elsewhere.<sup>6</sup> Many salient factors influencing prognosis in the alcoholic patient were brought out by this analysis.

Such factors as marital happiness, occupational success, intelligence, financial security, interest in sobriety clubs, good co-operation and emotional stability were indicative of good prognosis, whereas marked nervousness, even when the patient was sober, a history of recurrent delirium tremens, instability about occupation, financial indolence and alcoholism under thirty years of age indicated a poorer although not a hopeless prognosis.

This group of patients is believed to be one of the largest reported from a single source in the United States. Except for varying amounts of field rehabilitation, conditioned-reflex therapy was the only treatment that these patients received for their alcoholism. In our opinion the gratifying results obtained definitely prove the inherent value of conditioned-reflex therapy in the treatment of this disease. Even in patients who relapsed it was definitely worth while from both an economic and a social standpoint. This is better demonstrated in Table 1.

For example, 94 patients remained totally abstinent for more than 30 months before they relapsed.

Three hundred and twenty-one remained totally abstinent from 6 to 30 months. An average period of 11.2 months of abstinence was obtained in this group of relapsed patients. A total of 9715 man months, or 809 man years, of total abstinence was accomplished among the relapsed patients. Many have since been retreated and are sober but are not included as successful cases.

Another advantage of the conditioned-reflex treatment is the easy manner in which it blends with adjuvant therapies. This is particularly true of psychotherapeutic approaches, such as an interview under pentothal narcosis.<sup>7</sup> In assisting the patient to remain abstinent while a program of environmental and personality adjustment is carried out, conditioning therapy renders a valuable assistance to the psychotherapist. Of significance in the analysis of the relapsed patients is the fact that 30 per cent of the patients admitted had apparently been in need of psychotherapy. This was determined in a study of the "reasons" for relapse among these cases.

Since the close of this survey approximately 2000 additional cases have been treated. Many of these patients have been and are being given adjuvant forms of therapy in addition to the conditioned

TABLE 1. *Period of Abstinence in Patients Who Again Began to Drink after Treatment*

PERIOD OF ABSTINENCE AFTER TREATMENT	No. OF PATIENTS	PATIENT MONTHS*
mo		
Less than 1	97	54
1	54	148
2	74	140
3 to 6	228	1350
7 to 12	139	1341
13 to 18	84	1584
19 to 24	72	1584
25 to 30	26	728
31 to 36	19	627
36 and over	75	>2700
Totals	868	9715†

\*Number of patients multiplied by months of abstinence  
†Or 809 man years

reflex. This includes pentothal narcoanalysis and psychotherapy, intensive physical and social rehabilitation and, in a very few selected depressed cases, shock therapy. It is hoped that this additional therapy and evaluation will improve the prognosis in the alcoholic patients as well as encourage the use of a more comprehensive therapeutic program elsewhere.

#### SUMMARY AND CONCLUSIONS

Statistical evaluation of 2323 net cases treated by conditioned-reflex methods over a period of ten and a half years and data concerning 3125 admissions are presented.

Eighty-five per cent of patients treated by this method will remain abstinent for six months or longer, 70 per cent will remain abstinent for a year, 60 per cent will remain abstinent for two years,

Frech,<sup>34</sup> Sheehan<sup>35</sup> and Hadley<sup>36</sup> have reported that the difficulty in reading the endpoint was considerable and, moreover, that the specificity of the reaction was open to grave doubt, positive reactions having been obtained by the simple addition of sugar to the urine

The colorimetric test of Schmulovitz and Wylie,<sup>37</sup> based on the detection of estrin in the urine, appears also to be of limited value, since according to Pincus<sup>38</sup> it is not reliable in early pregnancy when estrin titers are frequently low

Fairly recently a colorimetric test has been described by Guterman<sup>39</sup> It is based on the observation by Venning and Browne<sup>40</sup> that pregnanediol (an excretion product of the corpus luteum hormone) is excreted in the urine of pregnancy in increasing amounts throughout gestation Too little time has elapsed since the advent of this technique to permit adequate evaluation, however, several reports have appeared suggesting that its accuracy is below that of the Aschheim-Zondek test or its Friedman modification, and, moreover, false-positive tests may occur under conditions of delayed menstrual periods<sup>41, 42</sup> Notwithstanding these reports, this chemical test for pregnancy, free of the encumbrances of the use of animals and based on sound endocrinologic principles merits careful evaluation

Other techniques too numerous to mention have been devised for the laboratory diagnosis of pregnancy None of them have successfully stood the rigid test of clinical trial, and they have therefore never gained any universal acceptance For the sake of completeness alone, perhaps the following few merit mention Prostigmin has been administered in problems of delayed menstruation on the hypothesis that prostigmin "will induce menstruation in a nonpregnant woman and should no menstruation occur, the woman is invariably pregnant."<sup>43</sup> Several skin tests have been advocated, on the assumption that the reactions that develop will serve to differentiate pregnant women from nonpregnant women Placental extract,<sup>44</sup> colostrum<sup>45</sup> and antuitrin-S<sup>46</sup> are some of the most commonly used agents In the placental test the pregnant woman reacts more strongly to the antigen, and in the antuitrin-S and colostrum tests the reverse is true Although these last few tests receive sporadic attention in the literature, it is fairly well agreed that to date they are not totally reliable

From this historical review it is evident that great strides in the diagnosis of pregnancy have been made, however, a test for pregnancy that is 100 per cent accurate and capable of being performed in a test tube within a few minutes has yet to be found

#### FUNDAMENTAL PHYSIOLOGY

Basically all the common pregnancy tests, such as the Aschheim-Zondek, Friedman, rat hyperemia

and frog tests, consist of animal assay methods of detecting the high levels of hormone produced during pregnancy Hence, they rest upon two fundamental facts that during pregnancy there is an increase in either the production or the excretion of these hormones, and that these hormones produced by the human female will effect demonstrable changes in lower animals

Present knowledge of the endocrinology of pregnancy has undergone many changes and much

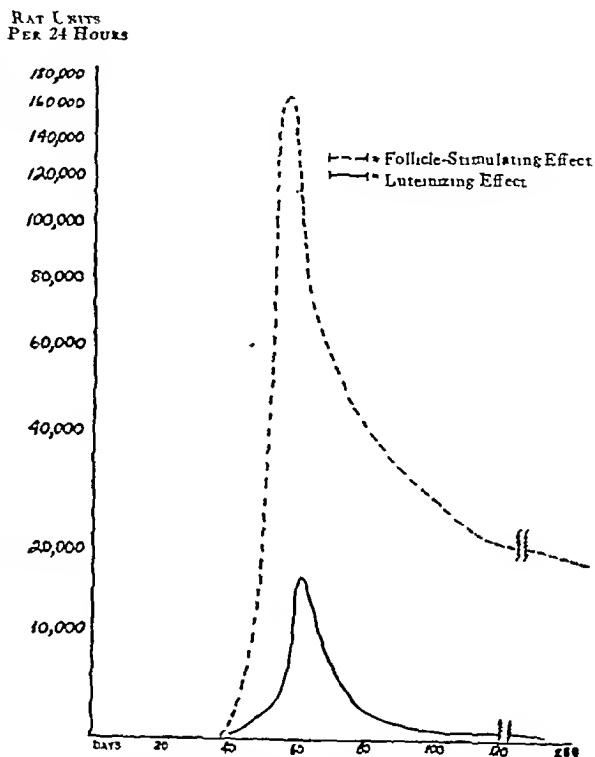


FIGURE 1 Urinary Excretion of Chorionic Gonadotropin during Pregnancy (Assayed on Rats)

development, but at present it is clear that the gonad-stimulating substances demonstrated in the urine of pregnant women by the Aschheim-Zondek test are at least largely of placental origin<sup>47-49</sup> Direct evidence of the formation of gonadotropin by placental cells was obtained by Jones, Gey and Gey,<sup>50</sup> who assayed this hormone from serially transplanted tissue cultures of these cells, in which the final explants were composed entirely of cells grown in vitro Although differences exist, this gonadotropin of placental origin is virtually identical with that of pituitary origin — hence the old designation anterior-pituitary-like (APL)<sup>45</sup>

The problem of whether this placental secretion is composed of one or two hormones similar to the pituitary follicle-stimulating hormone and luteinizing hormone is beyond the scope of the present paper Aschheim and Zondek demonstrated clearly

formed as long as four thousand years ago<sup>1</sup> Although many of the procedures advocated were mystical and apparently bizarre, one basic concept, intelligible from modern standards, arose in these early times and persisted to the sixteenth century — namely, the idea that urine from pregnant women stimulated plant growth These pregnancy tests based on the stimulation of plant growth and germination of seeds are still occasionally referred to in the relatively recent literature and have therefore been used for several thousands of years

Although the search for improved methods was constant, it was only in the early twentieth century that the pioneer work of Evans and his associates,<sup>2</sup> Smith and Engle<sup>3</sup> and Zondek and Aschheim<sup>4-6</sup> made possible the present era of accurate pregnancy diagnosis The demonstration by these authors of the complex inter-relation between the ovary and the pituitary body and the urinary reaction of these hormones produced for the first time the tools necessary for basing pregnancy diagnosis on sound scientific grounds In 1928 the epochal description of the Aschheim-Zondek<sup>6</sup> test appeared, reactivating interest in rapid, accurate diagnostic tests of pregnancy

Diagnostic laboratory procedures suggested by Abderhalden,<sup>7</sup> Kamnitzer<sup>8</sup> and Roubitschek<sup>9</sup> antedated somewhat the Aschheim-Zondek test However, by present standards, these tests were grossly inadequate and have long since been mostly forgotten

The Aschheim-Zondek test provided, for the first time, a means of diagnosing early pregnancy that was almost 100 per cent accurate Its accuracy remains unsurpassed to this day Since the description of this pioneer test, many variants have been proposed, all designed to cut down the time required for the performance of the test The Friedman test,<sup>10</sup> originating two years after the Aschheim-Zondek test, represents a simple modification employing isolated female rabbits With the use of this animal the time required for obtaining a diagnosis was cut from five to two days

Despite the widespread adoption of the Friedman test and its high degree of accuracy, the time element that it required remained a compelling force for further improvement In 1933 Shapiro and Zwarenstein<sup>11</sup> presented before the Royal Society of South Africa a new test for pregnancy, utilizing for the first time an amphibian, the female South African clawed frog (*Xenopus laevis*) The time for a reaction was reduced to within twenty-four hours, but the unavailability of the frog unquestionably blocked, to some extent, the widespread adoption of this technic However, this very valuable observation — namely, that amphibians would react to mammalian hormones — served as the forerunner of other frog tests, described below

With the knowledge that hyperemia is one of the first detectable changes produced in the ovary of infantile rats by gonadotropins, numerous investigators have adopted this tissue change as a criterion for a positive pregnancy reaction<sup>12-21</sup> Starting with procedures advocated by Eberson and Silverberg<sup>12</sup> and Reiprich,<sup>13</sup> in which the hyperemic change was read at an approximate twenty-four-hour interval, use as an endpoint earlier and more subtle color differences, the time has been reduced to two hours, in the form of the Kupperman-Greenblatt<sup>21</sup> test As might be anticipated, however, as the time for reading the reaction has been shortened, the color changes have become more and more slight This difficulty in reading the endpoint constitutes a serious block to the widespread acceptance of this technic

Within the past two or three years a totally new method of pregnancy diagnosis has developed utilizing male frogs It was shown by Robbins and Parker<sup>22</sup> that the reaction of the male frog to gonadotropic hormone could be easily demonstrated by microscopical examination of cloacal fluid The appearance of sperm indicated a positive reaction Perhaps even more significant, however, was the fact that this reaction occurred quickly, usually within the four-hour period following the administration of the hormone The use of this reaction for a diagnostic test for pregnancy was obvious, and within the past year Mainini<sup>23</sup> has suggested a technic using a South American species of toad (*Bufo arenarum henseli*), and soon thereafter Wiltberger and Miller<sup>24</sup> and Robbins and Parker<sup>25</sup> demonstrated that the common North American frog (*Rana pipiens*) was equally suitable

By the use of the *Rana pipiens*, laboratory diagnosis of pregnancy could be carried out within two hours, frequently sooner, and the endpoint was absolutely clear cut, sperm being either present or absent From these early experimental reports, it appears that the procedures have great promise, offering economy and speed as well as accuracy How well they will stand up under widespread clinical trial remains to be seen

Chemical procedures capable of performance in a test tube and obviating the inconveniences of animal tests have long been sought The urinary histidine test, reported by Voge<sup>26</sup> soon after the original description by Aschheim-Zondek, more recently studied in great detail by Kapeller-Adler and Haas,<sup>27-29</sup> has not achieved wide acceptance Young,<sup>30</sup> Seidman<sup>31</sup> and Krieger,<sup>32</sup> among others, doubted its value since it fell far short of the accuracy of the Aschheim-Zondek test and, moreover, had little value for the diagnosis of early pregnancy, being of chief value in the later stages of pregnancy The Visscher-Bowman<sup>33</sup> test, a color reaction that was first described in 1934, appears, in the light of clinical trial, to have little usefulness

sitive than the rat or mouse, on a gram for gram basis, however, its large bulk necessitates such large dosage of hormone that its relative sensitivity is of little practical advantage

As for the frog, work is still in the developmental stage. However, it appears that the female *Xenopus laevis* as well as the male *Bufo arenarum* and *Xenopus laevis* respond to the luteinizing hormone of the chorionic gonadotropin, the first by the extrusion of the ova, and the last two by the emission of spermatozoa. Although there are other substances to which the frogs will react, they do not interfere with the use of these animals for pregnancy diagnosis, since they are never encountered in the course of pregnancy.

Mainini<sup>23</sup> states that the *Bufo arenarum hensel*, the South American toad advocated by him for pregnancy diagnosis, will react to 40 international units of gonadotropin. From work performed in this laboratory<sup>56</sup> it appears that the average male *Rana pipiens* will react to the same dose of chorionic gonadotropin as the average immature rat, this apparent equal sensitivity, it should be noted, is not based on weight equality. However, it is of practical significance since it makes the individual *Rana pipiens* able to detect levels of hormone that up to now could only be detected by rats.

From the preceding brief summary it can be seen that the choice, performance and evaluation of a pregnancy test is not a simple matter. The choice of animal, in relation to the specific hormone to be assayed, is of great importance. The speed with which the target organ can react is constant and therefore predetermines the speed of the test, a factor of great importance in problems of therapy. The species sensitivity is of obvious significance, especially when one is dealing with hormone titers away from the peak period of elimination of hormone. Thus the immature rat becomes the animal of choice in urines or serums of probable low hormonal titer, especially when the titer of the pregnant urine is so low as to produce only follicle stimulation without the production of true corpora lutea.

#### COMMON TESTS

A list of pregnancy tests in use or developed during the past ten years is as follows:

##### Bio-assay technics

###### Rodents

Aschheim-Zondek technic<sup>6, 51, 57-59</sup>

Ovarian hyperemic test<sup>12-21</sup>

Ovulatory test<sup>60</sup>

###### Rabbits

Friedman test<sup>10, 61-63</sup>

###### Amphibia

Female *Xenopus laevis*<sup>11, 65-69</sup>

*Bufo arenarum hensel*<sup>23</sup>

*Rana pipiens*<sup>24, 25</sup>

Fish tests<sup>70</sup>

##### Chemical tests

Histidine tests — Kapeller-Adler<sup>27-29, 71, 72</sup>

Visscher-Bowman test<sup>33, 73, 74</sup>

Colorimetric test — Schmulowitz-Wylie<sup>27</sup>

Pregnanediol test — Guterman<sup>39, 75-77</sup>

##### Skin tests

Colostrum<sup>45, 76, 79</sup>

Placental extract (Grushkin)<sup>44, 80</sup>

Chorionic antuitrin-S test

(Gillfillen-Gregg)<sup>46, 80-82</sup>

Estrogen<sup>83</sup>

##### Miscellaneous technics

Pupillary test (Bercoffitz)<sup>84</sup>

Prostigmine<sup>42, 85</sup>

This list by no means includes all the technics developed since the advent of the Aschheim-Zondek test. Rather, it is intended to include either tests in current use, as indicated by the recent literature of the past ten years, or procedures that have appeared in the past ten years and have yet to be evaluated.

##### Aschheim-Zondek Test<sup>6</sup>

The oldest of all the so-called "modern" pregnancy tests, this remains to date one of the most widely employed and certainly one of the most accurate technics. As originally described it employs immature mice weighing 8 gm and approximately three weeks of age. Filtered morning urine, in amounts of 1.8 to 2.4 cc, is administered to each mouse in individual doses varying from 0.3 to 0.5 cc three times daily for two days. Ninety-six hours after the first injection the animals are sacrificed, and the ovaries examined for "blutpunkte," or corpora hemorrhagica, a change produced by the presence of chorionic gonadotropin in the urine. In some laboratories the immature rat has been substituted for the mouse because of its greater sensitivity to the hormone and resistance to toxic factors in the urine. Rats twenty-one to twenty-three days old are injected with 6 cc of urine given in 1-cc doses twice daily for three days. The animal is sacrificed on the fifth day, and the ovaries examined for follicle formation and corpus luteum formation. Corpora hemorrhagica are rarely found in the rat. In this laboratory, the presence of corpora lutea, indicating the presence of luteinizing hormone, is required as the minimum evidence of a pregnancy reaction. However, as has been described very early in pregnancy, follicle formation may occur alone in the rats' ovaries because the development of a follicle-stimulating effect antedates the appearance of the luteinizing effect in the first few weeks of pregnancy. Hence, in problems of the diagnosis of very early gestation, the follicle reaction, although not definitive, may well be the harbinger of a developing luteal reaction. The same cycle is followed in reverse at the time of delivery or of fetal

that two distinct changes occurred in the ovaries of the rat after the administration of urine from a pregnant woman. These organs responded either to two different hormones or to one hormone in two different ways, first by follicle formation and secondly by luteinization and the development of corpora lutea. As a result, when the rat is used for the determination of the titer of placental hormone during pregnancy two distinct endpoints must be followed, producing as it were two separate curves for gonadotropin production during pregnancy. The first endpoint is reached at the highest dilution of the urine that will produce definite corpora lutea formation. Beyond this dilution definite follicle formation is still present. The second endpoint is reached only when definite follicle formation is extinguished (Fig 1).

From this graph it can be seen that there is a considerable lag after conception, during which little hormone production can be detected. A rapid rise ensues, to a peak at approximately seven or eight weeks of gestation, followed by a rapid fall, so that in the last trimester levels of gonadotropic hormone are low. It is, therefore, perfectly possible to obtain a negative pregnancy reaction during the

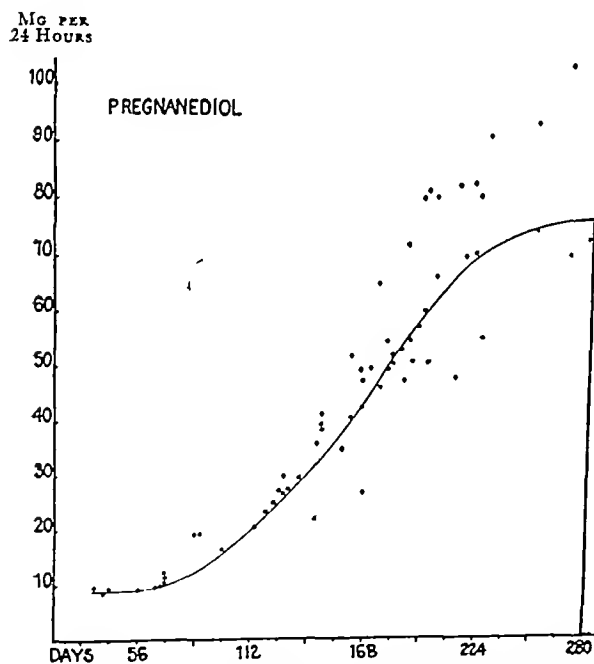


FIGURE 2 Urinary Excretion of Pregnanediol in 8 Cases of Normal Pregnancy (Reproduced from Penning<sup>53</sup> by Permission of the Publishers)

last trimester in the obvious presence of a living fetus. It is, moreover, very important to note that the follicle-stimulating effect begins first and is well marked at a time when virtually no luteinizing effect is present, and that it remains at a much higher titer throughout pregnancy. The importance of these facts is brought out below in a consideration of the so-called weakly positive test.

Other hormones produced in increased amounts during pregnancy are estrogen and progesterone, the latter forming the basis of an important chemical pregnancy test, the Guterman test for pregnanediol. Ample evidence exists to establish the fact that the placenta, in both man and animals, as well as the ovaries, forms these substances<sup>51,52</sup>. In fact, in the last months of the gestation, after the corpus luteum of the ovary degenerates, the placenta is the chief source of progesterone. Unlike the gonadotropins, these substances show progressively rising titers throughout the period of gestation and pass through no peak, abruptly falling either shortly before or at the time of delivery. Since the progesterone elimination almost exactly parallels the estrogen excretion, a curve of the latter substance will suffice to show the distribution of both hormones during pregnancy (Fig 2). It is therefore apparent that excretion of progesterone — that is, pregnanediol — will be least in the early stages of pregnancy and progressively more well marked in the later stages.

That pregnancy hormones will produce changes in lower animals is now well known<sup>54,55</sup>. Zondek and Aschheim<sup>54,55</sup> have classified the ovarian changes produced by gonadotropins as follows:

- APR I — follicle ripening and induction of vaginal estrus
- APR II — hyperemization of ovary and follicle hemorrhage
- APR III — formation of corpora lutea  
(APR = anterior pituitary reaction)

These gonadotropic reactions occur in a fixed sequence, with relatively fixed time relations, dependent only on the species of animal used, the type of hormone and the route of administration of the hormone. That is to say, the size of the dose and conditions of maintaining the animal have relatively no effect on the speed of the reaction. The first gross effect is hyperemization of the ovary, shortly thereafter, swelling, followed by ovulation, occurs, in turn followed by lutea formation. Up to recent date, the three animals most widely used for laboratory diagnosis of pregnancy have been the mouse, rat and rabbit. Each of these animals reacts in its own more or less characteristic fashion to the administration of gonadotropic hormone — the mouse and rabbit by the formation of corpora hemorrhagica, and the rat by the formation of cystic follicles that later become luteinized. Follicle hemorrhage or corpora hemorrhagica are rarely seen in the rat. Moreover, it is also known that the congestion and reddening of the ovaries (APR II) is most readily seen in the rat, the only animal in which the ovaries, at rest, are quite anemic. Species differences in sensitivity to chorionic hormone also occur; thus, for a given weight, immature rats are twenty-five times more sensitive to chorionic gonadotropin than mice. The rabbit in turn is more sen-

48 Collip J B Placental hormones *Canad M A J* 23 631-633 1930

49 Collip J B et al Placental hormones *Endocrinology* 15 315-323, 1931

50 Jones G E S Gey G O and Gey M K Hormone production by placental cells maintained in continuous culture *Bull Johns Hopkins Hosp* 72 26-38 1943

51 Mazer C and Goldstein L *Clinical Endocrinology of the Female* 519 pp Philadelphia & London W B Saunders Co 1932

52 Dorfman R I and Van Wagenen G Sex hormone excretion of adult female and pregnancy monkeys *Surg Gynec & Obst* 73 545-548 1941

53 Venning E H Further studies on estimation of small amounts of sodium pregnandiol glucuronide in urine *J Biol Chem* 126 595-602 1938

54 Zondek B Über die Funktion des Ovariums *Ztschr f Geburtsh & Gynäk* 90 372-380 1926

55 Zondek B, and Aschheim S Hypophysenvorderlappen und Ovarium Beziehungen der endokrinen Drüsen zur Ovarialfunktion *Arch f Gynäk* 130 1-45 1927

56 Parker F., Jr., and Robbins S L Unpublished data

57 Aschheim S Pregnancy tests *J A M A* 104 1324-1329 1935

58 Mack H C and Agnew G H Comparison of Aschheim-Zondek and Friedman tests in normal and abnormal pregnancy analysis of literature and report of results obtained in 1112 cases *Am J Obst & Gynec* 27 232-239 1934

59 Crew F A E Laboratory tests for early diagnosis of pregnancy *Brit M J* 2 1092 1094 1936

60 Bardick H O Further observations on induced ovulation in mouse as rapid test for pregnancy *Am J Physiol* 145 387-390 1946

61 King A G Friedman rabbit ovulation test in differential obstetric diagnosis *J Lab & Clin Med* 19 1035-1040 1934

62 Spielman F Friedman pregnancy test. *Am J Obst & Gynec* 27 448-450 1934

63 Best C H and McHenry E W Friedman modification of Aschheim-Zondek test for diagnosis of pregnancy *Canad M A J* 28 599 1933

64 Goldberger M A Salmon U J and Frank R T Value of Friedman test in diagnosis of intra uterine and extrauterine pregnancy *J A M A* 103 1210-1212 1934

65 Shapiro H A and Zwarenstein H Rapid test for pregnancy on *Xenopus laevis* *Nature* London 133 762 1934

66 Shapiro H A and Zwarenstein H Test for early diagnosis of pregnancy on South African clawed toad (*Xenopus laevis*) *South African M J* 9 202-203 1935

67 Elkan E. *Xenopus* pregnancy test. *Practitioner* 140 312-315 1938

68 Weinstein A I and Coates C W *South African Frog (Xenopus laevis) in Pregnancy Diagnosis* 134 pp New York N Y Biologic Research Foundation 1944

69 Robbins S L, Parker, F Jr and Doyle W C. Use of South African frog (*Xenopus laevis*) in diagnosis of pregnancy *New Eng J Med* 234 784-787 1946

70 Fleischmann W and Kann S Über eine Funktion des weiblichen Sexualhormons bei Fischen (Wachstum der Lebergröße des Bitterlings) *Arch f d ges Physiol* 230 662-667 1932

71 Langley W D Urinary histidine determination of histidine in urine Histidine in normal and in pregnancy urines *J Biol Chem* 137 255-265 1941

72 Page E W Excretion rates of histidine in pregnant and nonpregnant women *West J Surg* 51 482-490 1943

73 Messinger W J Presberg M H and Fellows M D Chemical pregnancy test of Visscher and Bowman *Am J Obst & Gynec* 35 295-298 1938

74 Dunn R D and Northway F J Results with Visscher-Bowman pregnancy test. *Am J Obst & Gynec* 35 298-300 1938

75 Hain A M, and Robertson E M Estimation of luteal activity and early diagnosis of pregnancy *Lancet* 1 1324 1939

76 Buxton C L Pregnanediol determination as aid in clinical diagnosis *Am J Obst & Gynec* 40 202-211, 1940

77 Guterman H S Further observations on value of pregnandiol test for pregnancy *J Clin Endocrinol* 5 407-411 1945

78 Goldman L M Kessler H B and Wilder M E Colostrum entaneons test for diagnosis of pregnancy statistical analysis of five hundred tests *J A M A* 119 130-132 1942

79 Allen E. and Donaldson L B Colostrum intradermal test for diagnosis of pregnancy *Am J Obst & Gynec* 45 208 215 1945

80 Lass P M Enderle E S and Kurzrok R. Skin tests for pregnancy *Endocrinology* 23 71-74 1938

81 Shorman A. Antitritin S test for diagnosis of pregnancy *J Obst & Gynec Brit Emp* 45 82 1938

82 Friedman J J and Fink H Evaluation of anterior pituitary-like substance intradermal test for pregnancy with study of possible relation of this test to prolactin content. *Am J Obst & Gynec* 36 116-119 1938

83 Hoffmann P R and Fouch F L Results of skin tests for pregnancy *Am J Obst & Gynec* 35 680-682 1938

84 Triantaphilopoulos B Die Schwangerschaftsreaktion nach Berco-witz. *Zentralbl f Gynäk* 62 2727-2730 1938

85 Carapetian H Combined method for treatment of delayed menstruation and test for early pregnancy preliminary report. *J A M A* 122 81-83 1943

CASE RECORDS OF THE  
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

TRACY B MALLORY, M D, Editor

BENJAMIN CASTLEMAN, M D, Associate Editor

EDITH E PARRIS, Assistant Editor

CASE 34351

PRESENTATION OF CASE

A two-and-a-half-year-old girl was apparently well until six days before admission to the hospital when her parents noted that she walked about bent over as if in discomfort and tended to draw the right leg upward. Except for some decrease in appetite and easy fatigability for several weeks she had no symptoms. Her birth and development were uneventful, and she had had none of the usual childhood diseases.

Physical examination revealed a well developed and well nourished child. The heart and lungs were

normal. There was no peripheral lymphadenopathy. Largely filling the right abdomen and extending from costal border to below the iliac crest and across the midline at the level of the umbilicus was a firm, smooth, fixed, nontender mass, which was not lobulated.

The temperature was 99.8°F. The blood pressure was 110 systolic, 80 diastolic.

The urine specimen concentrated to 1014, and there was no albumin or sugar. One white cell per high-power field was seen. The white-cell count was 9800. The serum protein was 7.2 gm, and the nonprotein nitrogen 31 mg per 100 cc. X-ray studies of the chest, skull and femurs were negative except for some elevation of both sides of the diaphragm. An intravenous pvelogram showed a huge ovoid mass in the right abdomen. This extended well to the left of the spine, and the tip was over the iliac crest. The mass was somewhat lobulated, and there was a suggestion of minute calcium specks at its lower pole. The liver was thought to be displaced upward. Both kidneys were promptly visualized, and the left appeared normal. The right renal calyces were displaced upward, and the ureter was displaced toward the midline and somewhat posteriorly. The renal drainage was normal.

On the fifth hospital day an operation was performed.

death. Hence, the luteinizing effect disappears before all follicle formation is lost. The value of the follicle-stimulating reaction is therefore quite obvious in questions of intrauterine fetal death and missed abortion. It is of importance to remember that elevations of pituitary follicle-stimulating hormones accompany the menopause, hence, any interpretation of these follicle changes in the rat ovaries can only be made against the background of a proper clinical history. By the use of either the immature mouse or rat, the results obtained with the Aschheim-Zondek test are universally reported as excellent. Aschheim,<sup>57</sup> in 1935, cited his accuracy as 98 per cent in positive reactions and 99.5 per cent in negative tests.

Mazer and Goldstein<sup>51</sup> reported on the results of 11 independent groups with correct positive reactions in 94 per cent and correct negative reactions in 97 per cent of the cases. Mack and Agnew<sup>58</sup> likewise compiled a series of 8685 cases tested by the Aschheim-Zondek technic with an accuracy of 96.6 per cent. In this laboratory, where equivocal ovarian changes in the rat are controlled by microscopical section and examination, the accuracy has closely approximated 100 per cent, only one false report having occurred in the past many years.

It is, therefore, not without reason that the Aschheim-Zondek test has remained a constant favorite. Its accuracy, reliability and sensitivity in well trained hands are goals for other procedures to attain. The one drawback to this procedure, aside from the necessity of maintaining rodents of proper size and age, has been the time required for the performance of the test—four or five days. As stated above, this time interval is fixed by the fact that it requires ninety-six hours for the ovaries of mice to form corpora hemorrhagica and one hundred and twenty hours for the rat ovaries to form corpora lutea.<sup>51, 55</sup>

(To be concluded)

## REFERENCES

- Bayon H P. Ancient pregnancy tests in light of contemporary knowledge. *Proc Roy Soc Med* 32:1527-1538 1939.
- Evans H A and Long J A. Characteristic effects upon growth oestrus and ovulation induced by intraperitoneal administration of fresh anterior hypophyseal substance. *Proc Nat Acad Sci* 8:38 1922.
- Smith P E and Engle E T. Experimental evidence regarding rôle of anterior pituitary in development and regulation of genital system. *Am J Anat* 40:159-217 1927.
- Zondek B. Die Schwangerschaftsdiagnose aus dem Harn durch Nachweis des Hypophysenvorderlappenhormons. Grundlagen und Technik der Methode. *Klin Wchnschr* 7:1404-1411 1928.
- Aschheim S. Die Schwangerschaftsdiagnose aus dem Harn durch Nachweis des Hypophysenvorderlappenhormons, praktische und theoretische Ergebnisse aus den Harnuntersuchungen. *Klin Wchnschr* 7:1453-1457 1928.
- Aschheim S and Zondek B. Schwangerschaftsdiagnose aus dem Harn (durch Hormonnachweis). *Klin Wchnschr* 7:8 1928.
- Editorial. Status of Abderhalden reaction. *J A M A* 75:1786 1920.
- Kammitzer and Joseph. Ein neues Verfahren zur Feststellung der intra- und extranternen Frühgravidität. *Med Klink* 18:396-398 1922.
- Rouhitschek R. Die Renale Schwangerschaftsglykosurie als Früh symptom der Gravidität. *Klin. Wchnschr* 1:220 1922.
- Friedman M H and Lapham M E. Simple rapid procedure for laboratory diagnosis of early pregnancies. *Am J Obst & Gynec* 21:405-410 1931.
- Shapiro H A., and Zwarenstein H A. Test for pregnancy on *Xenopus laevis*. *Tr Roy Soc So Africa* 22 (Min of Proc, 75 Oct. 18 1933) 1934.
- Ebersson F and Silverberg M H. Anterior pituitary hormone in urine: rapid method for diagnosis of early pregnancy (study of 175 consecutive cases). *J A M A* 96:2176-2182, 1931.
- Reiprich W. Eine neue Schwangerschafts-Schnell-Reaktion aus dem Harn ("30 Stunden-Reaktion"). *Klin Wchnschr* 12:1441 1444, 1933.
- Walker T F and Walker D V H. Modification of Aschheim-Zondek test. *J A M A* 111:1460 1938.
- Kelso R E. Twenty four hour test (Aschheim-Zondek modification) for diagnosis of pregnancy. *Am J Clin Path.* 10:793-799 1940.
- Frank R T and Berman R L. Twenty four hour pregnancy test. *Am J Obst & Gynec* 42:492-496, 1941.
- Salmon U J, Geist, S H, Salmon A A., and Frank, L L. Six hour pregnancy test. *J Clin Endocrinol* 2:167-170 1942.
- Ramsey T L, Faulkenstein A P and Sujkowski E J. Use of albino rat in pregnancy hormone test. *J Lab & Clin. Med.* 29:419-428 1944.
- Kline B S, Salmon Geist, Salmon, Frank six-hour rat test for pregnancy. *Am J Clin Path* 14:557-562 1944.
- Kupperman H S, Greenblatt R B and Noback, C R. Two and six-hour pregnancy test preliminary report. *J Clin Endocrinol* 3:548-550 1943.
- Kupperman H S and Greenblatt, R B. Two-hour pregnancy test. *South M J* 39:158 165 1946.
- Robbins S L, Parker F Jr and Bianco P D. Reaction of male South African clawed frog (*Xenopus laevis*) to gonadotropin. *Endocrinology* 40:227-229, 1947.
- Mainini C G. Pregnancy test using male toad. *J Clin Endocrinol* 7:653-658 1947.
- Wiltberger P B and Miller D F. Male frog *Rana pipiens* as a new test animal for early pregnancy. *Science* 107:198 1948.
- Robbins S L and Parker, F Jr. Use of male frog *Rana pipiens* in pregnancy diagnosis. *Endocrinology* (in press).
- Voge C I B. Simple chemical test for pregnancy. *Brit M J* 2:829 1929.
- Kapeller-Adler R. Über eine neue Methode zur quantitativen Histidinbestimmung und über deren Anwendbarkeit zur Untersuchung von biologischen Flüssigkeiten insbesondere von Glandularen. *Biochem. Ztschr* 264:131-141 1933.
- Idem. Über eine neue chemische Schwangerschaftsreaktion. *Klin Wchnschr* 13:21 1934.
- Kapeller-Adler R. and Haas F. Über den Ursprung des Histidins im Harn der graviden Frauen. *Biochem. Ztschr* 280:232-241 1935.
- Young A M. Five hundred and nineteen Voge hormone tests of urine for pregnancy. *J Lab & Clin Med* 19:153-155 1933-34.
- Seidman T R. Determination of urinary histidine as chemical test for pregnancy. *Am J Obst & Gynec* 29:451-453 1935.
- Krieger, V I. Histidine in urine as indication of pregnancy. *M J Australia* 1:599-602 1936.
- Visscher J P and Bowman D E. Chemical determination of pregnancy. *Proc Soc Exper Biol & Med* 31:460 1934.
- Frech H C Jr. Modification of Visscher-Bowman pregnancy test, with report on 513 observations. *Am J Obst & Gynec* 33:84-857 1937.
- Sheehan J F. Visscher-Bowman chemical test for pregnancy and urinary pigment. *Surg Gynec & Obst* 64:805-810 1937.
- Hadley H G. Note on Visscher-Bowman chemical test for pregnancy. *J Lab & Clin Med* 26:1374 1941.
- Schmulovitz, M J and Wylie H B. Chemical diagnosis of pregnancy by detection of estrin in urine. *J Lab & Clin Med* 21:210-216 1935.
- Pincus G, Wheeler G, Young G and Zahl P S. Colorimetric determination of urinary estrin. *J Biol Chem* 116:253-266, 1936.
- Guterman H S. Human pregnancy test based upon color reaction of pregnandiol in urine. *J Clin Endocrinol* 4:262-267 1944.
- Venning E M. and Browne J S L. Isolation of water soluble pregnandiol complex from human pregnancy urine. *Proc Soc Exper Biol & Med* 34:792 1936.
- McCormack G. Comparison of color chemical test with Friedman modification of Aschheim-Zondek test. *Am J Obst & Gynec* 51:722-725 1946.
- Morrow A G and Benua R S. Evaluation of Guterman pregnancy test. *Am J Obst & Gynec* 51:685-691 1946.
- Corber A A. Use of prostigmine in delayed menstruation and as test for early pregnancy. *Canad M A J* 53:67 1945.
- Gruskin B. Intradermal test for pregnancy. *Am J Surg* 31:59-61, 1936.
- Falls F H, Freda V C. and Cohen H H. Skin test for diagnosis of pregnancy. *Am J Obst & Gynec* 41:431-438 1941.
- Moody T E and Mandy H J. Antutrin-S skin test for early pregnancy. *Am J Obst & Gynec* 41:109-112 1941.
- Evans H M and Simpson M E. Comparison of anterior hypophyseal implants from normal and gonadectomized animals with reference to their capacity to stimulate immature ovary. *Am J Physiol* 89:371-374 1929. Sex difference in hormone content of anterior hypophysis of rat. *Ibid* 89:375-378 1929. Effect of pregnancy on anterior hypophysis of rat and cow as judged by capacity of implants to produce precocious maturity. *Ibid* 89:379 1929. Comparison of ovarian changes produced in immature animals by implants of hypophyseal tissue and hormone from urine of pregnant women. *Ibid* 89:381-387 1929.

So my diagnosis has to be a malignant tumor arising from the retroperitoneal space and invading the liver

### CLINICAL DIAGNOSIS

Neuroblastoma

### DR REYERSBACH'S DIAGNOSIS

Malignant tumor arising from retroperitoneal space and invading the liver

### ANATOMICAL DIAGNOSIS

*Hepatoma of liver*

### PATHOLOGICAL DISCUSSION

DR OLIVER COPE The X-ray Department actually favored a diagnosis of Wilms's tumor. The Surgical Service diagnosed it as neuroblastoma. However, we both agreed that it was retroperitoneal. In operating I thought it wise to approach it transperitoneally through the flank. It was not a neuroblastoma and had nothing to do with the kidney. So far as we could determine at operation it was a primary tumor of the liver and it was so large that it gave the impression of a retroperitoneal tumor. It arose in the right lobe of the liver and had grown upward and backward and appeared on the dome of the liver, with normal liver in front. The tumor invaded the left lobe to such an extent that it would be impossible to excise it without also excising the portal vein. Therefore excision seemed impossible in spite of the fact that we could have saved the left hepatic artery. There was no evidence of metastases or of a primary tumor elsewhere. It was such an unusual situation that we asked Dr Castleman to come to the operation and view it in its entirety. I presented him with a specimen, and that in itself was a major procedure because this was a very vascular tumor and it was difficult to control the hemorrhage.

DR BENJAMIN CASTLEMAN The piece that Dr Cope gave me was 15 cm in diameter, which was fairly large considering how friable the tumor was. I did a frozen section and thought that the best diagnosis was a primary liver-cell carcinoma, or a hepatoma, rather than a metastasis from a neuroblastoma. Neuroblastoma may metastasize to the liver and produce a large mass. Usually there is more than one tumor nodule. Here the mass seemed to be continuous from right to left. There was no surrounding cirrhosis, which one usually sees with hepatoma in adults, the cirrhosis being the predisposing cause of the hepatoma. That apparently is not true in hepatomas arising in children. I had never seen one in a child but Steiner,<sup>1</sup> who reviewed all the cases up to 1938, was able to collect over 70 cases of primary liver-cell carcinoma in children under sixteen years of age. It is interesting that over half these were in children under two years of age. He reported that there was no

cirrhosis associated with these cases, so that the etiology is probably congenital. He described a case in which the hepatoma was present at birth. The hepatomas in children are usually very malignant, and according to Steiner the average duration of life is four months after the tumor is discovered. The resections that had been done in those cases were unsuccessful although there have been some cases of hepatoma successfully removed both in adults and children. I can recall one that Dr Sweet<sup>2</sup> removed from a seventy-five-year-old physician. He was seen by Dr Sweet three years later and found to have nodules in the right upper abdomen, which were probably recurrences or metastases. However, he continued to practice during this three-year period.

### REFERENCES

- 1 Steiner M M Primary carcinoma of liver in childhood: report of 2 cases with critical review of literature. *Am J Dis Child* 55: 807-824 1938
- 2 Case Records of the Massachusetts General Hospital (Case 29571). *New Eng J Med* 229: 342-345 1943

### CASE 34352

#### PRESENTATION OF CASE

A thirty-six-year-old housewife entered the hospital with the chief complaint of difficulty in breathing.

For sixteen years prior to admission the patient thought she had had slight difficulty in swallowing food. Three years before entry a physician gave her belladonna because of a sensation of "food sticking in the throat." At this same time she began to have right-upper-quadrant postprandial distress, which disappeared when she was placed on a low-fat diet. About three years before entry she first became aware of dyspnea with the exertion of prolonged talking. She disregarded this, however, until eight months before admission when she had a sudden increase in dyspnea with loss of the voice. She believed that these difficulties came from the trachea just below the larynx, and found that she was partially relieved if she pulled the skin of the neck forward. The severe dyspnea gradually improved after a month but at the time of admission she was still aware of difficulty in drawing her breath and had a loose cough productive of white phlegm, sometimes with lumps of greenish matter in it but never blood. Food occasionally caught in the throat and at such times the patient had a sense of fullness under the mid-sternum.

The past history and review of the systems were essentially noncontributory.

Physical examination disclosed a well developed, well nourished woman who had evident respiratory distress with prolonged inspiration. She was not particularly hoarse. The thyroid gland was felt to be two and a half to three times enlarged but was symmetrical, soft, smooth and nontender. No

## DIFFERENTIAL DIAGNOSIS

DR GERTRUD C REYERSBACH This child obviously had a large right-sided abdominal tumor. We are asked to determine the type. I think it is possible to exclude certain conditions, such as duplication of the bowel, tumor of the pancreas, hydronephrosis, polycystic kidney and tuberculous lymphadenitis, without further discussion. There are no data to indicate that this child had an ovarian tumor. In lymphosarcoma one would expect a somewhat different clinical picture. In the absence of disturbances of the endocrine system we may exclude a suprarenal cortical tumor. Could this mass have been a Riedel's lobe of the liver? There are several reasons not to think so: the mass described was too large, there were signs of general involvement, and an operation was performed.

The history in this case is compatible with several conditions: neuroblastoma, which arises from cells of the sympathetic nervous system and is the most common neoplasm of the abdominal cavity in early childhood; Wilms's tumor, which is a congenital embryonal mixed tumor arising from the kidney anlage, and unattached retroperitoneal embryoma.

All these conditions are malignant and most frequently make their appearance during the first years of life with a peak between the second and third years. Actually this does not quite hold for the unattached retroperitoneal embryoma, which may be discovered later. In neuroblastoma and Wilms's tumor the first thing usually discovered is the abdominal mass, as in this child. The mild constitutional symptoms — namely, anorexia, fatigability, and the lack of cachexia — are typical of all conditions. Likewise, the sudden discovery of a large mass is typical of these conditions. It is due either to the fact that the mass was overlooked previously or that it had grown rapidly in a short while, such rapid growth is sometimes due to bleeding into a Wilms's tumor. The absence of urinary findings and the distortion of the renal pelvis on x-ray study are frequently seen in all three lesions. The unattached retroperitoneal embryoma usually grows on either side of the vertebral column from as high as the fourth cervical segment down to the internal genitalia. Its location is different from the one described here, and it is extremely rare. I am going to exclude it.

In favor of neuroblastoma are the symptoms of anorexia and fatigability, the presence of the mass on the right side, calcification in the tumor as seen on x-ray examination and displacement of the renal pelvis. Against it is the fact that the mass was described as oval and smooth, most neuroblastomas are described as nodular — certainly those that I have seen have been nodular. Also, the patients that I have observed showed anemia and fever at

the time the tumor was discovered. This child's temperature was only 99.8°F.

What is in favor of Wilms's tumor? The symptoms of anorexia, fatigability and displacement of the renal pelvis hold for this tumor also, and x-ray evidence of calcification is also described in Wilms's tumor. The mass is smooth and the border well delineated. Against it is the extension beyond the vertebral column.

I think that the child might have either of these two tumors. Both start retroperitoneally, and in this abstract there is a note saying that the mass arose from the costal margin. That puzzles me. I do not know how to interpret it. I do not know whether the neuroblastoma had metastasized to the liver, but I hope that the x-ray films will give some help.

DR STANLEY M WYMAN The mass is fairly well outlined, somewhat smooth and slightly lobulated. It extends past the midline to the left, down to the brim of the pelvis as well as upward to the costal margin, approximately filling the entire right midabdomen. The areas of calcification are fairly well seen, particularly in the lower pole of the mass. The film taken after the injection of dye shows good outlining of the right calyceal pattern. An interesting finding is that the calyces are displaced upward, but show no significant distortion or apparent invasion. The pelvis and ureter follow a relatively normal course. This film is an oblique view showing the mass lying somewhat anteriorly. The left margin can be well outlined, and the mass appears more anterior than posterior. In no film can one outline the lower margin of the right kidney. This mass cannot be differentiated from the kidney shadow, with which it appears continuous. The lateral view adds no appreciable information. The lungs appear clear. The bones as visualized show no evidence of destruction.

DR REYERSBACH Do you think that the mass is attached to the liver?

DR WYMAN I cannot say. I cannot identify the liver accurately per se. The lower border fades into this mass, and I cannot say whether it is a part of the mass or is overlying it. I cannot differentiate the liver from the mass any more than I can the kidney from the mass.

DR REYERSBACH Your statement that the mass appears to lie anteriorly makes me more discouraged. Both Wilms's tumor and neuroblastoma arise from the retroperitoneal space and are posterior. When I read over the abstract I looked up other tumors that would be more anterior, and they are extraordinarily rare. A tumor of a rib would not behave in that way. Any tumor of the liver in childhood is very rare. There is no indication that the child had an echinococcus cyst. Hemangiomas are usually small and probably would be discovered accidentally.

I am obliged to leave the diagnosis as a malignant tumor of the upper mediastinum

DR BENJAMIN CASTLEMAN Does anyone want to come a little closer to the diagnosis?

DR ALFRED KRANES The patient had an enlarged thyroid gland and pressure symptoms. I do not understand why Dr Lerman discounted the thyroid gland so readily. Did he do so simply because the gland was soft?

DR LERMAN It was soft, smooth, nontender and without any nodules whatever.

DR KRANES Would you agree that it was soft, Dr Lurie?

DR LURIE It was soft.

DR OLIVER COPE It takes considerable pressure to close the trachea off. The thyroid gland does it under two circumstances: in goiters that are fibrous, hard and invasive, as in either thyroiditis or carcinoma, and when the goiter is low enough to get caught in the upper thoracic strait. Dr Lerman is justified in eliminating the thyroid gland—either the goiter was not the cause or the description of it was wrong.

DR KRANES I had assumed that the description was wrong.

DR COPE Malignant lesions in the trachea and esophagus invading the underneath capsule of the thyroid gland should be mentioned. We have had rare cases of that type. We had a case in which the disease apparently arose as a sarcoma of the trachea and invaded the thyroid gland and gave rise to this type of compression. We had 2 cases that I can remember from the esophagus. In both the esophageal cases the primary lesion was overlooked, and a diagnosis of carcinoma of the thyroid gland made. It was not until operation that the primary etiology was disclosed. Dr Lerman is right in thinking of a malignant tumor elsewhere than the thyroid gland, and the upper mediastinum is a good location except that in this case we do not see it in the x-ray films.

DR LERMAN By the same reasoning, there is no x-ray evidence to point to the esophagus or trachea and such diagnoses would be pure guesswork.

DR COPE In the 2 cases that I mentioned the invading lesion was small and overlooked in the x-ray films.

DR EDWARD B. BENEDICT We had a case of a papillary tumor of the thyroid gland that invaded

the trachea and produced symptoms of dyspnea, hemoptysis and wheeze, which on bronchoscopy turned out to be a primary epidermoid carcinoma of the trachea.

DR LURIE When I first saw this woman my impression was that the lesion was entirely intralaryngeal. She had difficulty in inspiration and expiration but was able to do her work. When I looked at the larynx I was amazed to see that it had a fair airway, and the vocal cords anteriorly seemed to be lying in a reddened mass of mucous membrane that had bulged upward. With the larynx in complete abduction, a semi-doughnut projection of the trachea itself was seen. That made me think of rhinoscleroma, a very rare lesion—we have seen 4 or 5 cases in the Eye and Ear Infirmary. As I looked at this I debated a good deal whether I was justified in going in and trying to remove a piece of this mucous membrane through the larynx so that we could make a diagnosis. If we did that, I would have had to do a tracheotomy. If I did not succeed in getting a specimen, we were no better off than before. Having decided that, I began to wonder whether there was an extrinsic cause, and my first guess was the thyroid gland, especially a growth of the superior pole invading the larynx. I remember a case about twenty-five years ago in which I missed the diagnosis completely in trying to remove the tissue through the larynx and the patient died a year later from cancer of the thyroid gland. I finally asked Dr Richard H. Sweet to explore externally, and a thyroidectomy was done.

#### CLINICAL DIAGNOSIS

Carcinoma of thyroid gland, with invasion of trachea

#### DR LERMAN'S DIAGNOSIS

Malignant tumor of upper mediastinum, with compression of trachea

#### ANATOMICAL DIAGNOSIS

*Adenoma of trachea, with extension into thyroid gland*

#### PATHOLOGICAL DISCUSSION

DR CASTLEMAN I was present at this operation. The thyroid gland was symmetrical and slightly enlarged and on section was not remarkable. On

nodules were felt. Laryngoscopic examination revealed swollen mucous membranes of the vocal cords without impairment of function or tumor, and the tracheal mucosa below the larynx was reddened and edematous, with narrowing of the lumen apparently by extrinsic pressure.

Examination of the blood revealed a red-cell count of 4,400,000, with a hemoglobin of 12.2 gm, and a white-cell count of 6800, with 46 per cent neutrophils, 40 per cent lymphocytes, 6 per cent monocytes and 8 per cent eosinophils. The total protein was 5.7 gm per 100 cc, and the prothrombin time 17 seconds (control, 16 seconds).

X-ray films of the neck and chest showed marked narrowing of the trachea opposite the lower cervical and upper thoracic spine. There was a soft-tissue density adjacent to the upper thoracic spine on the left, which may have represented the subclavian vessels. No obvious retrosternal extension was seen. The lung fields were clear, and the heart was of normal size.

On the fourth hospital day an operation was performed.

#### DIFFERENTIAL DIAGNOSIS

DR JACOB LERMAN: I should like to see the x-ray films.

DR STANLEY M. WYMAN: The only films available are those of the chest, which show a definite area of narrowing in the upper trachea, at about the level of the sixth and seventh cervical and the first thoracic vertebrae. This narrowing is rather symmetrical and smooth. The detail, however, is not adequate to make much more of a statement than that. The prominence of the vascular tree in the mediastinum is seen on the left and appears to represent a prominent left subclavian artery, on the right there is no unusual prominence. The chest itself appears essentially normal. One cannot outline a definite mass in the lower part of the neck.

DR LERMAN: Is there anyone here who can verify the description of the thyroid gland? Was it soft, smooth and symmetrical?

DR MOSES H. LURIE: Yes. A barium swallow was done at the Eye and Ear Infirmary, and there was no evidence of outcropping.

DR LERMAN: I found on reading the protocol that I was thinking in terms of aneurysm of the aorta or of the great vessels. After seeing the

x-ray films I am obliged to discard this diagnosis completely.

The obvious place to look for trouble is the thyroid gland, although I am almost convinced that that was not the source of symptoms. I shall merely mention the various possible types of thyroid tumors that may produce such symptoms, particularly when such a gland encircles the trachea. A smooth goiter, a colloid goiter, with or without nodules, may encircle the trachea and produce compression with difficulty in breathing and the portion of the thyroid gland lying between the trachea and esophagus may also produce difficulty in swallowing. The more common type of thyroid tumor that does this is the result of chronic thyroiditis, either the Hashimoto or the Riedel type. However, from the description one has to exclude thyroiditis, which is a hard mass and often irregular. Similarly the description does not fit thyroid cancer, which is also a common cause for compression of the trachea. Either adenocarcinoma or papillary adenocarcinoma may produce compression by encircling the trachea. Either would produce a very hard, irregular tumor with evidence of tumor elsewhere in the neck or distally. In spite of the fact that the protocol emphasizes the importance of the thyroid swelling, I am forced to discard it as a source of symptoms.

What are the other possibilities? Anomalous vessels should be mentioned. There is not much evidence by x-ray examination or from the history, but anomaly of a large vessel could compress the trachea. However, such a condition would be discovered early in life. Benign mediastinal tumors, particularly benign cysts, most commonly dermoid cyst or teratoma, may produce compression of the trachea. More likely, because of the extensive involvement, a malignant mediastinal tumor has to be considered, such as lymphoma, sarcoma and so forth. I am afraid I cannot narrow it down further than this. I believe that the clinical and the x-ray evidence caused the surgeons to go after the thyroid gland as the cause of compression, but I am forced to conclude that there was a tumor in the upper mediastinum.

I should mention esophageal tumors, although the esophagus did not seem to play too large a role. Diverticulum of the esophagus producing compression of the trachea is a possibility. Also carcinoma of the esophagus is possible but unlikely.

I am obliged to leave the diagnosis as a malignant tumor of the upper mediastinum

DR BENJAMIN CASTLEMAN Does anyone want to come a little closer to the diagnosis?

DR ALFRED KRAVES The patient had an enlarged thyroid gland and pressure symptoms. I do not understand why Dr Lerman discounted the thyroid gland so readily. Did he do so simply because the gland was soft?

DR LERMAN It was soft, smooth, nontender and without any nodules whatever.

DR KRAVES Would you agree that it was soft, Dr Lurie?

DR LURIE It was soft.

DR OLIVER COPE It takes considerable pressure to close the trachea off. The thyroid gland does it under two circumstances in goiters that are fibrous, hard and invasive, as in either thyroiditis or carcinoma, and when the goiter is low enough to get caught in the upper thoracic strait. Dr Lerman is justified in eliminating the thyroid gland—either the goiter was not the cause or the description of it was wrong.

DR KRAVES I had assumed that the description was wrong.

DR COPE Malignant lesions in the trachea and esophagus invading the underneath capsule of the thyroid gland should be mentioned. We have had rare cases of that type. We had a case in which the disease apparently arose as a sarcoma of the trachea and invaded the thyroid gland and gave rise to this type of compression. We had 2 cases that I can remember from the esophagus. In both the esophageal cases the primary lesion was overlooked, and a diagnosis of carcinoma of the thyroid gland made. It was not until operation that the primary etiology was disclosed. Dr Lerman is right in thinking of a malignant tumor elsewhere than the thyroid gland, and the upper mediastinum is a good location except that in this case we do not see it in the x-ray films.

DR LERMAN By the same reasoning, there is no x-ray evidence to point to the esophagus or trachea, and such diagnoses would be pure guesswork.

DR COPE In the 2 cases that I mentioned the invading lesion was small and overlooked in the x-ray films.

DR EDWARD B. BENEDICT We had a case of a papillary tumor of the thyroid gland that invaded

the trachea and produced symptoms of dyspnea, hemoptysis and wheeze, which on bronchoscopy turned out to be a primary epidermoid carcinoma of the trachea.

DR LURIE When I first saw this woman my impression was that the lesion was entirely intralaryngeal. She had difficulty in inspiration and expiration but was able to do her work. When I looked at the larynx I was amazed to see that it had a fair airway, and the vocal cords anteriorly seemed to be lying in a reddened mass of mucous membrane that had bulged upward. With the larynx in complete abduction, a semi-doughnut projection of the trachea itself was seen. That made me think of rhinoscleroma, a very rare lesion—we have seen 4 or 5 cases in the Eye and Ear Infirmary. As I looked at this I debated a good deal whether I was justified in going in and trying to remove a piece of this mucous membrane through the larynx so that we could make a diagnosis. If we did that, I would have had to do a tracheotomy. If I did not succeed in getting a specimen, we were no better off than before. Having decided that, I began to wonder whether there was an extrinsic cause, and my first guess was the thyroid gland, especially a growth of the superior pole invading the larynx. I remember a case about twenty-five years ago in which I missed the diagnosis completely in trying to remove the tissue through the larynx and the patient died a year later from cancer of the thyroid gland. I finally asked Dr Richard H. Sweet to explore externally, and a thyroidectomy was done.

#### CLINICAL DIAGNOSIS

Carcinoma of thyroid gland, with invasion of trachea

#### DR LERMAN'S DIAGNOSIS

Malignant tumor of upper mediastinum, with compression of trachea

#### ANATOMICAL DIAGNOSIS

*Adenoma of trachea, with extension into thyroid gland*

#### PATHOLOGICAL DISCUSSION

DR CASTLEMAN I was present at this operation. The thyroid gland was symmetrical and slightly enlarged and on section was not remarkable. On

its posterior aspect was grayish tissue that looked like connective tissue. It was hard and fibrous and did not look at all granular as it would have been with carcinoma. I did a frozen section on a piece of it and found a tumor made up of uniform round cells and obviously epithelial. It reminded me of the adenomas that one sees in the bronchus. Dr Sweet then found that the surface of the trachea was involved with this same tumor.

DR LURIE: I then did a tracheotomy and looked into the mucous membrane of the trachea underneath the surface of the larynx and found that it was edematous, but there were no outcroppings and nothing that suggested a tumor mass.

DR CASTLEMAN: Dr Sweet took a biopsy of the trachea, and our final microscopical sections confirmed the diagnosis of adenoma. The cells were arranged in small glands corresponding to what is often called the mixed-tumor type of adenoma rather than the more common carcinoid type. By the mixed-tumor type I mean the type that is similar to the mixed-tumor of salivary-gland origin, it also resembles the cylindroma or epithelioma adenoides cysticum variety of the basal-cell epithelioma. This could be called a low-grade adenocarcinoma because it has invaded and infiltrated the posterior portion of the thyroid gland. I think we can say that the patient had had the tumor since the first symptoms began, sixteen years previously. It was very slowly growing and acted as any adenoma of the bronchus. There is still plenty of tumor left in the tracheal wall. We see adenomas of the bronchus with more tumor extrinsically than intrinsically, and it is not surprising that there was little intrinsic tumor in the trachea here. The problem arises regarding what should be done—whether a total laryngectomy should be performed or whether one should continue to follow her, knowing that the tumor is slowly growing but may metastasize to a regional lymph node and cause further difficulty by mediastinal spread.

This is the second case of tracheal adenoma that we have had here. The other was also of the same type and one that we diagnosed as epithelioma adenoides cysticum. It was in a man of sixty-eight who had had a local removal of the tumor two years previously, after having had symptoms for six months. Recently he developed a recurrence with

symptoms of marked dyspnea, wheeze and hemoptysis. Dr Sweet was able to resect a portion of the trachea, including a pedunculated tumor, 2 cm long, attached on a 6 mm base.

DR JOHN STANBURY: If she had a total thyroidectomy, what was the consistence of the thyroid gland?

DR CASTLEMAN: It was perfectly soft. The entire gland was removed. The only place it was not soft was on the posterior aspect, which was involved with tumor.

DR BENEDICT: I might mention that in looking up the literature, I found 507 cases of primary carcinoma and 19 adenomas of the trachea. We have had 30 adenomas of the bronchus all of which were in the major bronchi. I just asked Dr Lurie why he did not do a bronchoscopy and he said that he could not.

DR LURIE: We could have, but we would have had to do a tracheotomy right away. I thought from the way the patient acted and from the x-ray studies that the lesion was better handled by an external rather than an internal approach. To get some of this specimen I would have had to go through the entire thickness of the mucous membrane of the larynx and trachea.

DR BENEDICT: And there was no adenoma in the trachea?

DR LURIE: Nothing that I could demonstrate. She now has a tracheotomy tube, and the swelling in the larynx and trachea is gradually going down. The breathing space is better than it was before operation.

DR CASTLEMAN: Have you anything to add, Dr Schall?

DR LEROY A. SCHALL: This case has been covered so thoroughly that I do not believe I have anything to contribute. I saw the patient before operation and ruled against a bronchoscopy because of the swollen mucous membrane. I also thought that it was a surgical case and should be approached externally.

DR LURIE: Why do you think that a laryngectomy would cure the case? Was there infiltration in the esophageal wall?

DR CASTLEMAN: It is possible that there was invasion of the esophagus. I do not believe it was determined at operation.

# The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established 1828

Official Organ of

THE MASSACHUSETTS MEDICAL SOCIETY

and

THE NEW HAMPSHIRE MEDICAL SOCIETY

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND

PUBLISHED WEEKLY UNDER THE JURISDICTION OF THE  
COMMITTEE ON PUBLICATIONS

Richard M Smith M D, Chairman

James P O'Hare M D

Conrad Wesselhoft M D

Oliver Cope M D

John Fallon M D

Joseph Garland M D, Editor

ASSOCIATE EDITORS

Thomas H Lanman M D

Donald Munro M D

Henry Jackson Jr., M D

Clara D Davies, EXECUTIVE EDITOR

Robert O Leary, ASSISTANT EDITOR

EDITORIAL BOARD

C. Guy Lane M D

Henry R. Viets M D

Robert M. Green M D

Dwight O'Hara M D

Fletcher H. Colby M D

Robert L. Goodale M D

Chester M. Jones M D

Harvey R. Morrison M D

Maxwell Finland M D

James M. Faulkner M D

Carroll B. Larson M D

Francis D. Moore M D

C. Stuart Welch M D

Vernon P. Williams M D

Benjamin Castleman M D

Hugh R. Leavell M D

SUBSCRIPTION TERMS \$7.00 per year in advance, postage paid for the United States (medical students \$4.00 per year) Canada \$8.00 per year (Boston funds) \$9.50 per year for all foreign countries belonging to the Postal Union.

MATERIAL should be received not later than noon on Thursday three weeks before date of publication

THE JOURNAL does not hold itself responsible for statements made by any contributor

COMMUNICATIONS should be addressed to the *New England Journal of Medicine* 8 Fenway Boston 15 Massachusetts Telephone KE 6-2094

NEW ENGLAND ADVERTISING REPRESENTATIVE Edwin B Tyler 89 State Street, Boston Massachusetts Telephone LA 3 5516

## THE THORNDIKE AND ITS CASTLE

SOME twenty-five years ago the Thorndike Memorial Laboratory of the Boston City Hospital was formally opened by His Honor James Michael Curley. This laboratory, dedicated to clinical research, was made possible through the generosity of George L. Thorndike (born in Salem in 1847), an alderman of the City of Boston. It has continued to function through the years—for the public good, let it be remembered—owing partly to the foresight and good will of Mr. Curley and partly to the wisdom of its successive directors—Francis W. Peabody, George R. Minot and William B. Castle.

In a very literal sense this laboratory existed and functioned two years before its public dedication

in 1924, though much of the actual investigative work was carried on elsewhere, for the building was not then completed. One member of the staff worked in the private laboratory of Otto Folin (somehow he was neither Doctor nor Professor but simply and respectfully Otto Folin), who kept his notes on the backs of old envelopes and lectured in a superbly simple style.

Now there is more to this hospitality of Otto Folin than meets the eye. Then, as now, there was a close and cordial relation between the Thorndike and the Harvard Medical School. It was intended to be a co-operative enterprise and indeed it was. From the very start Francis Peabody made it clear to his staff—there were but four—that as their statures grew and as their interests changed there were open to the Thorndike men several channels of endeavor—the School, the Wards and the Laboratory. Yet the beginning and the end, the alpha and omega, were the same—the welfare of the patient. Francis Peabody wrote not long before his death: "What we need is less of the system and law that kills and more of the spirit that gives life." That spirit has always prevailed.

Basic research has its place. Without it progress would stand still, but beyond any question there must also be clinical investigation. And for clinical investigation there must be patients. For each there must be money. From the City of Boston come the patients, through the far-sighted generosity of the city officials comes, in large measure, the money and thus also comes the opportunity to investigate, and so to help, our fellow men.

Yet with all these golden opportunities the work of the Thorndike, now internationally known, would come to naught were there not wise and sympathetic medical guidance. There are problems of administration, problems of personnel and, of course, the decision as to what research shall be done by whom and in what manner. Such things require time, tact, knowledge, wisdom and considerable self-sacrifice.

The Thorndike has been especially fortunate in its directors. Each has had his own individuality and peculiarities.

The first, Francis Weld Peabody, brave soul that he was, needs praise from no man. With a subtle

force he launched the Thorndike on its course and early in its career laid down the major principle that the Laboratory, the Wards and the School were to be dedicated to one end—the education of the physician and the material benefit of the patient

After Dr Peabody's tragic and untimely death the directorship passed to his good friend, George Richards Minot, who was awarded the Nobel Prize not so very long after another good friend had said "Poor George, still stuffing his patients full of liver when you and I know it's quite useless" Dr Minot is a man of very varied interests. Being a horticulturist and botanist, he is justly proud of his garden and especially of his magnificent irises. He is a prolific writer of letters and there flows from his office a veritable flood of major and minor missives to friends and acquaintances all over the world. The only thing he dislikes is inactivity either in himself or in others. If Dr Peabody's motto was "*Do something useful*," Dr Minot's is "*Do something*." Those who have the good fortune to know him will recognize that in his heart of hearts he is a very kindly and a very thoughtful man. It is common knowledge that in spite of serious personal illness and in the face of many disappointments he had the faith, persistence and patience to further his own clinical investigation with patients on the wards and thus to initiate and perfect the therapy of Addisonian anemia. Dr Minot merits and surely will receive a cordial welcome whenever he chooses to revisit the Thorndike, whose destiny he guided for over twenty years.

And now on Dr Minot's retirement there comes a new director, William Bosworth Castle, Professor of Medicine, Master of Science (hon), as rugged an individualist as ever trod the floors of that mecca of individualists—the Thorndike Memorial Laboratory, Boston City Hospital. Yet new is hardly an apt word, for twenty-three years ago, when the Thorndike was still in its childhood, Big Bill was resident physician pursuing there the type of research that he is now directing.

Trained as a physiologist he thinks in terms of physiology and thinks with almost frightening clarity. Dr Castle's second outstanding quality—

unswerving integrity and honesty not only with others but also with himself—is scarcely less impressive than the first. The world knows him as a great investigator, but the men on "Two" and "Four"—the Second and Fourth Medical Services—know that, to boot, he is a very shrewd clinician. What is more important, he is a truly great and very unassuming man.

This, then, is the new director of the Thorndike Memorial Laboratory, and director of the Second and Fourth Medical Services of the Boston City Hospital. Under his guidance and with the continued help of the powers-that-be the Thorndike will continue to flourish and through clinical investigation the public will continue to be adequately served. This is as it should be.

---

### THE VAGINAL SMEAR AS A SCREENING TEST

Discussions of the periodic examination of apparently healthy people usually generate more heat than light. Before there will be real enthusiasm for applying a technic to broad segments of the population much more investigation is needed to determine the really essential elements of such examinations. We must know which procedures will be economically justified by the proportion of positive results when applied to large populations of varying sex, age and economic status.

The vaginal smear has been acclaimed in both the medical and the popular press as a most valuable adjunct in the diagnosis of uterine cancer. Since cervical cancer discovered early is often amenable to treatment, it is extremely important to evaluate this test and to determine its proper place in the definitive periodic examination that may be evolving.

Elsewhere in this issue of the *Journal* Lombard et al report promising preliminary results from a large series of vaginal smears made on patients in the Massachusetts cancer hospitals and state-aided cancer clinics. Final evaluation awaits further follow-up study. These investigators point out certain inaccuracies and drawbacks of the technic sufficient to suggest hesitation in accepting it as a routine measure applicable to the entire female

population of cancer-bearing age at present. Studies elsewhere have given similar results, though some are more enthusiastic than others.

There is need for further investigation to indicate best methods of obtaining specimens, selection of cases for the test, proportion of error that must be expected, cost of the examination and the most suitable administrative procedures. This type of report shows critical judgment and full appreciation of the really broad significance of screening tests for the detection of incipient disease among the general population.

### EFFECTS OF RUBELLA DURING PREGNANCY

LAST year Wesselhoeft<sup>1</sup> presented a very thorough review and discussion of the problems resulting from infection with German measles during pregnancy on the course of pregnancy and on the offspring. Aycock and Ingalls<sup>2</sup> also recently reviewed the subject of rubella, with particular reference to the problem of maternal disease as a principle in the epidemiology of congenital anomalies. At a recent meeting of the Midwestern Section of the American Federation for Clinical Research, Abel and Van Dellen<sup>3</sup> presented the results of their own survey of the effects of German measles during pregnancy. Their findings in 84 offspring of 82 mothers corroborated those of many authors quoted in the reviews mentioned above.

Three stillbirths were recorded from mothers having German measles during the first trimester of pregnancy. Twenty-five of the children were normal at birth. In seven of these the mother contracted the disease during the first trimester, eleven during the second and seven in the last. Fifty-six of the infants were abnormal at birth, thirty-six with a single defect and twenty with more than one defect. In forty-four (76 per cent) of these, the mother told of having German measles during the first trimester of pregnancy, eight in the second, one in the third and unknown in three. Nineteen of the infants had congenital heart disease, seventeen had cataracts, fourteen were deaf, and seven were mentally deficient. Gastrointestinal, eye, spinal and skeletal abnormalities also occurred in lesser numbers.

The most serious defects or combination of defects occur in women having German measles during the first trimester; defects are less serious and more infrequent in the second. In all, 87 per cent of the babies born of mothers having German measles during the first trimester were abnormal. No abnormalities developed in the third trimester.

Of particular interest is the manner in which these data were accumulated. One of the authors is a regular contributor to one of the popular syndicated health columns, which undoubtedly reaches millions of newspaper readers daily. This column was used as a medium for obtaining the information presented. He included a request for letters from mothers who had had German measles during pregnancy. They were asked to state the exact month of gestation in which the illness occurred and the effect on the offspring. Over 90 replies were thus obtained, and of these 82 were considered acceptable. The series includes two sets of twins, making a total of 84 children.

This method in reputable and critical hands undoubtedly opens up considerable possibilities for epidemiologic studies. The errors involved, however, are likely to be enormously greater than those obtained in studies of hospital histories or those based on personal surveys and interviews. It does, nevertheless, look like a very fertile field for obtaining at least a first approximation in many types of epidemiologic surveys.

### REFERENCES

1. Wesselhoeft, C. Rubella (German measles). *New Eng J Med* 236: 943-950 and 978-988, 1947.
2. Aycock, W. L. and Ingalls, T. H. Maternal disease as principle in epidemiology of congenital anomalies with review of rubella. *Am J Hyg* 62: 212-366-379, 1946.
3. Abel, S. and Van Dellen, T. R. Effect of German measles during pregnancy. *Am J Med* 4: 776, 1948 (Abstr.).

### PLANNED PARENTHOOD REFERENDUM

FINAL petitions asking that the planned-parent-hood question be placed on the November ballots in Massachusetts have been filed with the secretary of state of the Commonwealth. The 8429 signatures to these petitions, added to those obtained in 1947, make a total of 88,659. Numbered among the supporters of the thesis that physicians should be permitted to give contraceptive aid to married women for the protection of life or health, the Planned Parenthood League of Massachusetts claims 3363 Massachusetts physicians, or a majority of the resident members of the Massachusetts Medical Society.

In 1947 a bill providing for legalization of the contraceptive measure was initiated on a petition of 80,230 voters. After hearings before the Public Health Committee, this bill failed to pass either house.

Forty-six states of the Union now permit contraceptive advice to be given by physicians to married women for the protection of life or health.

## MASSACHUSETTS MEDICAL SOCIETY

### DEATHS

**CAPELES** — Thomas F. Capeles, M.D., of Haverhill, died on August 12. He was in his sixty-fourth year.

Dr. Capeles received his degree from Tufts College Medical School in 1909. He was a member of the New England Ophthalmological Society and a fellow of the American College of Surgeons and the American Medical Association.

A brother survives.

**CARROLL** — Henry G. Carroll, M.D., of Salem, died on August 11. He was in his sixty-fifth year.

Dr. Carroll received his degree from Dartmouth Medical School in 1907. He was a member of the New England Ophthalmological Society and a fellow of the American College of Surgeons and the American Medical Association.

His widow, two sons, a daughter and a sister survive.

**GRAINGER** — Edward J. Grainger, M.D., of Winthrop, died on July 25. He was in his seventy-first year.

Dr. Grainger received his degree from Harvard Medical School in 1903. He was formerly vice-president on the staff of the Winthrop Community Hospital.

His widow, two brothers and a half-sister survive.

**MARSH** — Arthur W. Marsh, M.D., of Worcester, died on June 24. He was in his eighty-second year.

Dr. Marsh received his degree from Harvard Medical School in 1895. He was a former president of Worcester District Medical Society, a member of the New England Surgical Society and a fellow of the American College of Surgeons and the American Medical Association.

His widow, two daughters, a brother and four grandchildren survive.

## NEW HAMPSHIRE MEDICAL SOCIETY

### DEATH

**ELKAVICH** — Frank D. Elkavich, M.D., of Troy, died on July 27. He was in his fortieth year.

Dr. Elkavich received his degree from McGill University Faculty of Medicine in 1937. He was an associate staff member of the Elliot Community Hospital in Keene and a former president of the Cheshire County Medical Society. He was a fellow of the American Medical Association.

His widow, a son, a daughter, his parents, a brother and two sisters survive.

## MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

### WOOD-TICK STUDY

The Massachusetts Department of Public Health is making a study of the wood-tick problem in the Commonwealth during the present season. This study was authorized by Chapter 36 of the Resolves of 1948.

The prevalence of ticks was rapidly declining by July 1, when the funds became available. Therefore, the most important part of the study this year is a survey to determine their geographical distribution. Much of the information, which is being collected on a questionnaire, is being supplemented by the identification of the ticks sent in by interested persons and of those collected by the personnel employed on the project.

The Department is most interested in receiving information about the prevalence of ticks outside the counties of Barnstable, Plymouth, Bristol, Nantucket and Dukes.

The co-operation of physicians in filling out questionnaires will be greatly appreciated. All information and any specimens collected should be forwarded to the Division of Communicable Diseases, 8 Beacon Street, Boston 8.

## MISCELLANY

### ALVARENGA PRIZE

In recognition of his studies on sludged blood the College of Physicians of Philadelphia has awarded the Alvarenga Prize for this year to Melvin H. Knisely, M.D., of the University of Chicago.

The Alvarenga Prize was established by the will of Pedro Francisco da Costa Alvarenga, of Lisbon, Portugal, an associate fellow of the College of Physicians of Philadelphia, to be awarded annually by the College of Physicians on each anniversary of the death of the testator, July 14, 1883.

## BOOK REVIEWS

*Gastritis*. By Rudolf Schindler, M.D. 8°, cloth, 462 pp., with 96 plates. New York: Grune and Stratton, 1947. \$10.00.

This is a painstaking and thorough study of an interesting disease by a pioneer worker who has had a vast experience in over twenty-five hundred cases in the last twenty-eight years, and who has worked hard to establish this difficult disease on a sound, anatomic and clinical basis.

The gross and microscopical pathology is given in great detail (seventy-four pages) as a basis for the disease and for correlation with symptoms. Gastritis is classified as acute and chronic, and chronic gastritis is divided into superficial, atrophic and hypertrophic and gastritis in other diseases (tumors, ulcers, postoperative). The causes of chronic gastritis are varied and often unknown. The author does not believe that alcohol plays an important part. Gastritis was found in about 40 per cent of the patients gastroscopied for gastric symptoms.

It is interesting to compare the visible changes in the gastric mucosa described by Wolf and Wolff in their fistula patient after emotional upsets with the changes in acute superficial gastritis, but Schindler does not believe that chronic gastritis is due primarily to mental events.

There is great divergence of opinion about the symptoms of gastritis and about the importance of the disease. Some authors consider it one of the most important clinical conditions, and others a symptomless and insignificant disease. The symptoms described — epigastric pain, loss of appetite, nausea, vomiting, weight loss, weakness, anemia and bleeding — seem general in type and not diagnostic. There is nothing characteristic about the ordinary physical examination, gastric analysis or x-ray picture in the author's opinion, and diagnosis is based solely on gastroscopy at present. There is real difficulty in correlating the symptoms with the picture seen at gastroscopy, and the author says, "for a long time to come the clinical picture of chronic gastritis will be subject to discussion and controversy."

For treatment the author's advice is to get rid of the cause if one can be found — infections, tobacco, vitamin deficiency and so forth — and to give a bland diet such as that used for peptic ulcer with hydrochloric acid or enzymes and perhaps liver extract in the atrophic form. The author takes a rather gloomy view of operations on the stomach for peptic ulcer and the frequency of postoperative gastritis and the difficulty of its treatment. The relation of gastritis to peptic ulcer, cancer and pernicious anemia is very fully described.

There are brief reports of 55 cases and nearly a hundred pages of photomicrographs. The color prints are clear and well chosen. The book is well written, illustrated and printed. It is a valuable contribution to this subject and is highly recommended to the internist and gastroenterologist.

*Textbook of Human Physiology*. By William F. Hamilton, Ph.D. 8° cloth, 504 pp. with 121 illustrations. Philadelphia: F. A. Davis Company, 1947. \$6.00.

The author makes it clear that the content of this book has been restricted to the things that the average medical student can encompass in the short time he is in the department of physiology. With this aim in view, much of importance has been left out in the hope that the clinic and the hospital will teach physiologic facts that the formal physiology course lacks the time to deal with. The author succeeds rather well in presenting the general outline of mechanisms whose normal or abnormal functioning is to be the central theme in the future life of the physician. There can be little doubt that the thirty-two chapters constitute merely the framework of physiology and that medical students will need to have their attention drawn to the urgent need for collateral reading. It seems to the reviewer that this textbook is more adapted for the use of college students than for that of medical students. Nevertheless, the book will serve a useful purpose in orientation in a course in human physiology.

*Diseases of the Joints and Rheumatism*. By Kenneth Stone, D.M. (Oxon), M.R.C.P. 8° cloth, 362 pp. with 58 illustrations. New York: Grune and Stratton, 1947. \$6.50.

This book contains much useful information about joints and about arthritis, but it fails to live up to its ambitious title. The classification of arthritis varies somewhat from that commonly employed, but it is logical and simple. The chapter on the physiology of joints is good. The author has an interesting theory in relating fibrositis and similar conditions to vagotonia. In future editions it is hoped that he will make a more complete discussion of symptoms and treatment of articular disease. The book is a useful but somewhat incomplete guide for the treatment of arthritis and allied conditions.

*Fatigue and Impairment in Man*. By S. Howard Bartley, Ph.D., and Eloise Chute, M.A. With a foreword by A. C. Ivy, Ph.D., M.D. First edition. 8° cloth, 429 pp. New York: McGraw-Hill Book Company, Incorporated, 1947. \$5.50.

The authors of this book are to be congratulated on a clearly written, comprehensive account of fatigue and impairment in man. The thesis is developed that very little of the work that has been done on fatigue refers to the experience of feeling tired and that fatigue is necessarily a reaction of the total organism. It is pointed out that the earliest studies dealing with impairment, work output and overt behavior have thrown light on fatigue merely in revealing what it is not, and in such approaches to the problem, considerations of bodily sensations, attitudes and matters of motivation have been almost totally neglected. No clear-cut distinction between fatigue and impairment has ever been made and constantly maintained.

Impairment is seen as referring to the condition of tissue, which is directly discovered only by physiologic and biochemical analysis, whereas fatigue is seen as an expression of the organization of the whole organism, which can be described only in personalistic terms. It is pointed out that fatigue is not an entity specified in quantitative units. The plan of the book is dictated by the distinction between fatigue and impairment, and after a chapter devoted to a detailed discussion of the various views on fatigue, electrophysiologic studies, anoxemia, lack of sugar, temperature

extremes and water-salt lacks, metabolism, hours and conditions of work in industries, drug action, neuromuscular activity, sleep, mental fatigue, personal factors in work situation, visual performance, conflict and frustration and chronic fatigue are considered. Each chapter is accompanied by many references and at the end of the book appears a valuable list of visual aids.

This book unquestionably represents a fundamental contribution to the important subject of fatigue and impairment in man.

## BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

*Bergey's Manual of Determinative Bacteriology*. By Robert S. Breed, New York State Experiment Station (Cornell University), Geneva, New York; E. G. D. Murray, McGill University, Montreal; and A. Parker Hitchens, University of Pennsylvania, Philadelphia. Sixth edition. 8° cloth, 1529 pp. Baltimore: The Williams and Wilkins Company, 1948. \$15.00.

This standard reference work, first published in 1923 and last revised in 1939, has been completely revised and reset in a double column format for the sixth edition. The type content has been increased about 20 per cent. The work is supervised by a new board of editors, with Robert S. Breed of the original board of chairmen assisted by a group of sixty contributors. Some changes have been made in the outline classification. The number of species of fission fungi has been increased from 1335 in the previous edition to 1630 in the present edition. There is a new source and habitat index. Many new binomials have been included in the index of names of genera and species. The preliminary text comprises a historical survey of classifications of bacteria, how bacteria are named and identified and rules of nomenclature. The descriptions of bacteria are then presented by orders, suborders and families. The two indexes mentioned above conclude the text. The printing is well done with a good type on a good light paper. The weight of the book is not excessive for its size. The work is an essential reference book for all medical and public libraries and for all bacteriologists.

*Life: Its nature and origin*. By Jerome Alexander. 8° cloth, 291 pp. New York: Reinhold Publishing Corporation, 1948. \$5.00.

This monograph has been written primarily for the general reader and each topic is treated in as simple and elementary a manner as possible. The fundamental objective of the work is to show that life is dominated by catalysis. In order are discussed the origin and physical basis of life, the nature of living units, the catalytic mechanism whereby life exists, persists and proceeds, immunology, genetics, evolution and embryology. There are special chapters on some catalytic aspects of disease and drugs and on philosophy, the guide to mental health. Each chapter has a list of references mentioned in the text. Author and subject indexes conclude the book. The text is well written and arranged and the book is well published in every way. The volume should be in all large medical and general libraries.

*Occupational Medicine and Industrial Hygiene*. By Rutherford T. Johnstone, M.D., consultant in industrial health, and lecturer at the University of California, Los Angeles. 8° cloth, 604 pp., with 117 illustrations. St. Louis: The C. V. Mosby Company, 1948. \$10.00.

This new work on occupational medicine has been divided into four parts. The first comprises general topics, including workmen's compensation, medicolegal aspects, functions of the industrial physician, teaching of industrial medicine, diagnosis and laboratory procedures in diagnosis. The second and third parts and a portion of the fourth discuss the substances used in industrial plants — the solvents, metal and dust — and their hygienic and pathologic aspects. There are special

chapters on tuberculosis and pneumonia in industry, the dermatoses, synthetics and special industrial processes. Industrial hygiene in general is dealt with in two chapters, and the final chapter concerns pre-employment examinations and placement. The appendixes list the chemicals in common trade-name products and organic solvents used for cleaning or degreasing. A good index concludes the volume. Pertinent references are appended to each chapter. The material is well organized, and the text well written. The publishing is excellent. The work is recommended for all medical and public-health libraries and to industrial physicians.

*Pathological Histology*. By Robertson F. Ogilvie, M.D., F.R.C.P. (Edin.), F.R.S.E., lecturer in pathology and assistant in forensic medicine, University of Edinburgh, senior pathologist, Royal Infirmary, Edinburgh, pathologist to the Leith and Deaconess Hospitals, Edinburgh, and examiner in pathology and forensic medicine for the triple qualification. With a foreword by A. Murray Drennan, M.D., F.R.C.P. (Edin.), F.R.S.F., professor of pathology, University of Edinburgh. Third edition 8°, cloth, 459 pp., with 260 photomicrographs in color. Baltimore: The Williams and Wilkins Company, 1947. \$10.00.

This third edition of an English textbook, first published in 1940, has been extensively rewritten, revised and amplified. Fifteen subjects and plates have been added. The volume is designed for the use of students and as a companion to a standard textbook on pathology. A good index concludes the volume. The text is well printed with a good type on good light paper, with the color plates as inserts, making the book not too heavy for its size. The color work is excellent. The printing was done in Great Britain, and the binding in the United States. The volume should prove valuable as a reference work in all medical libraries.

*History of Medicine. A correlative text, arranged according to subjects*. By Cecelia C. Mettler, Ed.D., A.M., Ph.D. Edited by Fred A. Mettler, A.M., M.D., Ph.D., associate professor of anatomy, College of Physicians and Surgeons, Columbia University. 8°, cloth, 1215 pp. Philadelphia: Blakiston Company, 1947. \$8.50.

Dr. Mettler, in this new book on the history of medicine, has divided her subject into large, well recognized medical specialties and further subdivided them into chronologic periods within the subjects. The subjects covered comprise anatomy and physiology, pharmacology, pathology and bacteriology, physical diagnosis, medicine, neurology and psychiatry, venereology, dermatology, pediatrics, surgery, obstetrics and gynecology, ophthalmology and otology, and rhinology. The period covered is from the time of primitive man to the nineteenth century. Such important subjects as dentistry, veterinary medicine and public health are omitted. The modern period is considered as the seventeenth to nineteenth centuries. The treatment by subjects deprives the scholar of the broad perspective of a period in all branches of medicine, but as this approach may be found in the histories of Baas, Garrison and others, the new style of Dr. Mettler provides a reference work of outstanding value. Throughout the text extensive quotations are given from fundamental writings of various authors. In the section under medicine, entitled "Background of Early American Medicine," foreign names predominate to such an extent that it is very difficult to get a picture of American medicine of the eighteenth century. At least the two earliest medical books printed in the United States in Boston in 1708 and 1720, the *English Physician* and the *Pharmacopoeia* of Nicolas Culpeper should have been noted. The text is well written and well printed in two columns on a coated paper too heavy for this type of book. The printing of personal names in heavy type is to be commended as good practice. A long list of selected readings is appended to each chapter. The volume concludes with comprehensive indexes of authors and subjects. Valuable historical maps are printed on the lining papers of the binding. This is a bad practice, since such printings are liable to defacement and destruction. This work is recommended as a reference source to all medical and general libraries and to all physicians interested in the history of medicine.

*Symposium on Medicolegal Problems Under the co-sponsorship of the Institute of Medicine of Chicago and the Chicago Bar Association*. Edited by Samuel A. Levinson, M.D., Ph.D., University of Illinois College of Medicine for The Committees of the Institute of Medicine and The Chicago Bar Association. 12°, cloth, 255 pp. Philadelphia: J. B. Lippincott Company, 1948. \$5.00.

The papers in this small volume were read and discussed at joint meetings by fourteen legal and medical authorities (including Professor Alan R. Moritz, of the Harvard Medical School) held at Chicago in 1945. The program was arranged by representative committees of the Institute of Medicine of Chicago and the Chicago Bar Association. The meetings were attended by physicians, lawyers, social workers, hospital managers, industrial commissioners, theologians and interested lay people. The subjects selected for discussion were the medical witness in court and expert testimony, artificial insemination and its medicolegal implications, the practice of pathology and its medicolegal problems, operations to produce sterility, medicolegal implications, trauma and tumors in industrial medicine, and scientific tests in evidence, including blood-grouping tests in disputed-paternity cases and chemical tests for intoxication. A physician and a lawyer, specialists in their particular fields, discussed each topic, the physician presenting the current medical opinion, and the lawyer interpreting the law. The discussions participated in by the group and audience were long, pertinent and instructive. Dr. Hawkinson, speaking on the medical witness and expert testimony, reviewed the history of attempts to regulate testimony, including the state plans, in which was mentioned the Massachusetts Briggs Law and the Minnesota plan of supervising and regulating medical testimony in the Minnesota courts, a joint plan of the State Medical Association and the State Bar Association. On the question of artificial insemination, with its medical, legal, social and religious problems, it was brought out that the law at present is at variance with scientific advance and that there is no law covering the whole problem. In the discussion of the practice of pathology, the question of various privileges claimed by physicians and the physician-patient relation were presented medically and legally. Also, an interpretation of the laws governing the human dead body was given. The Municipal Court of the City of Chicago, as early as 1922, was interested seriously in the problem of eugenic sterilization. In the discussion on this subject it was pointed out that the legal proof should guide the physician although he is convinced that there is sufficient scientific evidence to justify this type of operation. The consensus of medical opinion is that a single trauma does not produce tumors. The courts have held that, since the cause of tumors is unknown, trauma may be one of the unknown factors leading to tumor formation. The burden of proof rests on the scientist. The objective of the symposium was to bring into the open questions confronting the medical and legal professions. The meetings were very successful and a second series was held in 1947, it is hoped to make the meetings an annual affair. The text is well written in a simple style. The volume is well published in every way. The seemingly high price for a small volume is justified by the probable anticipated limited distribution. The book is recommended for all medical and legal libraries and to all persons interested in medicolegal problems.

*The Rh Factor in the Clinic and the Laboratory*. Edited by Joseph M. Hill, M.D., and William Dameshek, M.D. 4°, cloth, 192 pp., with illustrations and tables. New York: Grune and Stratton, 1948. \$4.25.

This monograph is the joint work of fifteen authorities in their particular fields. The first article is a survey of the significance of the Rh factor, and is followed by articles on the various aspects of the Rh factor in clinical medicine. The last article is a historical review of Mexican blood transfusion. The book is well published in every way and should be in all medical libraries.

*Laboratory Technique in Biology and Medicine*. By E. V. Cowdry, professor of anatomy, Washington University, and director of research, The Barnard Free Skin and Cancer Hospital, St. Louis. Second edition 8°, cloth, 269 pp. Baltimore: The Williams and Wilkins Company, 1948. \$4.00.

The first edition of this manual was published in 1943 under the title, *Microscopic Technique*. The second edition has been revised to include methods developed since 1943. The

material is arranged alphabetically by subjects and printed in two columns to conserve space and paper. The volume should prove valuable as a ready reference source for all medical libraries and physicians and technicians.

*Modern Treatment of Peptic Ulcer* By Asher Winkelstein, M.D., associate physician for gastroenterology and physician in charge of the Gastro-Intestinal Clinic, The Mount Sinai Hospital, New York City, and assistant professor of clinical medicine (gastroenterology), Columbia University, College of Physicians and Surgeons. 8°, cloth, 201 pp. New York: Oxford University Press, 1948. \$4.00.

This small work considers the various aspects of the treatment of peptic ulcer. Etiology, pathology and prophylaxis are discussed, and ten chapters are devoted to drip therapy. There are chapters on vagotomy, therapy with enterogastrome, urogastrome and the protein hyperalimentation therapy, followed by consideration of the psychosomatic aspects. A bibliography and index conclude the volume. The publishing is well done in every way. The book should prove of value to physicians interested in the subject.

*Oxford Loose-Leaf Medicine* (Sixteen reprints from the Supplements) 4°, paper. New York: Oxford University Press, 1947. Available only to subscribers to complete sets of *Oxford Loose-Leaf Medicine*.

In 1947 the *Oxford Loose-Leaf Medicine* was amplified by the publication of a large number of revisions of various articles that were issued. Sixteen of these articles have been reprinted as separate publications. This material is available only to subscribers to complete sets of the work. Notable among these reprints may be mentioned Bright's disease, by Henry A. Christian, headache, by Walter C. Alvarez, arterial hypertension, by David A. Man and scarlet fever, by James D. Trask and Paul L. Boissert. The publication is well done in the usual excellent style of the Oxford University Press.

*Introduction to the History of Science*. Vol. III. *Science and Learning in the Fourteenth Century*. By George Sarton, D.Sc., L.H.D., and L.L.D., professor of the history of science, Harvard University, and associate in the history of science, Carnegie Institute of Washington. In two parts. 4°, cloth, 1018 pp. Baltimore: Published for the Carnegie Institute of Washington by Williams and Wilkins Company, 1947. \$20.00.

Dr Sarton in the third volume of his monumental work on the history of science, covers the period of the fourteenth century. In the earlier sections the literature and learning from the time of Homer through the thirteenth century were presented in three large volumes. These early volumes, published in 1927 and 1931 and long out of print, have recently been reprinted by a photographic process and are now available at reasonable prices. This volume, comprising 2155 pages, has been issued in two large volumes, dividing the century into two equal parts. In the preface by the author there are noted corrections to Volume I and addenda to Volumes I and II. The style of the work has been maintained as originally planned. The general chapters preceding each half century — a survey of science and intellectual progress, religious background, the translators, education and the philosophical and cultural background — are intended for consecutive reading. The special chapters on each field of knowledge are intended for reference purposes. The sections on medicine comprise one hundred and sixty-one pages. Appended to each author considered are references to his works by recognized authorities. A complete table of contents for the century precedes the text. An addenda of forty-two pages, made necessary by the long time required for printing, and a general bibliography of forty-one pages conclude the text. A comprehensive general index of names and subjects of 174 pages, and special Greek, Chinese and Japanese indexes conclude the volume. The publishing is well done in every way. Dr Sarton has spent the best part of his life in producing this scholarly and outstanding reference work that is practically impossible to review textually without writing another book. The complete set should be in all libraries, public and private, general and special. It is recommended for all medical libraries. It is hoped that Dr Sarton will be able to continue his studies through the fifteenth century where the literature is tremendous in quantity and will live to see them published as the crowning achievement of his life.

*Clinical Laboratory Methods and Diagnosis: A textbook on laboratory procedures with their interpretation*. By R. B. H. Gradwohl, M.D., D.Sc., F.R.S.T.M. & H. (London), director to the Gradwohl Laboratories and Gradwohl School of Laboratory Technic, pathologist to Christian Hospital, and director, Research Laboratory, St. Louis Metropolitan Police Department, St. Louis. Fourth edition. In three volumes. 4°, cloth. Vol. I, 1296 pp., 362 illustrations and 41 color plates. Vol. II, 1114 pp., 328 illustrations and 9 color plates. Vol. III, *Parasitology and Tropical Medicine*. By R. B. H. Gradwohl, and Dr. Pedro Kouri, director, Institute of Tropical Medicine, professor of parasitology and tropical medicine, vice-dean of the Faculty of Medicine, Havana University, and director of Laboratorios Kuha, Havana. 864 pp., 420 illustrations and 7 color plates. St. Louis: The C. V. Mosby Company, 1948. \$40.00 for the set.

This authoritative reference set has been greatly expanded over the previous edition of 1943, and contains 55 per cent more text material and 51 per cent more illustrative material. The revisions and expansions are so numerous that they cannot be listed in detail. A chapter on electrocardiography has been added, and the section on parasitology has been expanded from 394 to 819 pages and made a separate volume on parasitology and tropical medicine. References to the literature are printed as footnotes in their proper places. Volumes I and II, on clinical methods and diagnosis, are pagged consecutively, with a comprehensive index at the end of the second volume. Volume III is pagged separately and has its own index. The material is well arranged, and the typography, paper, illustrations and color work are excellent. The work is exceptional and should be in all medical libraries as an essential reference source.

## NOTICES

### ANNOUNCEMENTS

Dr W. Charles Inman, assistant commissioner, Massachusetts Department of Mental Health, has been appointed superintendent of the Grafton State Hospital, North Grafton, Massachusetts. He will assume the duties of that position on September 16.

Drs Leland S. McKittick, John B. McKittick and Thomas S. Risley announce the removal of their offices to 1180 Beacon Street, Brookline.

Dr William F. Ryan announces the opening of his office for the practice of ophthalmology at 520 Commonwealth Avenue, Boston.

### RESIDENCIES IN PSYCHIATRY AND NEUROLOGY

The Veterans Administration has immediate openings for at least a hundred young doctors interested in taking residency training in psychiatry or neurology, or both, it was recently announced.

Veterans Administration hospitals offering these residencies are situated in almost every section of the country. All are under supervision of the deans' committees, mostly composed of members of university faculties of Class A medical schools.

Applicants for residency training in these fields must be citizens of the United States and graduates of a school of medicine approved by the Veterans Administration and the Council on Medical Education and Hospitals of the American Medical Association, and must have completed an internship acceptable to the Veterans Administration.

In general, these residencies cover a three-year program of specialty training, although one-year and two-year programs are also available at most of the hospitals.

Junior or first-year residents must have completed a satisfactory internship and must be considered ready for specialization. Intermediate or second-year residents must have

the qualifications of a junior resident in addition to the equivalent of one year's training in the specialty. Senior residents must have the qualifications of a junior resident in addition to two years' training in the specialty.

Interested doctors may obtain information and application forms regarding the residencies by writing to the chief medical director, Veterans Administration, Washington 25, D C.

Residency selection and residency grades for the applicant are recommended by the dean's committee supervising the program at the Veterans Administration hospital in which the applicant desires to train.

#### VETERANS ADMINISTRATION RESIDENCY-TRAINING PROGRAM IN NEUROPSYCHIATRY

A limited number of openings are available for appointment to the residency-training program in neuropsychiatry of the Veterans Administration Department of Medicine and Surgery. This program is under the jurisdiction of the deans of the Boston medical schools (Harvard, Tufts and Boston University). Training in this program, which may be from one to three years, is given at

Cushing Veterans Administration Hospital, Framingham, Massachusetts

Bedford Veterans Administration Hospital, Bedford, Massachusetts

The Mental Hygiene Clinic of the Boston Regional Office, Veterans Administration, Boston, Massachusetts

West Roxbury Veterans Administration Hospital, West Roxbury, Massachusetts

White River Junction Veterans Administration Hospital, White River Junction, Vermont

Emphasis in the entire program is on psychiatry, with dynamic orientation, and includes closed ward, open ward, outpatient, child psychiatry and neurology.

Further information may be obtained from the chief neuropsychiatrist, Veterans Administration, Branch Office No 1, 55 Tremont Street, Boston 8, Massachusetts.

#### JOHN AND MARY MARKLE FOUNDATION GRANTS

Medical schools in the United States and Canada are invited by the John and Mary R. Markle Foundation to make nominations for the second group of scholars in medical science on or before December 1, 1948. Each school, through the dean, may nominate one candidate. No nominations from individuals will be considered.

The program is designed to aid promising young men and women, planning careers in academic medicine, who have not yet made their reputations. They should have completed the usual fellowship training in some area of science related to medicine and should hold, or expect to hold, in the academic year 1949-1950 a full-time faculty appointment on the staff of a medical school.

Grants of \$25,000, payable at the rate of \$5,000 annually, will be made to the schools over a five-year period for the support of each scholar finally selected or his research, or both.

The number of scholars to be appointed in 1949 has not yet been determined. Sixteen were chosen in 1948. A new booklet describing the plan is available on request from the Foundation, 14 Wall Street, New York 5, New York.

#### INTERNSHIPS IN VETERANS ADMINISTRATION HOSPITALS

A limited number of internships in Veterans Administration hospitals will be offered qualified medical graduates. The internships will be limited to the seventy-five Veterans Administration hospitals now offering residency-training programs in co-operation with fifty-nine Class "A" medical schools over the country. They will be further limited to hospitals that have bachelor quarters available on the station grounds. A survey is in progress to determine what housing is available.

The two types of internship that will be available are as follows "straight," for surgery, general medicine and other "straight" subjects, and "rotating," in which interns study under a rotating schedule, surgery, general medicine and related subjects. Arrangements will be made for affiliated training for obstetrics and pediatrics in other than Veterans Administration hospitals. Such affiliated training may not involve more than 20 per cent of a year. The hospital at which the affiliated training is obtained must be approved for internship by the Council on Medical Education and Hospitals of the American Medical Association.

"Mixed" internships will not be offered.

Internships will be for one year, subject to reappointment for one year, if the reappointment is desired and recommended by the local dean's committee. The dean's committee, composed of members of university faculties or prominent local doctors, supervise the residency training program and will also supervise internship training.

Annual pay for interns will not exceed \$1,800 a year. Quarters, subsistence and laundry will be furnished. The stipend at each hospital will be determined by the Veterans Administration's chief medical director on recommendations of the deans' committees and in conformance with the existing scale of remuneration for interns in the locality.

Interns will be appointed in accordance with the national policy for all medical schools and hospitals, once each year on November 15, their tour of duty to begin the following July 1 or January 1 following July 1.

The new program is under the supervision of Dr. Paul B. Magnuson, chief medical director of the Veterans Administration, and Dr. Edward Harvey Cushing, assistant medical director for research and education in the Department of Medicine and Surgery, Veterans Administration. Those interested in residency training or internship should make application to the dean's committee at the university co-operating with Veterans Administration in the program, or to the manager of the hospital in the area in which they prefer to serve.

#### SILIFORM AMPOULES

Druggists and the medical profession are urged by the Food and Drug Administration, Federal Security Agency, to return all stocks of Siliform ampoules to the manufacturer, The Heilkraft Medical Company, Boston, Massachusetts. This injection drug, which should be sterile, is potentially dangerous since samples collected on the market contain living organisms. Siliform is injected by some physicians and osteopaths in the belief that it will relieve patients suffering with rheumatism as claimed by the manufacturer. The Food and Drug Administration found the contaminated samples after a routine inspection at the Heilkraft factory disclosed that the Siliform ampoules had been manufactured without sterilization. Intensive recall efforts by the manufacturer and the Food and Drug Administration since July 15 have not brought in all of the contaminated stocks. The article, which moves slowly, was shipped to 37 states from Maine to California and later was redistributed by wholesalers who cannot trace many of their sales. Some going back as far as 1946 have been found on the market. These ampoules may be in the hands of doctors, hospitals, clinics and retail and wholesale druggists.

#### SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, SEPTEMBER 2

FRIDAY SEPTEMBER 3

\*10:00 a.m.-12:00 p.m. Medical Staff Rounds. Peter Bent Brigham Hospital.

TUESDAY SEPTEMBER 7

\*12:15-1:15 p.m. Chnicroontgenological Conference. Peter Bent Brigham Hospital.

\*1:30-2:30 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children. Massachusetts General Hospital.

WEDNESDAY SEPTEMBER 8


\*12:00 p.m.-1:00 p.m. Clinical Conference. (Children's Hospital) Amphitheater. Peter Bent Brigham Hospital.

\*Open to the medical profession.

(Notices concluded on page 31)

NOTICES (Concluded from page 352)

- SEPTEMBER 7-11 American Congress of Physical Medicine Page 382 issue of April 15
- SEPTEMBER 7-11 American Occupational Therapy Association Page xv issue of July 8
- SEPTEMBER 9 Some of the Advances in Surgery Dr Frank H Lahey Pentucket Association of Physicians 8 30 p m Haverhill
- SEPTEMBER 13-15 American Academy of Pediatrics Olympic Hotel Seattle Washington
- SEPTEMBER 14 New England Society of Anesthesiologists Page 316 issue of August 19
- SEPTEMBER 16-18 Vermont State Medical Society Annual Meeting Burlington
- SEPTEMBER 20-23 American Hospital Association Page 310 issue of February 26
- SEPTEMBER 22 New England Conference of Industrial Physicians and Surgeons Page 244 issue of August 5
- SEPTEMBER 29 Mississippi Valley Medical Editors Association Page 170 issue of January 29
- OCTOBER 6-9 American Board of Ophthalmology Page 170 issue of January 29
- OCTOBER 18-22 American College of Surgeons Page 34 issue of July 1
- OCTOBER 27 New England Obstetrical and Gynecological Society Annual Meeting Hotel Somerset, Boston
- NOVEMBER 1-3 American Clinical and Climatological Association Page 382 issue of April 15
- NOVEMBER 3 and 4 Annual Meeting of National Committee for Mental Hygiene Inc. Page 282 issue of August 12
- NOVEMBER 8-12 American Public Health Association Page 420 issue of March 18
- NOVEMBER 10-13 Association of Military Surgeons of the United States Page 722 issue of May 15
- NOVEMBER 20-23 American Academy of Pediatrics Annual Meeting Chalfonte Haddon Hall Hotel Atlantic City New Jersey
- DECEMBER 7-9 Southern Surgical Association Annual Meeting Page 343 issue of April 8
- DECEMBER 9 and 10 New York State Society of Anesthesiologists Page 34 issue of July 1
- FEBRUARY 4 1949 American Board of Obstetrics and Gynecology Inc Page 244 issue of August 5
- MARCH 28-APRIL 1 1949 American College of Physicians Page 158 issue of July 22
- NOVEMBER 11-17 1949 Third Inter-American Congress of Radiology Page 158 issue of July 22



*When summer brings green apple days  
And the children are running both ways,  
Dr Wise shortly finds  
A stout potion that binds —  
In the ads that the Journal displays*

2

## TWO-WAY PROTECTION


**Tablets FERROSATE (Kenmore)**  
(Ferrous Sulfate gr iv)

are coated twice to provide a doubly protected Ferrous Sulfate offering these therapeutic advantages

- 1 Inner coating prevents premature oxidation in vivo
- 2 Outer coating increases palatability and aids in preventing tooth discoloration

Write Dept. N8 for professional sample.

**Kenmore Pharmacy, Inc.**  
500 Commonwealth Ave.  
Boston, Mass. U.S.A.



Advertisement

# From where I sit by Joe Marsh

## Jeb Had the Folks in Stitches!

*At the Friday Night Social, Jeb Crowell had the whole audience in stitches—doing a take-off on the blustering cocksure character who belittles everybody and everything that isn't from his own home town*

Well, we can laugh at that sort of character because from where I sit, Americans are just the opposite. We like to boast a bit perhaps, about the paint job on the new barn, or the missus' style of cooking—but we aren't intolerant of people who don't think or act the same way we do.

*In our town, for instance. Some folks like band concerts, others don't—some families serve beer with dinner, others, buttermilk. As for politics, there's plenty of healthy disagreement.*

But when it comes to denying folks the right to think or act as they choose no, we're simply like you—we don't believe in it, whether it goes for serving beer, or speaking one's mind on public affairs

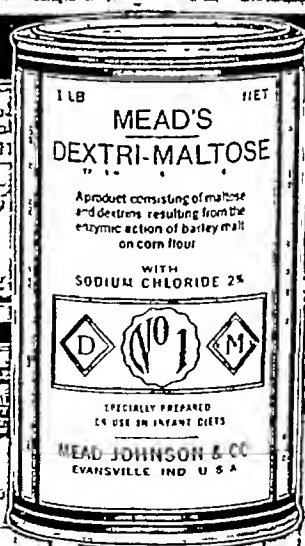
*Joe Marsh*

Copyright, 1948, United States Brewers Foundation

# BACKGROUND

The use of cow's milk, water and carbohydrate mixtures represents the one system of

infant feeding that consistently, for over three decades, has received universal pediatric



recognition. No carbohydrate employed in this system of infant feeding enjoys so rich and enduring a background of authoritative clinical experience as Dextri-Maltose.

# The New England Journal of Medicine

Copyright, 1948 by the Massachusetts Medical Society

Volume 239

SEPTEMBER 2, 1948

Number 10

## THE ROLE OF SODIUM IN THE PRODUCTION OF EDEMA\*

JOHN P. PETERS, M.D.†

NEW HAVEN, CONNECTICUT

THE term "edema" is applied to swellings produced by excessive accumulation of extracellular fluid without definite bounding membranes. These may be local or general. They are usually, but not always, associated with expansion of the total extracellular fluid of the body. They are even more loosely correlated with the total amount of water in the body. The simplest example of the formation of edema without change of the volume of fluid in the body is the swelling of the feet of a subject who stands still or rests in a relaxed position against a board at an angle of 60°. It is of the utmost importance in the analysis of edema to distinguish between the influence of exchanges between the body and the external environment on the one hand, and the distribution of fluid within the body on the other.

Although the extracellular fluid is more or less continuous, the distribution of this fluid need not be uniform. Pools of edema may occur because of local disturbances of the forces that determine the formation and removal of extracellular fluid. For example, in lymphedema fluid containing a high concentration of protein accumulates in the lower extremities because the lymphatic vessels are obstructed. If the subject is placed in the recumbent position with feet elevated, the fluid seeps into the flanks, which may become temporarily edematous.

The principal components of the extracellular fluid are sodium salts, chiefly the chloride, and water. The proportions of these components, which can diffuse freely throughout the extracellular fluid, are sedulously preserved by means discussed below. The accumulation of edema is limited, therefore, by the supply of either salt or water.

Motions of fluid between the blood capillaries and the adjacent spaces are governed, as Starling<sup>1</sup> showed, by the balance between two opposing forces, hydrostatic pressure and colloid osmotic pressure. In the simplest concept of the principle, the force

driving fluid from the capillaries is the blood pressure in these vessels, the force driving or drawing water back into the blood stream is the osmotic pressure of the proteins, and especially albumin, which has a smaller molecular size than globulin. Such a simplified concept assumes that the fluid about the capillaries contains no protein and is under no hydrostatic pressure. Actually, this fluid does contain variable amounts of protein and is under a certain hydrostatic pressure, the elasticity of the tissues, or tissue tension. The equilibrium between blood and extracellular fluid is, therefore, more precisely defined as follows: transudation is favored by capillary blood pressure and colloid osmotic pressure of perivascular fluid and opposed by colloid osmotic pressure of plasma and by tissue tension, factors that contribute to tissue tension are inherent inelasticity of tissues and distention of tissues by fluid because of imbalance of capillary-tissue exchange and variations of lymphatic drainage.

It is thus evident that the tendency to transudation cannot be correlated directly with either capillary blood pressure or serum albumin alone. Nevertheless, the applicability of the Starling principle to the formation of edema in a variety of conditions has been challenged because the presence and magnitude of edema is not directly correlated with either or both of these forces. The validity of this theory does not rest upon physical measurements of capillary blood pressure and colloid osmotic pressure. It follows naturally from thermodynamic laws if the composition of extracellular fluid is identical with that of an ultrafiltrate of plasma, which has been demonstrated by abundant evidence. The brilliant experiments of Krogh, Landis and others proved that hydrostatic pressure and colloid osmotic pressure in particular systems of the body are susceptible to accurate measurement. With present knowledge it can be asserted that if these measurements had been incompatible with the Starling principle, it would have been a reflection upon the measurements, not the principle.

It is fundamental to a critical evaluation of the formation of edema that physiologic and clinical

\*Presented at a meeting of the Boston City Hospital House Officers Association, Boston, April 20, 1948.

†John Slade Eli Professor of Medicine, Yale University School of Medicine.

hypotheses dealing with this process be compatible with basic mathematical, physical and chemical laws. If the simple relation between the concentration of serum albumin and transudation from the blood stream appears to be violated, conditions of equilibrium must be more carefully examined. One reason for discrepancies is the fact that capillary blood pressure is not uniform throughout the blood stream. Its measurement in the intact animal in any part of the blood stream is difficult, in most parts it is impossible. It must never be confused with arterial pressure, with which it may even be inversely related under certain circum-

stances. It may be attributed to constant slight seepage through the capillary walls, possibly with contributions from the cells bathed by this fluid. This protein cannot return to the circulation through the intact capillary walls, but is taken up selectively by the lymphatic vessels. This explains the stubborn character of lymphatic edema and the high concentrations of protein found in such fluid. Unfortunately, neither the volume nor the flow of lymph can be measured.

In certain parts of the circulation, especially the liver and portal circulation, the vessels appear to be regularly and of necessity more permeable to protein.<sup>1, 2</sup> This was first demonstrated by Starling,<sup>1</sup> who recognized that the blood pressure in the portal vein is so low that if there were not protein in the fluid about the capillaries in this region the tissues would become completely desiccated. There must be in these regions a continuous circulation of protein from blood stream to extracellular fluid and back through the lymphatic vessels and the thoracic duct to the blood stream. This has been demonstrated by means of foreign proteins and various materials that adhere to or combine with protein.

Among these materials are the dyes, including Evans blue (T-1824), employed for the measurement of circulating plasma volume.<sup>3</sup> These dyes are retained in the blood stream, not by their molecular size, but because they combine with albumin. Within five minutes of its injection into the blood stream Evans blue can be detected in high concentration in thoracic-duct lymph.<sup>4, 5</sup> This being true, no refinement of colorimetric techniques and no mathematical manipulations can make it an accurate measure of the circulating plasma. Always it must measure, in addition to the circulating plasma, part of the extracellular fluid into which it penetrates. If the volume of this extra circuit were constant and proportional to that of the circulating blood, and if the proportion of protein to water in it bore a constant relation to those in the plasma, the method might serve for the measurement of changes in plasma volume. But there is reason to believe that these factors are highly variable. If the protein and dye that escaped from the circulation were irrevocably lost, such a relative plasma volume could be estimated by mathematical extrapolation. But this system, so aptly devised for the well-being of the animal, was so damnably conceived to thwart the physiologist that part, and only a variable part, of the protein and dye is returned to the circulation again through the thoracic duct. The chief variables encountered in measurements of plasma volume by the dye method are as follows: those that are always operative include time of mixing and distribution in the blood stream, escape from the blood stream, return to the blood stream by lymph and permanent removal from plasma and lymph,

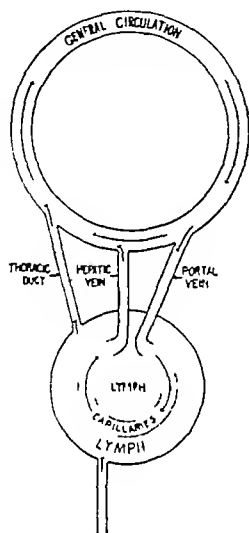


FIGURE 1 Schematic Representation of the Circulation  
The broken lines of the capillary walls in the portal circulation indicate that these vessels are permeable to protein

stances. It is more closely, but not precisely, related to venous pressure, which is notoriously subject to local variations. Although the colloid osmotic pressure of the blood plasma is relatively uniform throughout the blood stream, the colloid osmotic pressure and the hydrostatic pressure of the extracellular fluid are subject to local variations and are not everywhere susceptible to measurement. Finally, the Starling exchange is not the only means by which fluid can escape from the extracellular spaces, the lymph channels provide an alternate route. Drinker and others have shown that the flow of lymph in normal lymphatic vessels is accelerated whenever transudation from the capillaries increases. One of the forces responsible for this accelerated flow is presumably increased tissue pressure.

Normally, peripheral capillaries appear to be so impervious that extracellular fluid or subcutaneous edema fluid is almost free from protein. The small amounts of protein in normal extracellular fluid

those that are sometimes operative comprise variations of circulating blood volume during a test, variations of volume of the thoracic-duct lymph system (that part of the extracellular fluid, drained by the thoracic duct, into which the dye penetrates) and variations of flow of the thoracic-duct lymph during a test. Since all are uncontrollable and unmeasurable, it should be evident to reasoning persons that the method can have no real value. A rather naïve diagram (Fig 1) has been devised to illustrate this point in another way. The large circle above represents the general circulation, impervious to protein. Below is a shunt through the portal circulation, which contains a capillary bed, the broken outlines of which indicate that it is pervious to protein. This lies in a compartment representing the region drained by the thoracic duct. If the volume of the portal capillary bed merely expanded, without any increase of the total circulating fluid, the volume of plasma measured by the dye method would not change, although the amount of blood available to organs supplied by the general circulation would be reduced. If, when the portal capillary bed expanded, an equal volume of fluid entered the circulation, the volume of circulating plasma would increase, although only the usual amount would be available for organs in the general circulation. Thus far the dye method would give no misinformation about changes of circulating plasma volume. If, without any change of volume in the system, loss of protein and dye from the portal capillaries increased, the plasma volume by the dye method would seem to expand. This specious appearance of expansion would be greatly exaggerated if, at the same time, the thoracic-duct lymph compartment became larger.

In view of these considerations there should be no surprise that measurements by means of radioactive red blood cells or by carbon monoxide, which attaches itself to red blood cells, give smaller, and I should say more reasonable, values than dyes for changes of blood volume in pathologic or disturbed physiologic states.<sup>6,7</sup> Granted that red blood cells are not evenly distributed throughout the circulation, an unevenness that has, I believe, been grossly exaggerated, this will not correct the errors inherent in the dye methods. It merely invalidates the only alternative methods. These technical details have been discussed at length because a large body of physiologic and clinical theory dealing with circulatory disorders and fluid exchanges depends for its validity largely upon measurements of blood volume by dye methods.

The exchange of water between the extracellular fluid and the cells appears to be controlled almost entirely by the osmotic pressure of electrolytes in the extracellular fluid, which, in turn, depends mainly upon the concentration of sodium in the

fluid. This can be roughly symbolized by the equation

$$\frac{\text{Volume of E}}{\text{Volume of I}} \propto \frac{\text{Osmotic Pressure E}}{\text{Osmotic Pressure I}} \propto \frac{([Na] + [K])E}{([Na] + [K])I}$$

in which E and I represent extracellular and intracellular fluids respectively. The relative proportions of extracellular and intracellular fluid vary with the relative osmotic pressures of these fluids, which, in turn, depend upon the concentrations in the two mediums of those osmotically active components to which the cellular membranes are impervious. These are mainly sodium and potassium. The chief variable among these is the sodium of the extracellular fluid, which is, therefore, the principal determinant of the relative volume of the intracellular fluid. When the concentration of sodium falls the cells take up water and swell. When the concentration of sodium rises, the cells give up water and contract.

To form the 1000 to 1500 cc of urine ordinarily excreted by a normal person in a day, Smith<sup>4</sup> has estimated that about 180 liters of water must be filtered through the glomeruli in the course of twenty-four hours. With this fluid are filtered about 24,000 milliequivalents of sodium and 20,000 of chloride to yield 80 to 180 milliequivalents of sodium chloride in the urine. This means that more than 99 per cent of the water and a still larger proportion of the sodium and chloride from the glomerular filtrate must be reabsorbed in its passage down the tubules. This process of reabsorption is so regulated that reabsorption of sodium, chloride and water can be varied independently.

The various steps in this process of reabsorption have been partly elucidated by direct analyses of mammalian tubular fluid made by Walker et al.<sup>8</sup> in Richards's laboratory and by inferential evidence adduced by Shannon<sup>9</sup> and others. Attention will be centered on sodium salts and water. It need only be said about urea that its excretion is roughly proportional to filtration and requires a certain proportion of water. Reabsorption of water is therefore limited by the concentration of urea in the glomerular filtrate, which is, in turn, directly proportional to the rate of nitrogen metabolism and the concentration of urea in the blood. Sodium and chloride, on the other hand, can be almost or quite completely reabsorbed from the tubules.

The reabsorptive process is tentatively outlined in Table 1. As the 180 liters of isotonic glomerular filtrate pass through the proximal tubules, about 60 to 80 per cent of the water, all the glucose and fractions of other solutes are removed, together with a roughly equivalent amount of sodium and chloride. There remains an isotonic solution in which the ratio of sodium to chloride, originally about 1.3:1, has become 1:1—that is, the sodium bicarbonate has been reabsorbed, leaving prac-

tically all the remaining sodium as sodium chloride, together with the other solutes that will ultimately be found in the urine. In the loop of Henle a variable amount of sodium chloride is withdrawn. Obviously this is not withdrawn in solid form as the table suggests, but always in this step far more salt than water is reabsorbed. This leaves a hypotonic solution. Finally, in the terminal convoluted

The terminal reabsorption of water appears to be controlled chiefly by the antidiuretic principle of the posterior pituitary hormone, which Heller<sup>10</sup> has succeeded in separating from the pressor principle. The presence in the urine of antidiuretic principle has been demonstrated not only in states of dehydration in which there is need to conserve water but also in a variety of pathologic conditions

TABLE 1 *The Process of Reabsorption*

SITE OF ACTION	SOLUTION	VOLUME	SODIUM	CHLORIDE	RATIO OF SODIUM TO CHLORIDE	UREA NITROGEN
		<i>liters</i>	<i>mm</i>	<i>mm</i>		<i>gm.</i>
Glomerular filtrate	Isotonic	180.0	24,000	20,000	1.25:1	24
Proximal convoluted tubules	Isotonic	54.0	7,600	7,600	1:1	—
Loop of Henle	Hypotonic	54.0	140	140	1:1	—
Terminal convoluted tubules	Hypertonic	1.0	140	140	1:1	12

tubules water is abstracted to yield the fully elaborated urine, which is usually hypertonic.

If this description of the sequence of events is correct, sodium salts have a topographic priority over water in the process of reabsorption. Whether the sequence follows the order described or not, sodium salts have a functional priority over water and enjoy a greater degree of freedom. If an animal is deprived or depleted of sodium chloride these ions promptly disappear almost completely from the urine. The enormous quantities still provided to the tubules through the glomeruli are almost entirely reabsorbed. The administration of large amounts of water and procedures that alter the rate of glomerular filtration have no effect per se on the reabsorption of sodium chloride, although they may vary the volume of urine greatly. The terminal reabsorption of water, on the other hand, is limited by the quantity of solutes requiring excretion—that is, the quantity that escapes reabsorption in the proximal convoluted tubules and the loop of Henle. Among these are sodium salts. If, for any reason, these salts are not reabsorbed, the quantity of water that can be reabsorbed in the terminal process is proportionally reduced. Water, therefore, has an obligation to sodium salts that is not reciprocated. Moreover, water is similarly at the mercy of all solutes that find their way to the terminal segments of the tubules.

Since the reabsorption of both sodium salts and water involves the production of concentration gradients across the membranes of the tubular cells, these processes must require the expenditure of energy. If, therefore, the kidney is injured by disease, reabsorption of sodium chloride and water will diminish. In advanced renal insufficiency the ability of the kidneys to conserve both salt and water is impaired. This disability is manifested in polyuria. In this condition restriction of salt is contraindicated, it may even be advisable to give extra salt.

attended by edema, the nephrotic syndrome,<sup>11</sup> toxemias of pregnancy,<sup>12</sup> cirrhosis of the liver<sup>13</sup> and so forth. The obvious inference is that the oliguria of these conditions is partly or wholly induced through the influence of posterior pituitary activity. The obligation of water to sodium and the independent control of the two are illustrated by the action of the antidiuretic hormone. If this is given with a dose of water to an animal, the water will be almost entirely retained, though excretion of salt continues unchanged. If, on the other hand, the antidiuretic hormone is given with a dose of salt solution, it has little or no antidiuretic effect because the salt, which is not affected by the hormone, demands water for its excretion. Conversely, the administration of salt aggravates diabetes insipidus because the salt cannot be concentrated in the urine in the absence of the antidiuretic hormone.

The evidence concerning control of the reabsorption of sodium salts is less direct. Adrenalectomized animals and patients with Addison's disease tend to waste sodium in the urine. This wastage can be prevented by either cortical extract or desoxycorticosterone acetate. On the other hand, cortical extracts have no pronounced effect upon the excretion of salt by the intact animal. The reabsorption of sodium is increased by desoxycorticosterone acetate, but this is not a natural adrenal steroid. It is, moreover, impossible to demonstrate changes in adrenocortical activity that are related to salt excretion. Nevertheless, from inferential evidence it is tentatively proposed that reabsorption of sodium salts is governed by a steroid secreted by the adrenal cortex.

Regardless of the specific principle that controls reabsorption of sodium, the conditions that influence it may be examined. When the concentration of sodium salts in the serum alone is varied by administration of different quantities of these salts with adequate amounts of water, the excre-

tion of sodium varies directly with its concentration in the serum. Such a relation cannot, however, be discerned under normal dietary conditions and can be strikingly disturbed by certain procedures. The reabsorption of sodium is powerfully affected by factors other than its concentration in the serum. Among these factors is the state of hydration (or some function of the state of hydration) of the subject. If an animal is deprived of all water, some sodium may be immediately lost in the urine, but, after only a short interval, the excretion of both sodium and chloride falls to a minimum. This causes their concentrations in the serum and extracellular fluids to rise<sup>14, 15</sup>. The same phenomenon may be observed when animals are dehydrated by diuretic measures, such as injection of sodium sulfate without adequate amounts of water. This behavior has obvious beneficial effects by withdrawal of sodium chloride from the urine: the animal is enabled to excrete other solutes with a smaller expenditure of water, and the accumulation of sodium chloride in the extracellular fluids raises the osmotic pressure of these fluids, thereby causing water to emerge from the cells. This protects the extracellular fluid from extinction and provides additional water for the formation of urine. By this reaction the water loss is distributed throughout the whole water of the body.

The most powerful known stimulus to the reabsorption of sodium appears to be the need to conserve water. At first sight it seems illogical that this need should express itself primarily through an action on sodium rather than water. If, however, salt were not reabsorbed, the anti-diuretic hormone could not effectively limit the excretion of water. Moreover, the intracellular water would not be made available for the formation of urine.

Reabsorption of water—that is, activity of the antidiuretic hormone—appears to be promoted by an increase of the concentration of solutes, perhaps more specifically sodium salts, in the serum. This has been demonstrated directly by Verney<sup>16</sup>. It can also be inferred from the action of desoxycorticosterone acetate (Table 2). If this compound is injected into a normal animal that is given no water or only the usual amounts of water, serum sodium rises. At the same time the excretion of water is retarded. The consequence is an increase of the concentration of sodium and of the total amounts of sodium and water in the extracellular fluids. Apparently when the sodium of the serum rises the urine volume is reduced by action of the antidiuretic hormone, just as it is in dehydration. The increased concentration of sodium in the serum also has the effect of stimulating thirst. If, then, the animal has free access to water, it will drink enough to dilute the serum sodium to the normal concentration. This, in turn, inhibits antidiuretic activity. The actual effect of an excess of

desoxycorticosterone acetate, therefore, is to produce a state resembling diabetes insipidus. This differs, however, from posterior pituitary diabetes in several respects. In desoxycorticosterone diabetes insipidus the primary factor is thirst; in posterior pituitary diabetes insipidus it is polyuria. In the former the amounts of salt and water in the body are greater and in the postpituitary syndrome less, than normal. Although the desoxycorticosterone

TABLE 2 *Comparison of Findings in Two Types of Diabetes Insipidus*

POSTERIOR PITUITARY DIABETES	DESOXYCORTICOSTERONE DIABETES
Initial inhibition of reabsorption of water	Initial increase of reabsorption of sodium
Primary diuresis	Primary thirst
Deficient body water	Excess body water
Deficient body sodium	Excess body sodium

acetate syndrome is initiated by an increase in the amount of sodium in the body, so long as water is freely available the animal will drink enough water to keep the serum sodium normal or only slightly elevated. This point deserves emphasis: retention of sodium, if there is free access to water, because it stimulates thirst, is not associated with an excessive concentration of sodium in the serum. High serum sodium is almost invariably a sign of dehydration.

A patient with postpituitary diabetes, if deprived of water, will become dehydrated and will develop hypernatronemia and hyperchloremia. These disorders will be exaggerated if salt is given. This cannot easily be demonstrated in the clinic because withdrawal of water, especially if salt is given, is extremely distressing to such patients. We have recently encountered a striking example of this state. A young woman who had recently had a craniopharyngioma removed was admitted to the hospital because of headaches, dizziness, nausea, vomiting and confusion. Because of signs of increased intracranial pressure an exploration was immediately undertaken. A cyst, found in the third ventricle, was aspirated and removed. The patient withstood the operation surprisingly well. Besides a transfusion of 500 cc of blood she was given 1000 cc of physiologic saline solution and 1000 cc of 10 per cent glucose solution intravenously. The next morning her pulse was rapid and her blood pressure low, but she was conscious and did not appear to be in shock. On inquiry it was found that she had voided 3000 cc since the operation—more fluid than she had received, despite the dehydrating effect of the procedure and a moderate elevation of temperature. It was then discovered that her serum sodium, which had been 142 mm (upper limit of normal) before the operation, had risen to 171 mm, with chloride

tically all the remaining sodium as sodium chloride, together with the other solutes that will ultimately be found in the urine. In the loop of Henle a variable amount of sodium chloride is withdrawn. Obviously this is not withdrawn in solid form as the table suggests, but always in this step far more salt than water is reabsorbed. This leaves a hypotonic solution. Finally, in the terminal convoluted

The terminal reabsorption of water appears to be controlled chiefly by the antidiuretic principle of the posterior pituitary hormone, which Heller<sup>11</sup> has succeeded in separating from the pressor principle. The presence in the urine of antidiuretic principle has been demonstrated not only in states of dehydration in which there is need to conserve water but also in a variety of pathologic conditions

TABLE 1 *The Process of Reabsorption*

SITE OF ACTION	SOLUTION	VOLUME	SODIUM	CHLORIDE	RATIO OF SODIUM TO CHLORIDE	UREA NITROGEN
		<i>liters</i>	<i>mm</i>	<i>mm</i>		<i>gm</i>
Glomerular filtrate	Isotonic	180.0	24,000	20,000	1.25:1	24
Proximal convoluted tubules	Isotonic	54.0	7,600	7,600	1:1	—
Loop of Henle	Hypotonic	54.0	140	140	1:1	—
Terminal convoluted tubules	Hypertonic	1.5	140	140	1:1	12

tubules water is abstracted to yield the fully elaborated urine, which is usually hypertonic.

If this description of the sequence of events is correct, sodium salts have a topographic priority over water in the process of reabsorption. Whether the sequence follows the order described or not, sodium salts have a functional priority over water and enjoy a greater degree of freedom. If an animal is deprived or depleted of sodium chloride these ions promptly disappear almost completely from the urine. The enormous quantities still provided to the tubules through the glomeruli are almost entirely reabsorbed. The administration of large amounts of water and procedures that alter the rate of glomerular filtration have no effect per se on the reabsorption of sodium chloride, although they may vary the volume of urine greatly. The terminal reabsorption of water, on the other hand, is limited by the quantity of solutes requiring excretion—that is, the quantity that escapes reabsorption in the proximal convoluted tubules and the loop of Henle. Among these are sodium salts. If, for any reason, these salts are not reabsorbed, the quantity of water that can be reabsorbed in the terminal process is proportionally reduced. Water, therefore, has an obligation to sodium salts that is not reciprocated. Moreover, water is similarly at the mercy of all solutes that find their way to the terminal segments of the tubules.

Since the reabsorption of both sodium salts and water involves the production of concentration gradients across the membranes of the tubular cells, these processes must require the expenditure of energy. If, therefore, the kidney is injured by disease, reabsorption of sodium chloride and water will diminish. In advanced renal insufficiency the ability of the kidneys to conserve both salt and water is impaired. This disability is manifested in polyuria. In this condition restriction of salt is contraindicated, it may even be advisable to give extra salt.

attended by edema, the nephrotic syndrome,<sup>11</sup> toxemias of pregnancy,<sup>12</sup> cirrhosis of the liver<sup>11</sup> and so forth. The obvious inference is that the oliguria of these conditions is partly or wholly induced through the influence of posterior pituitary activity. The obligation of water to sodium and the independent control of the two are illustrated by the action of the antidiuretic hormone. If this is given with a dose of water to an animal, the water will be almost entirely retained, though excretion of salt continues unchanged. If, on the other hand, the antidiuretic hormone is given with a dose of salt solution, it has little or no antidiuretic effect because the salt, which is not affected by the hormone, demands water for its excretion. Conversely, the administration of salt aggravates diabetes insipidus because the salt cannot be concentrated in the urine in the absence of the antidiuretic hormone.

The evidence concerning control of the reabsorption of sodium salts is less direct. Adrenalectomized animals and patients with Addison's disease tend to waste sodium in the urine. This wastage can be prevented by either cortical extract or desoxycorticosterone acetate. On the other hand, cortical extracts have no pronounced effect upon the excretion of salt by the intact animal. The reabsorption of sodium is increased by desoxycorticosterone acetate, but this is not a natural adrenal steroid. It is, moreover, impossible to demonstrate changes in adrenocortical activity that are related to salt excretion. Nevertheless, from inferential evidence it is tentatively proposed that reabsorption of sodium salts is governed by a steroid secreted by the adrenal cortex.

Regardless of the specific principle that controls reabsorption of sodium, the conditions that influence it may be examined. When the concentration of sodium salts in the serum alone is varied by administration of different quantities of these salts with adequate amounts of water, the excre-

rather than in the kidneys themselves but this will not alter the nature of the argument) The most crucial problem related to the formation of edema is the discovery of the criteria by which the kidneys determine whether to accelerate or retard the reabsorption of sodium

Obviously, accumulation of fluid in the extracellular compartment is a matter of indifference to the kidneys. If it were not, they would dehydrate all the rest of the body in behalf of a milk leg or a lymphedema. On the contrary, they will reabsorb salt and water for the sake of the patient at large while the edema is forming. In these conditions, if water and salt are not given, the blood volume diminishes as the edema accumulates. Presumably, the kidneys, finding that fluid is escaping from the circulation, conclude that there is need to conserve water and therefore respond by reabsorbing more than the usual quantity of sodium salts.

The edema that accompanies hypoalbuminemia, whether this is referable to plasmapheresis, nutritive deficiencies or albuminuria, appears to originate in a similar manner. The sequence of events in all these states is as follows: escape of fluid from the circulation, retention of sodium and chloride, and retention of water. In terms of renal physiologic mechanisms implemented by their appropriate agencies, these processes are expressed as follows: the development of a serum albumin deficit causes a reduction of colloid osmotic pressure that results in the escape of fluid from the circulation, reduction of the circulating blood volume accelerates the reabsorption of sodium salts (presumably through the influence of increased secretion of an adrenal cortical hormone), resulting in the accumulation of sodium salts in the serum, and increased concentration of sodium in the serum causes thirst and accelerates reabsorption of water through in-

edema but little, if at all, and by diluting the sodium salts in the extracellular fluid, it should inhibit the action of the antidiuretic hormone, permitting the water, but not the salt, to be excreted. Limitation of water, on the other hand, would have only a slight effect on the edema because it would increase the concentration of sodium salts in the serum, thereby stimulating antidiuretic activity. (Also, it would be a cruel measure because it would create intolerable thirst.) Administration of sodium salts

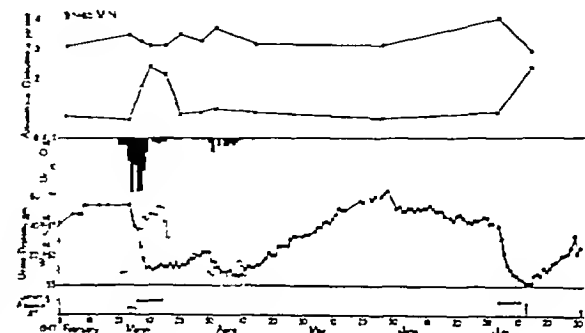


FIGURE 3 Effect of Human Serum Albumin Injections upon the Edema of a Patient with a Nephrotic Syndrome. Concentrations of albumin and globulin in the serum are shown in the top segment of the figure. The arrows in the lower segment indicate injections of salt-poor human serum albumin. (The serum albumin was furnished by the Administrator of the National Blood Program, American Red Cross, or recommendation of the Subcommittee on Blood and Blood Derivatives of the Red Cross Medical Advisory Committee.)

would conduce to edema because it would exaggerate the dehydration reaction, thus stimulating antidiuretic activity. Restriction of sodium salts would minimize the dehydration reaction and the stimulus to antidiuretic activity. The term "dehydration reaction" is applied to reabsorption of sodium by the kidneys to conserve water. Essentially, this describes the behavior of patients with edema of either nephrosis or heart failure.

If these phenomena were analyzed from the standpoint of exchanges of water and salt alone, the impression would be derived that the primary and initial reaction was retention of sodium, an impression that would gain additional support from the observation that mercurial drugs, which act by inhibiting the reabsorption of chloride, are effective diuretics in these forms of edema. The sequence that has been proposed is vividly illustrated by the effect of serum albumin in Figure 3. The patient, an eighteen-year-old girl in the nephrotic phase of a glomerular nephritis, had generalized edema that was resistant to salt restriction and the usual diuretic measures. Her serum albumin was less than 1 per cent. After a preliminary period of observation she was given daily intravenous injections of salt-poor human serum albumin, which

TABLE 4 Effect of Water and Salt on Edema

FACTOR	EFFECT ON SODIUM SALTS IN BODY	EFFECT ON ANTIDIURETIC ACTIVITY	EFFECT ON DEHYDRATION REACTION
Excess of water	Diluted	Inhibited	—
Limitation of water	Increased	Stimulated	—
Excess of sodium	Increased	Stimulated	Exaggerated
Limitation of sodium	Diminished	Diminished	Minimized

creased secretion of posterior pituitary antidiuretic hormone, resulting in the retention of water, which, with the retained salt, produces edema.

It is evident at a glance that if an "increase of capillary blood pressure" is substituted for "the development of a serum albumin deficit" the remainder of the sequence would follow unchanged (Table 4). If this sequence is in any large measure correct it has certain corollaries. First of all, the administration of water without salt should increase the

comparably elevated. It was obvious that she had developed acute diabetes insipidus. Since she could not take fluid this expressed itself in an extreme dehydration reaction. She was immediately given a continuous intravenous drip of glucose solution and intermittent injections of small amounts of pituitrin. The data are shown in Figure 2. Unfortunately the urine volume could not be recorded because urgency, together with her somnolent state, led to frequent

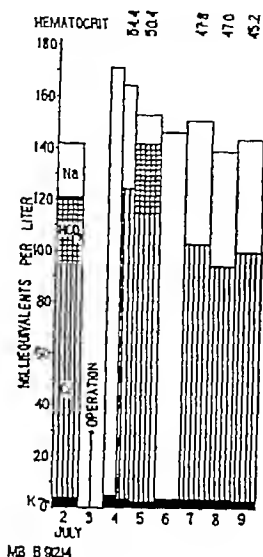


FIGURE 2. Concentration of Electrolytes in the Serum of a Patient Who Developed Acute Diabetes Insipidus after Operation for the Removal of a Cyst in the Third Ventricle

involuntary urination in the bed. The polyuria could not be entirely controlled by pituitrin because of the side reactions produced by this preparation.

This is a long, but necessary, preamble to the discussion of edema, which is limited chiefly to the subject of cardiac edema, because this includes most of the features involved in edemas of every kind and because the present controversy about the subject is challenging. The sequence of events in the production of cardiac edema has been conventionally conceived as outlined in the left-hand column of Table 3.

According to this concept failure of the heart causes the blood to back up, increasing the venous pressure and thereby the capillary blood pressure. This provokes transudation of fluid from the capillaries with consequent reduction of the volume of circulating plasma. This last, in turn, provokes the kidneys to reabsorb more than the usual quantities of sodium salts and water. This seems a logical sequence, compatible with existing physiologic theory.

Because, they claim, retention of sodium precedes the rise of pressure, and because measurements by

means of dyes indicate that the plasma volume does not contract, but rather expands, Warren and Stead<sup>17</sup> have proposed a reversed sequence, which they term "forward failure." According to this hypothesis the primary event is retention of sodium salts by the kidneys, which they attribute to some disturbance of the circulation to these organs. This leads to a similar retention of water. The consequent expansion of the volume of circulating plasma increases the capillary blood pressure, which, in turn, accelerates transudation and thus produces edema. From the standpoint of therapy the order of events is of great importance. The premises on which the theory of "forward failure" is based, therefore, require serious examination.

Those who would carry this theory so far as to suggest that the Starling principle is not operative in cardiac edema deserve no consideration, for

TABLE 3. Origin of Cardiac Edema

STARLING <sup>1</sup>	STEAD <sup>17</sup>
1 Increased venous pressure and capillary pressure	1 Retention of salt and water
2 Transudation	2 Expansion of plasma volume
3 Hemoconcentration	3 Increased venous and capillary pressure
4 Retention of salt and water	4 Transudation

reasons mentioned above. Since the venous pressure is increased in heart failure at one time or another, there must be back pressure in the capillaries that will inevitably provoke transudation. Landis<sup>18</sup> has pointed out that this is not delayed until gross salt retention has occurred. Patients with minimal heart failure excrete sodium salts normally and remain free from edema when they are at rest in the recumbent position, but develop edema when they are erect with legs dependent. This formation of edema, as Perera<sup>19</sup> has shown, is attended by hemoconcentration.

If Stead is right, reasons must be found for expansion of the blood volume and simultaneous retention of sodium. The latter, it has been shown, is the characteristic reaction to the need to conserve water. Why, then, should it be called into play when there is an obvious excess of water in the body? The disorders encountered in disease may be regarded as normal physiologic responses to unusual conditions produced by pathologic processes. It is proper, then, to assume that retention of sodium in heart failure is provoked by the usual stimulus, the need to conserve water. This term must, however, be interpreted in terms of the kidneys; it cannot be the actual need to conserve water to which the kidneys respond, but conditions that lead the kidneys to believe that there is a need to conserve water. (This decision may, of course, be made in the adrenal cortex or some other organ

to reabsorption of water is excessive concentration of sodium salts in the extracellular fluid. The question of the volume and location of the circulating blood and its regulation still requires open-minded inquiry.

I should not be altogether ingenuous if I did not admit that nervous control of renal function, of which physicians are only beginning to become aware and which has been neglected in this discussion, might prove to be an important factor in the phenomena of circulatory disorders.

Finally, sodium is spoken of more freely than available data warrant. The measurement of sodium has been a protracted, meticulous procedure for which few laboratories are equipped, and which is ill adapted to the regulation of therapy in the clinic. Sodium figures have been interesting chiefly in retrospect, too often as records of errors in the evaluation of other evidence. It has been generally assumed (and I plead guilty on this score) that the concentration of sodium can be estimated from the sum of the concentrations of bicarbonate and chloride with the aid of astute clinical observation. It is, of course, recognized that in diabetic acidosis and advanced renal insufficiency replacement of bicarbonate and chloride by other anions (ketone acids, phosphate, sulfate and so forth) invalidates such estimations.<sup>25</sup> The frequency with which such estimations fail in heart failure has been less widely appreciated. In fact, the concentration of sodium in the serum in heart failure has been more discussed than investigated.

The nature of all the discrepancies between sodium and bicarbonate and chloride in heart disease cannot be discussed for lack of time. Only one matter is truly relevant to the subject, the concentration of sodium salts in the serum in heart failure. If retention of these salts were the primary event in heart failure, serum sodium in this condition should be regularly elevated or in the upper normal range. Furthermore, the logical first measure in the treatment of cardiac edema would be the administration of mercurial diuretics, which specifically inhibit reabsorption of sodium salts by the kidney. This has indeed been advocated. It has even been claimed, without any adequate evidence, that these compounds have a beneficial action upon the heart itself. In a certain proportion of patients with heart failure, serum sodium is slightly elevated. But in another group, for reasons that have not been altogether elucidated, it may be subnormal.<sup>26</sup> In the latter, mercurial diuretics are distinctly contraindicated.

A man of sixty-three, with long-standing heart failure, having neglected to take his digitalis, was admitted to the hospital with a puffy face, orthopnea, distention of the neck veins, pulmonary congestion, bilateral hydrothorax, a greatly enlarged heart, an enlarged liver, probable ascites and massive generalized edema. The venous pres-

sure was equivalent to about 200 mm of water, the circulation time (dechlorin) was 40 seconds, and the vital capacity 1.5 liters. He was given 1 cc of mercurhydrin intravenously on admission, which provoked no diuresis. In fact, he voided only 150 cc of urine during the next thirty hours. On the morning after admission he seemed much worse. The blood nonprotein nitrogen was found to be slightly elevated, whereas the serum albumin, chloride and sodium were greatly reduced. Digitalization was begun at once, and on the following day, since chloride, sodium and bicarbonate were still low, he was given 500 cc of 3 per cent sodium chloride intravenously. His condition improved strikingly, and his urine volume increased. Within three days his weight had decreased 7 kg, and venous pressure had fallen to normal. In this case mercurials were obviously contraindicated. The low sodium presumably contributed, as it will, to the circulatory failure. There are exceptions even to the rule that salt must be withheld in heart failure. It is possible that digitalis alone would have been effective. The state of the patient was so critical that it was impossible to conduct the experiment one step at a time. Such cases constitute a challenge to those who argue for primary retention of sodium chloride in heart failure. Their incidence must not be overlooked by the clinician. Measurement of sodium should be more generally practiced as soon as simple and practical flame photometers become available.

\* \* \*

My object has been not so much to solve, as to pose, the problems of cardiac edema. I hope that I have clearly distinguished in the discussion fact from speculation. I have tried to emphasize that in the clinic, as in the laboratory, plausibility is no substitute for sound reasoning based on fundamental scientific principles, that generalization from particulars is dangerous, and that no single organ or system in a complex integrated organism can be considered *in vacuo* apart from the whole.

## REFERENCES

1. Starling E. H. Fluids of body. *Harter Lect* (New York, 1908) Chicago: W. T. Keener and Co. 1909.
2. McCarrell, J. D., Thayer S., and Drinker C. K. Lymph drainage of gall bladder together with observations on composition of liver lymph. *Am. J. Physiol.* 133:79-91 1941.
3. Gregersen M. L., and Rawson R. A. Disappearance of T-1824 and structurally related dyes from blood stream. *Am. J. Physiol.* 135:698-707 1954.
4. Smith H. P. Fate of intravenously injected dye (brilliant vital red) with special reference to its use in blood volume determination. *Bull. Johns Hopkins Hosp.* 36:325-342 1925.
5. Ferrebee J. W., Leigh O. C., and Berliner R. W. Passage of blue dye T-1824 from blood stream into lymph. *Proc. Soc. Exper. Biol. & Med.* 46:549-553 1941.
6. Hahn P. F., et al. Red cell and plasma volumes (circulating and total) as determined by radio iron and by dye. *J. Exper. Med.* 75:221-232 1942.
7. Gibson J. G., 2nd, Peacock, W. C., Selman A. M., and Sack, T. Circulating red cell volume measured simultaneously by radioactive iron and dye methods. *J. Clin. Investigation* 25:538-547 1946.
8. Walker A. M., Bott, P. A., Oliver J., and MacDowell M. C. Collection and analysis of fluid from single nephrons of mammalian kidney. *Am. J. Physiol.* 134:580-597 1941.

induced an excellent diuresis. By the end of six days she had lost 10.5 kg (23.1 lb). With this water a comparable quantity of chloride was excreted. At this point, when she was practically free from edema, further injections of albumin caused no further loss of weight or chloride. The immediate effect of the injections was to raise the serum albumin, which led to the absorption of fluid into the blood stream. Expansion of the circulating plasma was demonstrated by means of the hematocrit. The proteinuria, however, increased so greatly that the rise of serum albumin was not sustained after the injections were discontinued. After the injections were discontinued, although the serum albumin fell rapidly to its original level, the edema reaccumulated only gradually. At the same time urinary chloride sank to a minimum and remained there until the edema had reaccumulated. The retention of fluid kept pace with the retention of chloride, which may be considered as equivalent to sodium in this case. From the standpoint of salt and water, the primary factor in the development of the edema was salt. Its slow accumulation can be attributed to restriction of salt, water was at no time restricted. From this point of view the action of injections of albumin differs in no respect from that of mercurial diuretics, although its *modus operandi* is altogether dissimilar. Mercurial diuretics inhibit reabsorption of sodium, thereby removing the stimulus to antidiuretic activity. Albumin expands blood volume, thereby removing the stimulus to reabsorption of sodium salts.

Reduction of the volume of the circulating blood or plasma, therefore, appears to cause the kidneys to reabsorb salt in efforts to conserve water, even if there is an excessive amount of water in the body as a whole. Why, then, should the kidneys respond in a similar manner in heart failure if the blood volume in this condition is greater than normal? The presenting phenomena in fully developed heart failure are excessive transudation from the blood stream, as evidenced by the presence of edema, increased venous and capillary blood pressures, which should tend to diminish the volume of the circulating plasma, and increased reabsorption of sodium by the kidneys, a reaction usually provoked by contraction of the volume of circulating plasma. There is reason to believe that the degree of expansion of the blood volume in heart failure has been exaggerated. Heart failure presents precisely that combination of disorders in which dye methods should be most unreliable, a condition in which the liver is distended with blood and fluids containing large amounts of protein and dye. The evidence for expansion of volume by other methods is not altogether consistent. Stewart<sup>20</sup> found that diuresis in heart failure occurred only if the specific gravity of the plasma fell. In an article by Merrill and Stead<sup>21</sup> the most striking instance of diuresis

is associated with a sharp drop of hematocrit. In some of my own studies values for hemoglobin and hematocrit indicate hemoconcentration in heart failure. There is indubitable loss of fluid from the circulation in certain types of heart failure—namely, paroxysmal dyspnea and coronary occlusion. Stead and Ebert<sup>22</sup> are so impressed with the importance of expanded volume that they have advocated venesection for the treatment of the shock syndrome of coronary occlusion. That their patients died seems not to have dismayed them. Transfusions have been given to patients with the shock of coronary occlusion, with signal benefit. Unfortunately, preconceptions so prevail that this life-saving measure is too often delayed until the shock has become irreversible.

If retention of sodium and consequent expansion of blood volume were the primary causes of cardiac edema, further expansion of blood volume should have a deleterious effect. This has not been satisfactorily demonstrated. Hypertonic glucose has been advocated for the treatment of heart failure under the pretext that the glucose was required by the heart muscle. Actually, it produces transitory hemodilution. McCann and Brown<sup>23</sup> induced diuresis in a patient with congestive heart failure by intravenous injection of concentrated human blood plasma. I have recently given injections of salt-poor human serum albumin to patients with heart failure. The cases thus far selected have been of a desperate type, mainly patients with advanced renal insufficiency as well as heart failure. Although no striking successes can be reported, dire forebodings of disaster have not been realized.

Granted that the circulating blood volume is expanded, if the reasoning concerning renal activity is logical, it must be so expanded that the kidneys are unaware of it or do not participate in it. It is not inconceivable that the circulating blood is pooled somewhere—for instance, in the liver and other viscera—and is thereby diverted from the kidneys. If expansion of blood volume is a response to such a dislocation of the circulation it should be regarded as a compensatory or protective reaction, even if it should prove to be misdirected. It may, of course, be not the actual volume of circulating plasma but some function usually related to the volume of circulating plasma—such as renal blood flow—that apprises the kidney of the need to conserve water.

This is not idle speculation. If the earlier physiologic argument has adhered to fact, the rationale for restriction of salt in both cardiac and nephrotic edema is clear. The relative ineffectiveness of limiting the intake of water is also explained. To be sure, edema cannot be formed without water, but the strongest physiologic stimulus to reabsorption of sodium is dehydration produced by deprivation of water. And the strongest stimulus to thirst and

OBSERVATIONS

*Nail Changes in Vasospastic Conditions*

These consist of a remarkable thinning of the proximal nail fold, with a more gradual merging into the translucent cuticle. The latter membrane is greatly widened, and does not end abruptly at its distal or free edge, as it does normally. Instead it extends out for several millimeters, to merge almost imperceptibly with the nail plate (Fig 2)



FIGURE 2 Typical Lesion in Arteriospastic Disease  
*Widening of the cuticle ("pterygium") and thinning of the nail fold are observed in Raynaud's disease of long standing*

The cuticle lesion described is the one termed "pterygium" by dermatologists. Concerning it, Pardo-Castello<sup>3</sup> states

This epidermal membrane may in some pathologic conditions advance 2 to 3 or more millimeters over the nail plate and become adherent to its outer surface. This is seen accompanying such conditions as peripheral neuritis, leprosy, sclerodactylia, and atrophy of the nails of different nature. It is a common condition in the last two toe nails in apparently normal persons. It is also seen in onychophagia.

This picture may be found in apparently all varieties of vasospastic disease, including the cold, stiff, splinted extremity, more outspoken vasospastic states and, most characteristically, Raynaud's disease and scleroderma (Fig 2, 3, 4 and 5)



FIGURE 3 Pterygium in Disseminated Scleroderma

I am convinced that pterygium is characteristic of the severer grades of Raynaud's disease, especially in the fingers. It is an apparently constant finding in fingers in which secondary scleroderma has set in, and it seems to be an accurate herald of coming scleroderma if that change has not yet become evident. Moreover, pterygium is just as

characteristic in primary or generalized scleroderma as in the secondary form.

Pterygium may be seen in the toes, but less often and less pronounced than in the fingers (Fig 4). The fairly common normal pterygium of the toes,

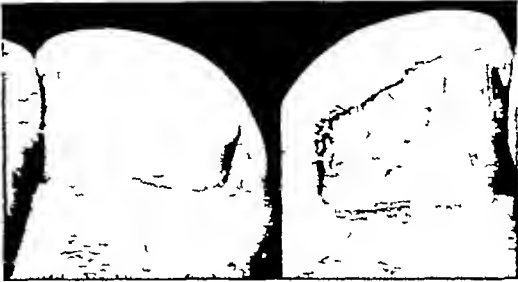


FIGURE 4 Pterygium in the Great Toes in a Patient with Post-Trench-Foot Syndrome

which is not characterized by thinning of the nail fold described above, is excluded from this discussion.

I have not seen the lesion developing in the presence of purely organic obstruction. On the other hand, it can be demonstrated in a variety of diseases, in all of which there are vasospastic reflexes mediated through the sympathetic nervous

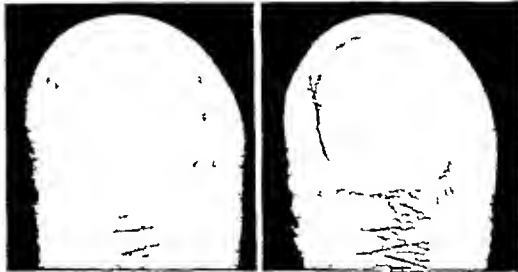


FIGURE 5 Correction of the Nail Lesion in Raynaud's Disease  
*In the photograph on the left, ten days after sympathectomy, typical changes are still present. In that on the right, five weeks after operation the nail fold has resumed its normal thickness and the cuticle its normal sharply delimited character.*

system. One may postulate either that the effect is due to the direct influence of nerve on tissue or that the mechanism involves a differential diminution in the various parts of the digital circulation. The latter possibility would be consistent with the known diminution in these diseases in the blood flow through the nail fold, from which the cuticle grows.

Whatever the mechanism, sympathectomy promptly does away with the lesion. In three or four weeks after the operation, the nail fold has become full, and the new cuticle is seen growing

- 9 Shannon J A Control of renal excretion of water effect of variations in state of hydration on water excretion in dogs with diabetes insipidus *J Exper Med* 76 371-386 1942 Control of renal excretion of water rate of liberation of posterior pituitary antidiuretic hormone in dog *Ibid* 76 387-399 1942
- 10 Heller H Renal excretion of pituitary (posterior lobe) extracts *Nature* 151 502 1943
- 11 Robinson F H Jr and Farr L E Relation between clinical edema and excretion of antidiuretic substance in urine *Ann Int Med* 14 42-54 1940
- 12 Teel H M and Reid D E Observations upon occurrence of antidiuretic substance in urine of patients with pre-eclampsia and eclampsia *Endocrinology* 24 297-310 1939
- 13 Rall E P Robson J S, Clarke D H and Hoagland C L Factors influencing ascites in patients with cirrhosis of liver *J Clin Investigation* 24 316-325 1945
- 14 Elkinton J R and Taffel M Prolonged water deprivation in dog *J Clin Investigation* 21 787-794, 1942
- 15 Winkler A W Danowski T S, Elkinton J R and Peters J P Electrolyte and fluid studies during water deprivation and starvation in human subjects and effect of ingestion of fish, of carbohydrate and of salt solutions *J Clin Investigation* 23 807-815, 1944
- 16 Verney E B Absorption and excretion of water antidiuretic hormone *Lancet* 2 739 1946
- 17 Warren J V and Stead E A Jr Fluid dynamics in chronic congestive heart failure interpretation of mechanisms producing edema increased plasma volume and elevated venous pressure in certain patients with prolonged congestive failure *Arch Int Med* 73 138-147, 1944
- 18 Landis E M Brown E, Fauteux M and Wise C Central venous pressure in relation to cardiac "competence" blood volume and exercise. *J Clin Investigation* 23 237-255 1946
- 19 Perera G A Increased plasma volume in cardiac insufficiency its correlation with right sided failure *J Clin Investigation* 24 708-711 1945
- 20 Stewart H J Mechanism of diuresis alterations in specific gravity of blood plasma with onset of diuresis in heart failure. *J Clin Investigation* 20 1-6 1941
- 21 Merrill A J Edema and decreased renal blood flow in patients with chronic congestive heart failure evidence of "forward failure" as primary cause of edema *J Clin Investigation* 25 389-400 1946
- 22 Stead E A Jr and Ebert R. V Shock syndrome produced by failure of heart. *Arch Int Med* 69 369 383 1942
- 23 Schwartz, W B Treatment of shock accompanying myocardial infarction *Am Heart J* 33 169 174 1947
- 24 McCann W S and Brown H R. Jr Use of concentrated plasma protein solutions in congestive heart failure *Internat Clin* 1 109 115 1942
- 25 Hald P M Heinsen A J and Peters J P Estimation of serum sodium from bicarbonate plus chloride *J Clin Investigation* 26 983 990 1947
- 26 Peters J P Unpublished data

## NAIL CHANGES IN FUNCTIONAL AND ORGANIC ARTERIAL DISEASE\*

EDWARD A EDWARDS, M D †

BOSTON

IT IS the purpose of this paper to show that the nails undergo specific changes in vasospastic and in organic peripheral arterial disease and are sensitive indicators of the severity of the underlying state

Raynaud<sup>1</sup> made more detailed notation of such changes than subsequent writers did Thus he

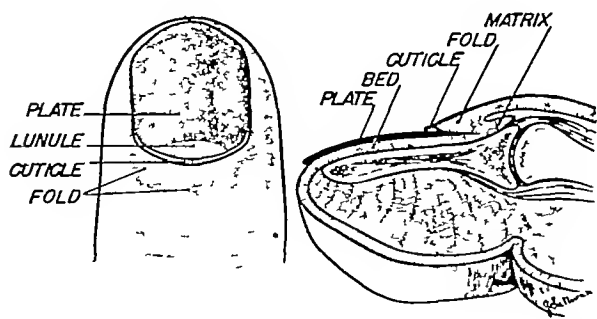


FIGURE 1 Normal Anatomy of the Nail

stated that the nails may be cast off by vascular disease attacking them at their "root", that growth of the nail stops during an episode of necrosis, and that they begin to grow when this episode is over, then showing a transverse depression, and that

ulceration of a digit may give loss of support of the nail at its extremity and result in a curving of the nail round the end of the digit Heller's<sup>2</sup> more recent monograph gives the impression that nail changes occur infrequently in vascular disease, consisting mainly of necrosis or ulceration concomitant with that of the digit He does mention that in scleroderma the nails are frequently involved by atrophy, thickening and deformation Pardo-Castello<sup>3</sup> states that in peripheral vascular disease, disturbances are frequent, with Beau's lines (transverse depressions indicating periods of retarded growth), partial loosening, atrophy, distortion and, finally, destruction by gangrene

Before these changes are considered it may be useful briefly to describe the normal appearance of the nail and its associated parts Reference may first be made to a longitudinal section of the nail (Fig 1) The nail plate, ordinarily referred to simply as the nail, consists of dead cornified material pushed distally by the growth of the parent cells of the nail matrix, and lying on the epithelial nail bed The surface of the digit shows the nail plate overlain by the skin, known here as the *nail fold*, which is arbitrarily divided into proximal and lateral parts The nail fold is cemented to the nail plate by its surface cornified cells, visible as the translucent cuticle The cuticle is thicker and more evident at the proximal nail fold, with a width of 1 mm or less It is all that remains of the eponychium that in the early embryo covers the entire nail plate One may also note the lunule, the white crescentic area of nail bed seen through the proximal end of the nail plate in the fingers

\*From the Department of Surgery, Tufts College Medical School. Aided by a grant from the Charlton Research Fund Tufts College Medical School

†Instructor in surgery Tufts College Medical School clinical associate in anatomy Harvard Medical School consultant in peripheral vascular diseases Joseph H Pratt Diagnostic Hospital surgeon-in-charge Vascular Clinic Boston Dispensary

An occasional change in pronounced ischemia due to a variety of diseases is so-called diffusion of the lunule (Fig 9). This appearance is described by Pardo-Castello as follows:

Diffusion of the lunula is a very common condition in leprosy and other dystrophic conditions of the extremities. The lunula loses its sharp anterior limit, spreads forward, and seems to invade all the nail bed. This is due to the formation in the nail bed of a granular layer loaded with keratohyalin, and finally results in defective cornification. Many cases of total leukonychia may be explained in this manner.

The distortion of nail growth gives rise to no apparent pain. The patient may complain of pain about the nails, however, if the ischemia is extreme. In such cases the local tissues are hyperesthetic, and the slightest pressure gives rise to severe pain. In the toes, the pain may be interpreted by both the patient and the doctor as due to ingrown toenail. Ingrown toenail may or may not be present, but it should be realized that the very recent onset of such symptoms in an older person is usually due to an ischemic hyperesthesia. Relief from the pain will be obtained by the cessation of weight bearing and an increase in arterial flow. Operative interference on real or imagined ingrown toenails in the presence of ischemia may result in gangrene.

#### *Nonspecific Lesions in Functional and Organic Disease*

In cases of great severity, the nail plates may be loosened and painlessly shed. This fact was mentioned by Raynaud<sup>1</sup> in several of his cases.

Primary infections of the nails are not seen with any characteristic frequency. On the other hand, the acral ulceration of arterial disease may involve the nails, with resultant distortions of their structure. Chronic subungual infection may also be seen in relation to the frequent ischemic osteomyelitis of the terminal phalanges (Fig 7).

#### SUMMARY

The nails show specific pathologic changes in both arteriospastic and organic arterial diseases and are sensitive indicators of the severity of the underlying state. In arteriospastic states, changes that may be grouped under the dermatologist's term of pterygium are described. They consist of a thinning of the nail fold and a widening of the cuticle. The normal abrupt demarcation between nail fold and cuticle, and between cuticle and nail plate is lost. Sympathectomy quickly restores the nail fold and cuticle to normal.

In organic arterial disease the nails do not show these changes. There is rather a thickening, roughening, and darkening of the nail plate, which hides the nail bed. An increase in arterial circulation by any means gives rise to a more nearly normal growth of the plate. Less specific changes include the growth of claw nails, or the presence of "diffusion of the lunule" in organic states, and the loosening and shedding of the nail plate in severe disease of either vasospastic or organic origin.

Painful nails are often an expression of the hyperesthesia of severe ischemia, in which operations for ingrown toenail usually cause gangrene.

Primary infections of the nails are uncommon in peripheral vascular disease, but the nails may be involved in acral ulceration, or may show subungual abscess over an osteomyelitis of the terminal phalanx.

372 Marlborough Street

#### REFERENCES

1. Raynaud M. *De l'asphyxie locale*. 174 pp. Thèse Paris 1862.
2. Heller J. Die Krankheiten der Nägel. In *Handbuch der Haut und Geschlechtskrankheiten*. Edited by J. Jadassohn. Vol. 1. Part 2. Berlin: Julius Springer, 1927.
3. Pardo-Castello A. *Diseases of the Nails*. Second edition. 193 pp. Springfield, Illinois: Charles C. Thomas, 1941.

in its normal, sharply delimited manner. Remnants of the old cuticle are seen adhering to the nail plate (Fig 5)

#### *Nail Changes in Organic Arterial Occlusion*

Severe ischemia, whether resulting from arteriosclerosis or from the less common thromboangitis



FIGURE 6 Typical Lesion in Organic Arterial Disease, Showing Distortion, Thickening and Pigmentation of the Nail Plate in Ischemia Due to Arteriosclerosis

obliterans, gives rise to a distortion of the growth of the nail plate (Fig 6). I have no data to offer on the likelihood that the same lesion occurs in other, less common, varieties of organic occlusion. There are no accompanying nail-fold and cuticle

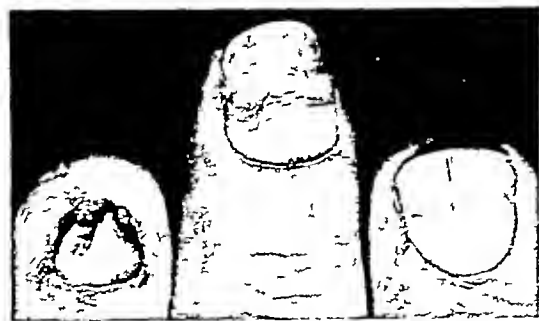


FIGURE 7 Improved Nail Growth in a Case of Buerger's Disease Four Months after Sympathectomy

The distorted plates are being displaced by a more normal growth. The distortion of the nail of the index finger (left) was associated with osteomyelitis of the terminal phalanx.

changes as seen in the vasospastic diseases. The linear growth is retarded to the extent that the nail may not have to be trimmed for months or years. The nail plate may gain in thickness, becoming heavy and rough. The roughening is usually caused by the presence of transverse or eccentrically placed, parallel ridging. The nail plate is darkened, but it is impossible to say whether this is due to a contained pigment or to external soiling of its roughened surface. The thickened and darkened plate effectively shuts off the underlying nail bed from view.

The distortion of nail growth may take the form of a claw nail (onychogryposis).

An increase of blood supply, obtained by any means, is signalled by a return of the roughened

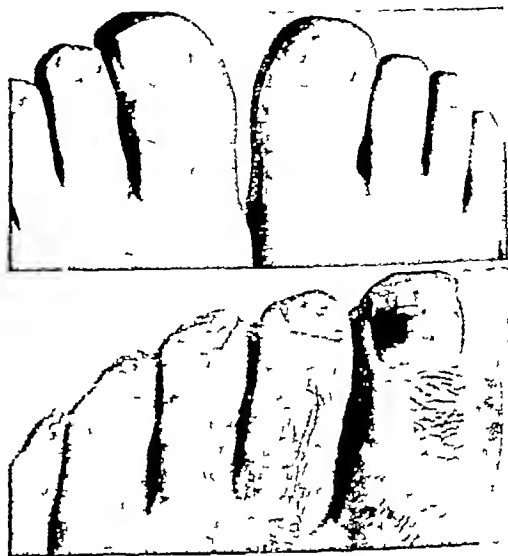


FIGURE 8 Improved Nail Growth in Buerger's Disease. In the upper photograph, taken after suction-pressure treatment, the deformed nail is being pushed forward by a more normal growth. In the lower photograph of the same patient, taken after a relapse two years later, a similar correction of growth followed the administration of testosterone propionate.

nail to normal growth (Fig 7 and 8). This results in a rapid distal displacement of the old mis-shapen nail by a new, more normal portion, through which may now be seen the nail bed, of a variable pink

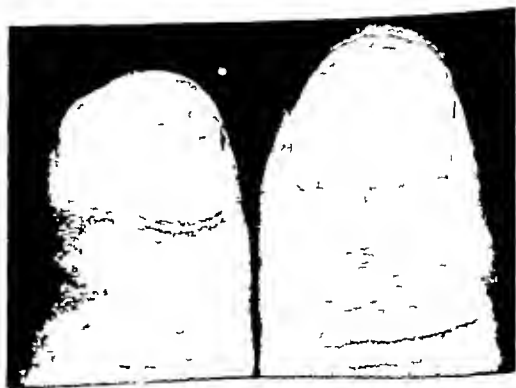


FIGURE 9 Diffusion of the Lunule in a Patient with Multiple Congenital Arteriovenous Communications of the Forearm, Hands and Fingers

The contrast between the old diseased nail and the newer, more normal portion serves as a striking indication of the improvement of the circulation. It is clinically useful to utilize the reversal of nail change in evaluating the benefit of therapy.

An occasional change in pronounced ischemia due to a variety of diseases is so-called diffusion of the lunule (Fig 9). This appearance is described by Pardo-Castello as follows:

Diffusion of the lunula is a very common condition in leprosy and other dystrophic conditions of the extremities. The lunula loses its sharp anterior limit, spreads forward, and seems to invade all the nail bed. This is due to the formation in the nail bed of a granular layer loaded with keratohyalin, and finally results in defective cornification. Many cases of total leukonychia may be explained in this manner.

The distortion of nail growth gives rise to no apparent pain. The patient may complain of pain about the nails, however, if the ischemia is extreme. In such cases the local tissues are hyperesthetic, and the slightest pressure gives rise to severe pain. In the toes, the pain may be interpreted by both the patient and the doctor as due to ingrown toenail. Ingrown toenail may or may not be present, but it should be realized that the very recent onset of such symptoms in an older person is usually due to an ischemic hyperesthesia. Relief from the pain will be obtained by the cessation of weight bearing and an increase in arterial flow. Operative interference on real or imagined ingrown toenails in the presence of ischemia may result in gangrene.

#### *Nonspecific Lesions in Functional and Organic Disease*

In cases of great severity, the nail plates may be loosened and painlessly shed. This fact was mentioned by Raynaud<sup>1</sup> in several of his cases.

Primary infections of the nails are not seen with any characteristic frequency. On the other hand, the acral ulceration of arterial disease may involve the nails, with resultant distortions of their structure. Chronic subungual infection may also be seen in relation to the frequent ischemic osteomyelitis of the terminal phalanges (Fig 7).

#### SUMMARY

The nails show specific pathologic changes in both arteriospastic and organic arterial diseases and are sensitive indicators of the severity of the underlying state. In arteriospastic states, changes that may be grouped under the dermatologist's term of pterygium are described. They consist of a thinning of the nail fold and a widening of the cuticle. The normal abrupt demarcation between nail fold and cuticle, and between cuticle and nail plate is lost. Sympathectomy quickly restores the nail fold and cuticle to normal.

In organic arterial disease the nails do not show these changes. There is rather a thickening, roughening, and darkening of the nail plate, which hides the nail bed. An increase in arterial circulation by any means gives rise to a more nearly normal growth of the plate. Less specific changes include the growth of claw nails, or the presence of "diffusion of the lunule" in organic states, and the loosening and shedding of the nail plate in severe disease of either vasospastic or organic origin.

Painful nails are often an expression of the hyperesthesia of severe ischemia, in which operations for ingrown toenail usually cause gangrene.

Primary infections of the nails are uncommon in peripheral vascular disease, but the nails may be involved in acral ulceration, or may show subungual abscess over an osteomyelitis of the terminal phalanx.

372 Marlborough Street

#### REFERENCES

- 1 Raynaud M. *De l'asphyxie locale*. 174 pp. Thèse, Paris 1862.
- 2 Heller J. Die Krankheiten der Nägel. In *Handbuch der Haut- und Geschlechtskrankheiten*. Edited by J. Jadassohn. Vol 15. Part 2. Berlin: Julius Springer 1927.
- 3 Pardo-Castello, V. *Diseases of the Nails*. Second edition. 195 pp. Springfield, Illinois: Charles C Thomas 1941.

## A POSTOPERATIVE MASTECTOMY DRESSING\*

LEO H. POLLOCK, M.D.†

KANSAS CITY, MISSOURI

THE postoperative dressings of a radical mastectomy wound may be assisted and simplified by discriminate application of adhesive tape. This easy method, which I have used for many years, is not mentioned in the literature.

A strip of plain or elastic adhesive, 2.5 to 4.2 cm wide, is flamed. The strap is started over the lower

toral muscles. It then crosses the ridge of the shoulder to end over the upper part of the scapula. A thin piece of sterile gauze may be placed over the incision under the adhesive.

The procedure works very well with any type of skin incision, either transverse or longitudinal. The attachment of the skin flaps to the chest wall is helped by scattered mattress sutures, placed between them and by various types of pressure dressings. The important point in the method is the selective molding of the skin to the concavity in front of the head of the humerus before the outer

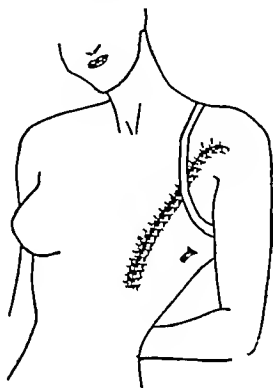


FIGURE 1 Curved Adhesive Strap, Molding the Skin to the Chest Wall in a Longitudinal Incision

This supports the posterior axillary fold to lessen the tension on the suture line. It greatly decreases the padding needed to obliterate the dead space.

aspect of the scapula. It is brought across the axilla by one hand as the other presses the posterior axillary fold anteriorly and upward. The medial

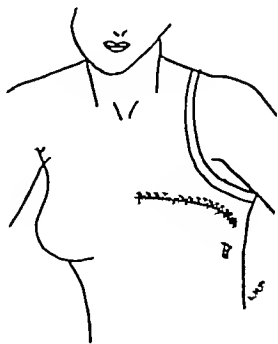


FIGURE 2 Adhesive Strap Approximating the Upper Skin Flap to the Chest Wall When a Transverse Incision Is Used. This minimizes the use of voluminous dressings.

or upper skin flap is pushed toward the incision as the adhesive curves upward in the infraclavicular depression resulting from the removal of the pec-



FIGURE 3 Left Radical Mastectomy Wound on the Sixth Postoperative Day

The adhesive strip fits into the depression resulting from the removal of the pectoral muscles. This has obliterated the dead space. The full-thickness skin grafts are holding well. Tension on the edges is removed by the strip supporting the posterior axillary fold.

dressings are applied (Fig. 1). It minimizes the voluminous padding to obliterate the dead space. Also, the amount of padding is materially decreased by the application of similarly curved adhesive strips over it (Fig. 2). The strap supports the weight of the posterior axillary fold, which may be a dehiscent force in an obese or muscular patient. It lessens the circular constrictions on the chest that accompany swaths, binders and broad transverse adhesive straps relied upon for pressure.

\*From the Surgical Service, Menorah Hospital.

†Attending surgeon, Menorah Hospital.

The condition of the wound on the sixth day after operation is shown in Figure 3

Should a defect develop in the suture line, this method of strapping promotes healing by helping to approximate the edges and decreasing edema of both the skin and granulation tissue. One need

not remove the outer dressings to take out the drain. A heavy silk suture may be attached to the end of the drain and then fastened lineally to the lower edge of the outer pad. The drain may be extracted by pulling on the loose end of the thread.

1310 Bryant Building

## FAVISM\*

ALBERT P. ROSEN, M.D.,† AND JAMES J. SCANLAN, M.D.‡

PROVIDENCE, RHODE ISLAND

**F**AVISM as a cause of hemolytic anemia, though not uncommon in the Mediterranean basin, especially in Sardinia and Sicily, is rare in the United States. The first case to appear in the American literature was reported by McRae and Ullery<sup>1</sup> in 1933. Since then individual cases have been reported by Hutton,<sup>2</sup> Eads and Kash,<sup>3</sup> Josephs<sup>4</sup> and Wharton and Duesselmann.<sup>5</sup> It is the purpose of this report to review briefly the clinical features and possible etiology and to describe a typical case, as well as to call attention to the fact that the fava bean (broad bean) in addition to being imported is now being grown in this country. It appears very probable that many more cases would be discovered here if this entity were considered in the differential diagnosis of acute hemolytic anemia.

The syndrome, caused either by ingestion of the seed or by inhalation of the pollen of *Vicia faba*, is characterized by gastrointestinal complaints and sudden appearance of hemolytic anemia, followed by hemoglobinuria, jaundice and vascular collapse.

Symptoms occur after the inhalation of the pollen, in a matter of minutes to a few hours, after ingestion of the bean there is a delay of five to forty-eight hours. The symptoms vary in severity. A mild form is not uncommon, resulting in malaise, yawning, headache, vertigo, nausea, vomiting, diarrhea, pyrexia, abdominal pain and, at times, loss of consciousness. These symptoms usually disappear in a few days. The severer form includes hemoglobinuria, marked pallor and icterus. The urine becomes red or black. The icterus increases, and hepatomegaly and splenomegaly usually ensue. Recovery takes place within a week, but the symptoms may persist for several weeks. The blood picture during the attack reveals a marked reduction in red cells with anisocytosis, reticulated cells, polychromatophilic cells and erythroblasts. There is a marked leukocytosis during the first week. Death occurs almost only in children, and the mortality is 8 per cent.<sup>6</sup>

Three theories have been proposed in the pathogenesis of favism: infectious, toxic and allergic. Luisada,<sup>6</sup> in his comprehensive review of the Italian literature, presents a fair amount of evidence pointing to allergy as the mechanism in this syndrome. Robinson<sup>7</sup> also favors allergy, peripheral blood and bone-marrow smears in 3 of his cases revealed an increase in eosinophilic cells.

Sensitivity to the fava bean can be determined by skin tests, the optimum time being about six weeks after an attack. Apparently there is a refractory state during which skin tests are negative even in persons sensitive to the products of *V. faba*.

Josephs<sup>4</sup> points out that the disease appears to have a racial background identical with that of Cooley's anemia. Possibly this peculiar racial background serves to explain a manifestation of allergy that is certainly unique.

The treatment consists essentially of whole-blood transfusions to correct the anemia and of supportive measures. Epinephrine is recommended if there is vascular collapse.

## CASE REPORT

T. F. (C. V. C. H. 70704), a 5-year-old boy of Italian descent, entered the hospital on February 15, 1948, because of abdominal pain, red urine and jaundice of 30 hours' duration.

On the afternoon before entry, the child complained of crampy abdominal pains and vomited. That evening he complained of headache. The cramps continued intermittently throughout the night, and he had two loose, brown stools, neither of which appeared abnormal. His mother noted that his urine was "wine colored," a color that persisted with each micturition until admission. The temperature was 101°F, and he was observed to be "very pale." On the next morning it was noticed that his skin was yellow, and this became increasingly evident as the day wore on. The cramp-like abdominal pains recurred and he began to vomit frequently. A physician advised hospitalization.

The past history yielded no positive information concerning recent exposure to toxic fumes or chemicals. The patient had been apparently well until the sudden gastrointestinal upset. There were no cases of malaria in the family or immediate neighborhood. He had received no injections or transfusions and there was no history of familial anemia or of syphilis in either parent. However, two years before admission at the age of 3, he had had a similar episode of "jaundice" accompanied by nausea, vomiting, fever and the passage of red urine. This had lasted for 2 weeks and had cleared up spontaneously without medication. A further note

\*From the Pediatric Service, Charles V. Chapin Hospital.

†Fellow, Emma Pendleton Bradley Home, formerly assistant clinical director, Charles V. Chapin Hospital.

‡Intern, St. Joseph's Hospital.

of interest in the history was the fact that the patient had had eczema in infancy and had a known allergy to eggs.

Physical examination revealed an acutely ill, pale and drowsy boy. He sighed and yawned conspicuously. There was a marked generalized lemon-colored icterus with an underlying pallor of the skin, the mucous membranes and scleras were markedly icteric. There was a moderate generalized lymphadenopathy. The eyes, ears, nose and throat were normal. The lungs were clear to percussion and auscultation. The heart sounds were loud and forceful, and there was a Grade III precordial systolic murmur. The apical rate was 130, there was a normal sinus rhythm, and the heart was not enlarged to percussion. There was generalized abdominal tenderness and some muscle guarding. The spleen edge, which was sharp and notched, was palpable 5 cm below the left costal margin. The liver was not palpated, but there was a suggestion of a mass in the right upper quadrant. The genitalia, extremities and nervous system were normal.

The temperature was 101.6°F by rectum, and the blood pressure was 98/68.

Examination of the blood revealed a red-cell count of 1,520,000, with a hemoglobin of 38 per cent (5.5 gm), and a white-cell count of 33,150, with 71 per cent neutrophils, 9 per cent large lymphocytes, 19 per cent small lymphocytes and 1 per cent eosinophils. The hematocrit was 35 per cent. The smear showed red cells with marked central pallor, anisocytosis, poikilocytosis, some target cells and spherocytes. There was moderate polychromatophilia and a reticulocyte count of 3.8 per cent.

The urine, which was Burgundy-red and had a specific gravity of 1.016, gave an acid reaction and contained 1.2 gm of albumin per 100 cc. of urine. It was packed with red cells, occurring singly, in clumps and in casts.

The patient was given 500 cc. of compatible whole blood in addition to 5 per cent glucose in water and saline solution. The next morning his color had improved noticeably, and the icterus had diminished in intensity. He was more alert and took soft-solid foods with relish. A second urinalysis yielded Burgundy-red urine, with a specific gravity of 1.025 and a neutral reaction, and containing 1.5 gm of albumin per 100 cc and rare red cells and a few white cells in the sediment.

The clotting time was 2 minutes, 33 seconds, and the bleeding time was 1 minute, 58 seconds. A cell-fragility test showed initial hemolysis in 0.38 per cent sodium chloride and complete hemolysis in 0.32 per cent.

The blood chemical findings were normal except for a slightly elevated icteric index.

X-ray films of the skull demonstrated some prominence of the digital impressions but no "hair-on-end" appearance or thickening of the skull table. The left hand had 4 carpal ossification centers, and the right hand 3 centers.

The temperature showed a mild elevation until the 4th hospital day, when it became normal. Recovery was uneventful. The icterus disappeared, the spleen receded, and the heart murmur became less prominent. The red-cell count on the 5th hospital day was 3,950,000, with a hemoglobin of 75 per cent. Daily urinalyses showed a rapid clearing and a gradual decrease in albumin content, as well as a disappearance of the cellular elements.

The etiology of the hemolytic episode was unexplained until at the suggestion of an attending physician\* an investigation into the history was made pertaining to the ingestion of fava beans. It was found that on the day before the onset of the illness, the patient's grandmother had cooked a quantity of fava beans, of which the patient had eaten four plates full. Further questioning revealed that the child had eaten fava beans just prior to the attack of icterus 2 years previously.

## DISCUSSION

The diagnosis of favism appears to have been warranted in this case on the basis of the history of two attacks of hemolytic anemia associated with the ingestion of fava beans and the physical and laboratory findings. Skin-testing agents for fava-bean sensitivity were not available at the time of

writing so that permission was requested of the mother, which she refused to grant, to feed the boy a few fava beans. In view of the 8 per cent mortality rate, the issue was not pressed.

Luisada<sup>6</sup> believes more cases will be seen in the United States for the following reasons: the fava bean is now cultivated in New York, New Jersey, Illinois and California, a large Mediterranean population lives in certain parts of the United States, and the fava bean is a staple article of the diet, and the beans are being imported from Italy as a canned food.

The beans can be purchased in practically all the grocery stores in the Federal Hill section of Providence, which is populated mainly by people of Italian background.

Apparently, the syndrome also affects peoples of Jewish stock. The bean is frequently used by them under the name of "bub." The case reported by Eads and Kash<sup>3</sup> occurred in a male of Spanish-Jewish descent. Robinson<sup>7</sup> reports 6 cases in Palestine in which the patients were at first thought to have Lederer's anemia. An interesting point in his paper may be worth repeating. There is evidence that the incidence of blackwater fever increases in March, the time of the ripening of the fava bean, and yet malaria in March is uncommon. This supports the observations of other authors<sup>4</sup> that a good many cases of favism have been misdiagnosed as blackwater fever because of the hemoglobinuria and splenomegaly. Wharton and Duesselmann<sup>5</sup> believe that some of the cases of hemolytic anemia classified as Lederer's anemia may possibly be explained by an allergic phenomenon similar to or identical with favism.

Apparently, the disease can affect any age group. Of the 5 cases reported in the American literature, 3 were in adults,<sup>1-3</sup> and 2 were in children.<sup>4, 6</sup> The case presented above is the sixth reported in the United States and the third case that involved a child.

All the American cases occurred in males, which follows the European trend in that males are affected much more frequently than females.

## SUMMARY

A case of favism in a five-year-old boy is presented with a review of the clinical features. More cases of this syndrome will be seen in the United States because the fava bean is now cultivated here.

## REFERENCES

1. McRae T and Ullery J C Favism report of case *J A M A* 101 1389 1391 1933
2. Huttou J E Favism unusually observed type of hemolytic anemia *J A M A* 109 1618-1620 1937
3. Eads J T and Kash R M Favism report of case *U S Nat M Bull* 41 1720-1724 1943
4. Josephs H W Favism *Bull Johns Hopkins Hosp* 74 295 298 1944
5. Wharton H J and Duesselmann W Favism short review and report of case *New Eng J Med* 236 974 977 1947
6. Luisada A Favism singular disease chiefly affecting red blood cells. *Medicine* 20 229 250 1941
7. Robinson P Favism in children *Am J Dis Child* 62 701 707 1941

\*We are indebted to Frank J Jacobson M D for suggesting favism as the possible diagnosis.

## MEDICAL PROGRESS

### PREGNANCY TESTS (Concluded)\*

STANLEY L. ROBBINS, M D †

BOSTON

#### *Friedman Test*<sup>10</sup>

This technic was developed within a few years of the original mouse test and represents a modification employing rabbits in place of mice. It is based on the principle that female rabbits ovulate only upon stimulation by the male and, therefore, do not spontaneously ovulate or have corpora hemorrhagica. The administration of gonadotropin likewise produces ovulation and corpora hemorrhagica, and hence their presence after the administration of urine indicates a positive pregnancy reaction.

The technic for the performance of the test is composed of the intravenous administration of first morning urine into the ear vein with examination of the ovaries forty-eight hours later. The amount of urine administered and the number of doses employed vary widely from the original description of six doses of 4 cc each over a two-day period to a single injection of 15 to 20 cc of urine. Some laboratories are employing blood serum (6 cc) in place of urine with equally satisfactory results.<sup>86</sup> Inspection of the ovaries may be performed under anesthesia, and if the reaction is negative, the animal may be re-used, and the cost per test thus reduced.

The great advantage that this modification has over the Aschheim-Zondek test is its relative speed—forty-eight hours as compared to four to six days. Although follicle hemorrhage may occur as early as fourteen hours after the administration of the urine, it only becomes a definite reaction in twenty-four to forty-eight hours.<sup>87</sup> Larger doses of chorionic gonadotropin prove fruitless in speeding this change. Because of its relative speed the test has achieved widespread acceptance with invariably good results. The numerous reports in the literature cite accuracy from 100 per cent<sup>10</sup> to 98-99 per cent.<sup>61-64</sup> Certain drawbacks to the use of this technic are worth noting. It is necessary to have constantly at hand a colony of isolated, relatively large female animals, each weighing 3 or 4 pounds. The animals are very sensitive to toxic urines and are easily killed, and, thirdly, occasional focal hemorrhages that occur may closely

resemble true ovulatory hemorrhages, making the test difficult to read.

#### *Ovarian Hyperemic Tests*

One of the first effects of chorionic gonadotropin on the ovaries of immature rats is the development of a superficial hyperemia. This change appears within two hours and reaches its peak in sixteen to twenty-four hours, long before corpora hemorrhagica or corpora lutea appear. On the basis of this ovarian color change, numerous procedures have been developed, perhaps best referred to as the two-hour rat test,<sup>20, 21</sup> the six-hour rat test<sup>17</sup> and the twenty-four-hour rat test.<sup>12-16</sup>

As indicated above, the color changes produced in a positive pregnancy reaction begin in two hours. At that time the color change is subtle and is based on a comparison of the faint hyperemization of the ovary with the pale serosa of the other viscera. Since the urine in this two-hour technic is administered intraperitoneally, a resultant possible nonspecific inflammatory reaction of the other viscera may mask the slight ovarian color change. A great danger exists, therefore, of false-negative results, reported by Zondek, Sulman and Black<sup>88</sup> to be as high as 45 per cent. As more time elapses, the color change becomes more definite, but even the six-hour and twenty-four-hour tests have failed to gain wide acceptance because of this difficulty in reading the endpoint. It can best be summed up by saying that in the hands of the original investigators the procedures appear to give good results, but difficulty in reading the endpoint, for all but the most experienced, makes it of limited value to laboratories in general.

#### *Frog Tests*

As long ago as 1933 Shapiro and Zwarenstein<sup>11</sup> presented the first report of the use of the female South African frog in pregnancy diagnosis, based upon work by Hogben.<sup>89</sup> Subsequent references by these authors occurred in the ensuing two years,<sup>65, 66</sup> and in 1938 Elkan<sup>67</sup> introduced the procedure in England. Three years later Weisman and Coates<sup>68</sup> popularized this technic in the United States. Since that time numerous reports have appeared receiving the test with great enthusiasm. Accuracy is cited as between 96 and 100 per cent.<sup>90-93</sup>

The test is based on the fact that the female *Xenopus laevis*, like the rabbit, never ovulates un-

\*From the Mallory Institute of Pathology, Boston City Hospital.  
†Assistant professor of pathology, Boston University School of Medicine; instructor in pathology, Tufts College Medical School; instructor in pathology, Harvard Medical School; assistant pathologist, Mallory Institute of Pathology, Boston City Hospital.

less stimulated either by the male or by the administration of gonadotropic hormone. Hence, isolated female frogs, when injected with urine from pregnant women, react to a positive test by the extrusion of hundreds of grossly visible ova, usually in twenty-four and occasionally in forty-eight hours. If no eggs appear the test is negative. In either case, after an appropriate rest (four weeks after a positive test and one week after a negative test) the animal can be re-used throughout a ten-year to eleven-year life. Recently, blood serum has been found to be as useful as urine in this technic.<sup>84</sup> The advantages of this procedure are numerous. The endpoint is definite and simple to read—the presence or absence of ova. The speed exceeds that of the Friedman test. Re-use of the animals and their ease of maintenance make the procedure not only adaptable for small laboratories, but also very cheap. In 1946 Parker, Robbins and Lovelidge<sup>95</sup> succeeded in successfully rearing these animals in the United States and demonstrated the complete usefulness of these captive-bred amphibia for pregnancy diagnosis, thus removing the objection of the unavailability of these animals in this country. The sole remaining objection to the widespread use of this technic is the need to obtain and concentrate large volumes of urine, 40 to 80 cc, for each frog, a fastidious and protracted procedure. As pointed out above, in the course of breeding experiments it was noted that the male *Xenopus laevis* reacted to gonadotropic hormone and that this reaction was readily visualized by microscopical examination of the cloacal fluid. This reaction was further notable in that the male frog appeared to be considerably more sensitive to chorionic gonadotropin than the female, smaller quantities of urine sufficing to produce reactions in the male. Whereas concentrates of 40 cc of urine were required to produce a reaction in the female *Xenopus laevis*, 10 cc of whole urine sufficed for the South American male *Bufo arenarum* and 5 cc of whole urine for the North American male *Rana pipiens*. The technic of the test is essentially the same, using either the North or the South American frog. Only the quantities of substances administered differ. With the North American *Rana pipiens* 5 cc of whole urine or 5 cc of blood serum<sup>35, 56</sup> is administered to each of a pair of frogs. Cloacal fluid from the external cloacal orifice, obtained by use of a glass pipette, is examined unstained by the hanging-drop technic, one and two hours after injection. The reactions are clear cut, all or none, comprising the presence of spermatozoa in a positive test and their total absence in a negative test. As can be noted, the reaction develops within two hours, frequently in half an hour, and therefore the entire test sometimes requires only two and a half hours to perform. Re-use of the frogs is possible, but their low cost and the difficulty in feeding them make such use both unnecessary and

inadvisable. In the present state of knowledge, this reaction in the male *Rana pipiens* appears to be due to the presence of the luteinizing chorionic hormone. The frog does not appear to react to follicle-stimulating hormone derived from menopausal urine. An accuracy of 98 per cent has been achieved in this laboratory with this pregnancy test. Although this procedure still requires the use of animals, it most closely approaches in simplicity and speed the concept of a test-tube technic that is easy to read. Its value in the differential diagnosis of acute conditions of the abdomen with relation to ectopic pregnancy or any other emergency in which speed is of greatest urgency is obvious.

#### *Pregnanediol Test of Guterman*<sup>39</sup>

Of the several chemical procedures reported to be of use in the diagnosis of pregnancy, the only one that appears to hold any great promise is the test developed by Guterman.<sup>39</sup> This test is based on the observation by Venning and Browne<sup>10</sup> that pregnanediol is present throughout pregnancy although in low concentration in the first trimester. The test comprises essentially an extraction of the acid hydrolyzed pregnanediol and the development of a color complex by the addition of sulfuric acid. Reports of the accuracy of this procedure have been somewhat equivocal. Guterman<sup>39</sup> has recently cited his accuracy as 92 per cent in 248 tests, whereas Morrow and Benua<sup>42</sup> and McCormack<sup>44</sup> imply that low-titer urines may give false-negative reactions, and nonpregnant women with delayed menses may give false-positive reactions owing to the high level of corpus luteum hormone in the secretory phase of the menstrual cycle. The test has the fundamental disadvantage of dealing with the lowest titer of hormone when early diagnosis is required, in contrast to the extremely high titers of the last trimester when the diagnosis is obvious clinically. In conditions other than pregnancy associated with a high gonadotropic excretion, such as moles and chorionepitheliomas, this test is very useful since it is said to remain negative and therefore to differentiate these conditions from pregnancy.<sup>77</sup>

In the recent literature occasional reference is made to the various skin tests listed, to the histidine-excretion tests and to the prostigmine test. However, since these procedures in their present state of development contribute nothing to the diagnostic methods described above, they have not been described in any detail.

#### DISCUSSION

Any discussion of pregnancy tests must begin by emphasizing certain facts. All bio-assay techniques, which comprise the commonly used tests for pregnancy, depend in essence upon the presence in the urine or the blood stream of chorionic gonadotropic

hormone, the result of functioning chorionic epithelium in contact with the blood stream. It does not necessarily imply a living fetus. These tests, therefore, cannot distinguish between normal or abnormal pregnancies or tumors containing chorionic epithelium. It is possible in cases of intrauterine death of the fetus or of inevitable missed abortions to have viable, functioning chorionic tissue maintain a positive pregnancy reaction for some time. Moreover, even after all the functioning tissue has died, time is required for the excretion of the hormone already produced. Depending on the original level of hormone that existed, this time may vary from several days to a week. Rarely, cases of persistence of detectable chorionic hormone have been encountered months after total removal of a hydatid mole. When fetal death is suspected clinically and a positive pregnancy reaction is encountered, a repeat assay should be performed some time later, when the hormone is almost certain to have become lower or to have disappeared from the urine or serum. It is also obvious that in extremely early pregnancy negative reactions may be encountered, frequently termed as "false-negative reactions," when the test is performed before the prolactin titer has had time to rise to a detectable level. In general, the Aschheim-Zondek test, the Friedman and the frog tests are able to detect early pregnancy approximately seven days after the first missed period. However, since hormone titers of pregnancies show great variation from person to person, this time required for an adequate luteinizing hormone level to develop cannot be stated as an absolute time period applicable to all.

In many cases in which the test has failed to conform to the course that the pregnancy followed, the reaction has been termed an error in diagnosis. This use of the term "error" is unfortunate since at the time of the performance of the test the hormone titer may have been at some transitional level when the titer was either rising or falling. A test performed one or two weeks later would have dealt with a newly established level that would have conformed to the future course of the gestation.

The second point to be remembered is that no pregnancy test — and for that matter no laboratory test — is infallible. Reports constantly emphasize the closeness with which these various diagnostic procedures approach 100 per cent accuracy, rather than the percentage of errors inherent in each technic. Thus, although a test may be 99 per cent accurate, the one error in a hundred is small solace to the physician or patient who falls heir to this sole discrepancy. Technical errors and insensitive or physically unfit animals contribute to errors in diagnosis. Moreover, well documented cases of normal pregnancy are cited in which it was impossible to obtain a positive Aschheim-Zondek test.<sup>96</sup> Such cases are fortunately extremely rare,

nonetheless they contribute to the so-called errors in pregnancy diagnosis. It is perhaps only fair to point out that in the absence of these pregnancy reactions it has never been established that the so-called "negatively reacting" normal pregnancies ever elaborated any chorionic gonadotropin. So much for the errors inherent in the laboratory diagnosis of pregnancy.

The question whether urine or blood serum is a better substance to use in any of these diagnostic procedures is an important one. To the best of my knowledge at present they may be used interchangeably. Smith and Smith<sup>96</sup> have long advocated the use of serum because unextracted urine is frequently toxic, killing all the animals to which it is administered. This death of laboratory animals is a most bothersome problem in laboratory technique since time is lost, valuable animals destroyed and almost invariably before a successful test has been achieved the specimen that is being assayed is used up and time must be wasted getting a new specimen. Serum, by contrast, appears to be remarkably free of this objection. Although it might at first appear that the titer of hormone should be higher in the serum than it is in the urine, this conclusion is not correct. Zondek et al.<sup>98</sup> state on the contrary that the titer of hormone appears in lower concentration in the serum than in the urine. This fact is particularly true when first morning concentrated urine specimens are used, since the amount of hormone excreted in a twenty-four-hour interval is uninfluenced by the volume of urine and hence reaches higher levels in concentrated urines. It is for this reason that when urines are to be used for pregnancy diagnosis it is advisable to restrict fluids and use the first morning urine. Notwithstanding this differential in hormone levels, if blood serum is titered on frogs or rats against first morning urine in an unselected series of normal pregnancies, the serum appears to give results as good as if not better than those obtained with urine — that is, it appears to give higher titers. It is possible that this difference in hormone level is more apparent than real and may be due to either a renal threshold holding back serum hormone and producing a low urine titer or to the fact that the urine may, by its toxic effects, depress the sensitivity of the animals. In any event, in the interests of a less toxic, more constant source of hormone, blood serum appears to be preferable to urine.

Is it possible to say that any one of the tests described above is better than the others? No, since each procedure has its own peculiar advantages that suit it best to specific indications.

The Aschheim-Zondek test, despite the time it requires for performance, is to this day unsurpassed for accuracy, especially when the equivocal ovarian changes are controlled by microscopical slide examination. In view of the dual changes possible

less stimulated either by the male or by the administration of gonadotropic hormone. Hence, isolated female frogs, when injected with urine from pregnant women, react to a positive test by the extrusion of hundreds of grossly visible ova, usually in twenty-four and occasionally in forty-eight hours. If no eggs appear the test is negative. In either case, after an appropriate rest (four weeks after a positive test and one week after a negative test) the animal can be re-used throughout a ten-year to eleven-year life. Recently, blood serum has been found to be as useful as urine in this technic.<sup>94</sup> The advantages of this procedure are numerous. The endpoint is definite and simple to read—the presence or absence of ova. The speed exceeds that of the Friedman test. Re-use of the animals and their ease of maintenance make the procedure not only adaptable for small laboratories, but also very cheap. In 1946 Parker, Robbins and Lovelidge<sup>95</sup> succeeded in successfully rearing these animals in the United States and demonstrated the complete usefulness of these captive-bred amphibians for pregnancy diagnosis, thus removing the objection of the unavailability of these animals in this country. The sole remaining objection to the widespread use of this technic is the need to obtain and concentrate large volumes of urine, 40 to 80 cc, for each frog, a fastidious and protracted procedure. As pointed out above, in the course of breeding experiments it was noted that the male *Xenopus laevis* reacted to gonadotropic hormone and that this reaction was readily visualized by microscopical examination of the cloacal fluid. This reaction was further notable in that the male frog appeared to be considerably more sensitive to chorionic gonadotropin than the female, smaller quantities of urine sufficing to produce reactions in the male. Whereas concentrates of 40 cc of urine were required to produce a reaction in the female *Xenopus laevis*, 10 cc of whole urine sufficed for the South American male *Bufo arenarum* and 5 cc of whole urine for the North American male *Rana pipiens*. The technic of the test is essentially the same, using either the North or the South American frog. Only the quantities of substances administered differ. With the North American *Rana pipiens* 5 cc of whole urine or 5 cc of blood serum<sup>25, 86</sup> is administered to each of a pair of frogs. Cloacal fluid from the external cloacal orifice, obtained by use of a glass pipette, is examined unstained by the hanging-drop technic, one and two hours after injection. The reactions are clear cut, all or none, comprising the presence of spermatozoa in a positive test and their total absence in a negative test. As can be noted, the reaction develops within two hours, frequently in half an hour, and therefore the entire test sometimes requires only two and a half hours to perform. Re-use of the frogs is possible, but their low cost and the difficulty in feeding them make such use both unnecessary and

inadvisable. In the present state of knowledge, this reaction in the male *Rana pipiens* appears to be due to the presence of the luteinizing chorionic hormone. The frog does not appear to react to follicle-stimulating hormone derived from menopausal urine. An accuracy of 98 per cent has been achieved in this laboratory with this pregnancy test. Although this procedure still requires the use of animals, it most closely approaches in simplicity and speed the concept of a test-tube technic that is easy to read. Its value in the differential diagnosis of acute conditions of the abdomen with relation to ectopic pregnancy or any other emergency in which speed is of greatest urgency is obvious.

### *Pregnanediol Test of Guterman<sup>99</sup>*

Of the several chemical procedures reported to be of use in the diagnosis of pregnancy, the only one that appears to hold any great promise is the test developed by Guterman.<sup>99</sup> This test is based on the observation by Venning and Browne<sup>10</sup> that pregnanediol is present throughout pregnancy although in low concentration in the first trimester. The test comprises essentially an extraction of the acid hydrolyzed pregnanediol and the development of a color complex by the addition of sulfuric acid. Reports of the accuracy of this procedure have been somewhat equivocal. Guterman<sup>77</sup> has recently cited his accuracy as 92 per cent in 248 tests, whereas Morrow and Benua<sup>42</sup> and McCormack<sup>41</sup> imply that low-titer urines may give false-negative reactions, and nonpregnant women with delayed menses may give false-positive reactions owing to the high level of corpus luteum hormone in the secretory phase of the menstrual cycle. The test has the fundamental disadvantage of dealing with the lowest titer of hormone when early diagnosis is required, in contrast to the extremely high titers of the last trimester when the diagnosis is obvious clinically. In conditions other than pregnancy associated with a high gonadotropic excretion, such as moles and chorionepitheliomas, this test is very useful since it is said to remain negative and therefore to differentiate these conditions from pregnancy.<sup>77</sup>

In the recent literature occasional reference is made to the various skin tests listed, to the histidine-excretion tests and to the prostigmine test. However, since these procedures in their present state of development contribute nothing to the diagnostic methods described above, they have not been described in any detail.

### DISCUSSION

Any discussion of pregnancy tests must begin by emphasizing certain facts. All bio-assay techniques, which comprise the commonly used tests for pregnancy, depend in essence upon the presence in the urine or the blood stream of chorionic gonadotropic

this fall or rise in level obviously indicates recurrence of tumor. It is for these reasons that simple qualitative urine tests for the detection of the mere presence of a positive reaction have no value in postoperative tumor diagnostic work and are definitely to be discouraged since they may well cause totally unnecessary alarm.

### REFERENCES

- 86 Evans N. and Krajian A. A. Note on Friedman pregnancy test using blood serum. *Am J Clin Path Tech. Sect.* 8:97 1944
- 87 Boehm E. E. Use of zipper in Friedman test. *Am J Clin Path Tech Sect.* 5:168 1941
- 88 Zondek, B. Solman F., and Black R. Hyperemia effect of gonadotropins on ovary and its use in rapid pregnancy test. *J A M A* 128:939-944 1945
- 89 Hogben L., Charles E. and Slome, D. Studies of pituitary VIII. Relation of pituitary gland to calcium metabolism and ovarian function in *Xeropus*. *J Exper Biol* 8:345-354 1931
- 90 Scott, L. D. Concentration and detoxification of human urine for biological pregnancy diagnosis. *Brit. J. Exper Path* 21:520-524 1940
- 91 Foote, E. C. and Jones, G. E. S. Evaluation of Hogben pregnancy test. *Am J Obst & Gynec* 51:672-677 1946
- 92 Ekan, R. E. New test for pregnancy. *Post-Grad M J* 22:87-97 1946
- 93 Weissman A. L. and Coates C. W. Frog test (*Xeropus laevis*) for pregnancy: report on 1000 tests over period of 4 years of study. *West J Surg* 52:171-174 1944
- 94 Rosenfeld, S. S. and Rosenfeld V. W. Reaction of *Xeropus laevis* Daudin (South African clawed frog) to human pregnancy serum: new test for pregnancy. Preliminary report. *J Lab & Clin Med* 29:327-329 1944
- 95 Parker F., Jr., Robbins S. L. and Lovendge A. Breeding rearing and care of South African clawed frog (*Xeropus laevis*). *Am Naturalist* 81:8-49 1947
- 96 Smith O. W. and Smith, G. V. Tests for pregnancy. *J Clin Endocrinol* 4:551 1944
- 97 Tenney, B. Jr., and Parker F. Jr. Significance of weakly positive Aschheim-Zondek test. *New Eng J Med* 218:61 1938
- 98 Barrett, M., and Smiles, J. M. Diagnosis of hydatidiform mole by biological assay. *Lancet* 1:1428-1430 1939
- 99 Payne F. L. Hormone studies in presence of hydatidiform mole and chorioepithelioma. *Surg., Gynec & Obst* 73:86-95 1941

## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

EDITH E. PARRIS, *Assistant Editor*

### CASE 34361

#### PRESENTATION OF CASE

A six-year-old schoolboy entered the hospital because of persistent vomiting.

Until three weeks before admission the patient had no complaints. He then began to have anorexia and became moderately constipated. Eight days prior to admission he began to vomit on the average of one to three times a day. The vomiting was preceded by episodes of crampy, periumbilical pain. No fever had been present prior to admission.

Physical examination revealed a listless, rather poorly nourished boy lying flat in bed, with respirations of 40 to 50 per minute. A diffuse forceful apex impulse was visible extending almost to the anterior axillary line. A gallop rhythm was present, without murmurs or friction rubs. The remainder of the examination was negative. One observer felt the liver edge 3 cm. below the costal margin.

The temperature was 99.2°F., and the pulse 120. The blood pressure was 90 systolic, 66 diastolic.

Examination of the blood revealed 12.5 gm. of hemoglobin and a white-cell count of 13,000, with 51 per cent neutrophils, 34 per cent lymphocytes, 2 per cent monocytes and 13 per cent band forms. Urinalysis showed a specific gravity of 1.030, with no albumin, sugar or formed elements in the sediment. The serum nonprotein nitrogen was 23 mg., and the total protein 5 gm. per 100 cc. The pro-

thrombin time was 18 seconds (control 15 seconds). The sedimentation rate was  $\pm 5$  mm. per hour (normal, up to 20 mm. per hour). The Schick, blood Hinton and tuberculin (dilution of 1:1000) tests were negative for diphtheria bacilli.

A throat culture was negative for beta-hemolytic streptococci, diphtheria bacilli and pneumococci. An electrocardiogram showed a sinus tachycardia, with a rate of 160, and a PR interval of 0.13 second. The QRS complex was 0.07 second, and the T waves were flat in Lead I and inverted in Leads 2 and 3.

An x-ray film of the chest showed a marked increase in density in both lungs, more marked at the bases. The heart was enlarged, particularly to the left, with a cardiothoracic ratio of 11.5:18.5. A small amount of fluid was present in both costophrenic sinuses. The cardiac pulsations were diminished but regular. Diaphragmatic motion was free and equal. A plain film of the abdomen showed the liver to be slightly larger than normal. The spleen was not enlarged.

On the third hospital day the patient complained of pain below the tip of the sternum. The pulse rose to 160, and he appeared to be in shock. Following this episode he was placed in oxygen, and digitoxin was started, with definite improvement for the next few hours. During the next few days he remained about the same while digitoxin and oxygen were continued. A repeat electrocardiogram showed a rate of 140, with a PR interval of 0.14 second.

On the sixth hospital day the child was found to be drowsy, and later a right hemiplegia involving the face, arm and leg was noted. A lumbar puncture revealed a clear fluid and an initial spinal-fluid pressure equivalent to 170 mm. of water. No cells were present, and a Pandey test was negative. Repeat x-ray films at this time disclosed considerable mottled density in the right lung, radiating from the right hilar area peripherally. On the left, behind the heart, was a large area of dense lung. The

in the rat ovary, diagnosis of weak titers make the Aschheim-Zondek test of great value in detecting early gestations and complications of pregnancy such as miscarriages. The value of this weakly positive Aschheim-Zondek test has been brought out by Tenney and Parker.<sup>97</sup> In a series of 60 patients weakly positive tests, performed at a time when they should have been strongly positive, indicated in every case a complication of pregnancy. It is highly likely that assays performed on this same series with other technics would have yielded only completely valueless negative results.

The Friedman test has been up to the present time one of the most widely used tests because of its great accuracy and simplicity of performance. However, of recent date the shortage of rabbits and their rising cost have seriously discouraged many laboratories from the use of this animal. It was, in fact, these difficulties that catapulted the female *Xenopus laevis* into such wide usage. Not only was the female-frog test somewhat faster, but it was moreover, because of the possible re-use of the frogs, considerably cheaper. The male-frog technics at present appear to hold the greatest promise. The animals are widely available, easy to keep and cheap, and a positive diagnosis may be returned while the patient waits. Certainly, in cases of ectopic pregnancy, this procedure may prove life saving.

The determination of pregnanediol in the urine is the only chemical test for pregnancy of any significant value. It is unfortunate that its sensitivity is low in very early pregnancy and that its specificity has been questioned in cases of delayed menstruation. Further analyses are required to evaluate this technic more adequately.

No discussion of the laboratory diagnosis of pregnancy would be complete without a consideration of the functioning tumors, chorionepithelioma and hydatidiform mole. Inasmuch as these tumors usually develop after an abortion, miscarriage or pregnancy, their laboratory differential diagnosis from normal pregnancy is most important. It is well known that both of these tumors elaborate and excrete large amounts of gonadotropin, usually considerably more than that encountered in a normal pregnancy. Differences in the titer of hormone, as obtained in our laboratory, can best be expressed as pregnancy produces luteinizing hormone in the thousands of rat units, hydatidiform mole in the tens of thousands, and chorionepitheliomas in the hundreds of thousands. It is impossible to express these general differences any more specifically since enormous variation in titer may exist at different ages of the same tumor, and certainly between different tumors. The factors important in determining the levels of hormone that a given tumor will produce include the amount of chorionic tissue present, its proximity to blood supply and, most of all, the important question of whether it is a

functioning tumor capable of elaborating hormone. Not only are rare pregnancies incapable of elaborating chorionic gonadotropin but also rare hydatids and chorionepitheliomas may elaborate virtually no hormone. The exact explanation for this curious behavior is not certain, however, it is possible that the absence of this capacity is a function of the degree of anaplasia of the tumor. The well known tendency of these tumors to undergo necrosis is another cause of wide differences in hormone production. It must therefore follow that no arbitrary hormone titers for these tumors can be specified. In the differentiation of these tumors from pregnancy, on the basis of the level of hormone produced, careful consideration to the possible duration of the pregnancy must therefore be taken into account. At the peak production, titers of luteinizing hormone up to 15,000 rat units per twenty-four hours may be found in pregnancy. It is entirely possible for small hydatid moles or chorionepitheliomas to produce less hormone than this amount.<sup>98</sup> On the other hand, titers of hormone over 25,000 rat units for a twenty-four-hour sample and certainly over 50,000 rat units, according to the standards employed at our laboratory, almost certainly indicate the presence of either a mole or a chorionepithelioma.

In brief, quantitative assays of hormones may or may not be diagnostic of themselves, and, in general, they are best used as confirmatory evidence rather than diagnostic criteria. It should be emphasized that assays for hormonal titers or levels should be performed only on twenty-four-hour urine samples. Quantitative urine assays on spot samples of urine are of little value.

More difficult than the problem of differentiating pregnancy and neoplasms is that of following patients after surgical removal of one of these lesions. A widespread misconception prevails that after successful removal of a mole or a chorionepithelioma the hormone promptly disappears from the circulating blood and urine within a matter of a few days. It is not appreciated that the time required for the gonadotropin to disappear is extremely variable, depending not only upon the original height of the hormone level but also upon the rate of excretion of the hormone. As pointed out above, levels of detectable gonadotropin have persisted for months after successful removal of a mole.<sup>99</sup> Any single quantitative determination, then, is of limited value since it may represent persistence of hormone from the preoperative level. It is much better practice to follow the hormone level by serial quantitative titer assays so as to determine whether the hormone is increasing or decreasing in the blood. Falling levels, however long after the removal of a tumor they occur, can only signify that no new hormone production has occurred and that, therefore, the patient is free of functioning chorionic epithelium. Any reversal of

these areas one after another, and I think that a tumor would have been excluded by palpation of the abdomen, and certainly x-ray studies would have been instituted to determine whether one was present.

The second area of involvement appears to have been the heart. If we have some suggestion from the electrocardiogram of pericarditis, of pericardial effusion particularly, after the child had been in the hospital for three days, the episode of pain below the tip of the sternum might have been due to increase in pericardial fluid and pericarditis. The pain might also have been due to coronary obstruction with infarct of the heart or an extremely diffuse myocarditis. We have been seeing the latter frequently caused by an agent that is probably a virus rather than a bacterium. The heart shows definite involvement without evidence of interventricular or interauricular defect, congenital malformation or involvement of the valves.

The third area is the lung, and I am more perplexed now than on reading the description. I thought from the description that we were dealing with either an infarct or abscess or reaction to aspiration of vomitus. To explain the brain changes one could consider the possibility of metastatic abscess from the lung.

I mentioned previously the possibility of sarcoid involving the bowel as being responsible for the vomiting. There, too, we can find a possibility of involvement of the lungs and brain. We had such an experience recently in a child who had this disease and then hemiplegia many years after the initial bowel involvement.

This child had no evidence of a marked infection. The temperature was never high, near the end it was approximately normal, and there was very little change in the white-cell count. Yet the possibility of infection must be entertained seriously. The only infectious disease that might account for the changes would be subacute bacterial endocarditis, and we would have to assume involvement of the bowel with infarct. We are not given any evidence that that occurred — no blood in the stool and no other sign of infarct. But involvement of the bowel, the heart, the lung and the brain can be explained entirely by subacute bacterial endocarditis.

I have not mentioned the other possibilities of vascular disease. If we assume vascular accident or infarct in the brain, we should mention periarthritis nodosa, which is capable of producing all these changes in various locations. We should mention rheumatic fever with arteritis and diffuse myocarditis, possibly occurring in an extremely early attack with no evidence of previous damage to the valves. If the child lost a great deal of fluid during these three weeks of vomiting, presumably dehydration might have been of great importance, and then the possibility of sinus thrombosis must be entertained, with secondary cerebral hemorrhage and necrosis.

I am afraid I have exhausted the list of probable causes of such a group of changes, and I find nothing in the record that would permit me to make a positive diagnosis with any degree of confidence. I think that if I were to choose the most likely diagnosis to explain everything, I would choose rheumatic fever, rheumatic myocarditis, with arterial involvement in a number of places. I am not sure that would go with the pulmonary picture that we have demonstrated by x-ray examination. I think I would have to explain the brain hemorrhage, which this must have been, on the basis of arterial lesions in the brain on a rheumatic etiology or possibly secondary to the complication of the vomiting and rheumatic fever — also, aspiration abscess in the lung with metastasis to the brain. I can go no farther than that.

A PHYSICIAN: What about the congenital heart disease?

DR. FARBER: That is what I had in mind when I mentioned subacute bacterial endocarditis superimposed on an interventricular or interauricular defect, which would be responsible for very few symptoms and would explain why nothing was picked up earlier.

DR. TRACY B. MALLORY: What was the diagnosis on the ward, Dr. Wallace?

DR. WALLACE: We thought that the patient had myocarditis, but we could not determine the etiology. We thought he probably had a thrombosis or infarction to account for the cerebral signs.

A PHYSICIAN: Were any blood cultures taken?

DR. WALLACE: Two — and they were both negative.

#### CLINICAL DIAGNOSIS

Acute myocarditis, type undetermined

#### DR. FARBER'S DIAGNOSES

Rheumatic fever, with rheumatic myocarditis and arteritis?

Subacute bacterial endocarditis, with multiple infarcts?

Aspiration of vomitus, with lung abscess and metastatic brain abscess

#### ANATOMICAL DIAGNOSES

*Cardiac hypertrophy, idiopathic*

*Cardiac mural thrombosis, both ventricles*

*Embolism and infarction of lung, kidney, spleen (and brain)*

*Myocardosis, focal*

*Endocardial thickening*

*Focal necroses of liver*

*Hydropericardium, slight*

*Pericarditis, fibrous, localized*

#### PATHOLOGICAL DISCUSSION

DR. MALLORY: Dr. Castleman scheduled this case for discussion, asked Dr. Farber to present the clinical side and me the pathological side, and then wisely left town. I wish that Dr. Farber were

bronchial markings throughout this region were observed to terminate very close to the origin of the left main bronchus, which was elevated above its usual position. The area of density lay within the posterior portion of the lower lobe. There was a small area of emphysema adjacent to the lower lateral heart margin. In the upper portion of the left lung mottling of the lung parenchyma was noted, similar in character to that noted on the right. There was a small amount of fluid within the pleural space on the right, particularly notable within the minor septum.

Penicillin and aspirin were administered without appreciable effect. The temperature, which had become elevated prior to the onset of hemiplegia, remained slightly elevated during the remainder of the hospital course, fluctuating between 99.6 and 100.4°F. The white-cell count showed a rise to 17,500, with 90 per cent neutrophils. The patient continued to fail slowly, and the nonprotein nitrogen rose to 72 mg per 100 cc. He was seen by numerous consultants during the next few days. On the sixteenth hospital day he died, approximately eight hours after a second cerebral accident.

#### DIFFERENTIAL DIAGNOSIS

DR SIDNEY FARBER\* May I ask for a cardiac expert to interpret the electrocardiograms?

A PHYSICIAN They could represent pericarditis.

DR FARBER I would like to ask for one or two bits of information before going on. The first question has to do with the character of the vomitus, whether it appeared in relation to meals and whether there was any blood in it. Also was there any blood in the stools at any time?

DR EDWARD P. WALLACE The vomitus was bile stained and related to eating. The boy took fluids but did not vomit while in the hospital. One stool specimen was normal.

DR FARBER He did not lose enough chloride to cause you to replace them artificially?

DR WALLACE One chloride determination was normal.

DR FARBER I wonder if we might see the x-ray films.

DR STANLEY M. WYMAN The films of the chest show a definitely enlarged heart without characteristic configuration. One cannot trace the posterior border adequately, but it appears to protrude backward considerably farther than usual. Throughout both lung fields there is a poorly defined, hazy mottling extending peripherally almost to the extreme lung margins. At this time the pleural spaces appear free of fluid. The liver margin comes down to the crest of the ilium, the liver may be slightly enlarged. The next examination five days later shows the heart shadow still larger but the film was taken with the patient lying on his back, and the x-ray tube was closer to the patient, causing

some magnification. The right-lung field has not changed materially, nor has the left upper lung. In the left-lower-lung field, however, behind the heart is a sharply defined area of density without any visible pulmonary markings in this region. The bronchi coming to this area extend a distance of 3 cm and terminate in an irregular fashion. The left main bronchus appears definitely elevated and compressed. The question arises whether the density lying behind the heart is in the lung or adjacent to the lung in the mediastinum. Again, I cannot identify the upper posterior heart border in the lateral view. There is very little, if any, fluid in the pleural spaces.

DR FARBER Is the consolidation of the lung consistent with an infarct?

DR WYMAN I cannot point to a definitely localized lesion to suggest infarct. The picture seems to be too diffuse and widespread and to emanate from the hilus.

DR FARBER Is there evidence of aspiration of vomitus, with occlusion of the bronchus in the next to the last film?

DR WYMAN It is conceivable, but I do not see any lung markings at all in that area. It would make me assume that the lung was "drowned", yet I can trace the bronchus down a fair distance. I believe that fluoroscopically the heart showed diminished but regular pulsations.

DR FARBER I confess that I am a little more confused than when I read the history. Some of these x-ray findings are not what I would have anticipated from the history.

I can begin in several different ways. The first and most obvious is to begin with the vomiting. The patient was well until the onset of the illness, which began five weeks or so before he died. We must assume that he was well until that time. We assume also that he had no abdominal operation previously and that adhesions, volvulus and obstruction cannot have played any part in this history. Among the conditions that could be responsible for this picture we must mention congenital malformations and tumors of the bowel involving the duodenum or a duplication of the duodenum, jejunum or stomach. Vomitus preceded by periumbilical pain could be produced by pressure from without, by tumor or by infection of the bowel or an inflammatory process such as that found in sarcoidosis. I think we ought to consider whether we should think of neoplasm any further. The story is perfectly consistent with the occurrence of a tumor either within the wall of the bowel or in the region of the intestinal tract with compression of the bowel. If we were to think of the most common tumors to do this, we would mention lymphosarcoma, with or without leukemia, the embryoma of the kidney or unattached in the kidney region and neuroblastoma. It is conceivable for lymphoma particularly to involve all

\*Pathologist in-chief, Children's Hospital, Boston.

beneath this there were several small cystic areas. In one portion there appeared to be expansion and erosion of the cortex of the bone. An intravenous pyelogram was negative.

The patient was suspended in Russel's traction, and later a Kirschner wire was inserted in the proximal right tibia for traction. Further x-ray examination revealed numerous areas of diminished density within the calvarium, limited mainly to the diploe. The thoracic spine showed only scoliosis and moderate hypertrophic changes. Changes interpreted as metastatic involvement were seen in many ribs, and there was a fracture in the seventh rib. A suggestion of several lytic lesions was noted in the scapula and in the body of the left humerus. No lesions were seen in the lungs though they could not be ruled out. Several suggestive areas were seen in the left pubis and ischium, and a definite, rounded, lytic zone was present in the right wing of the ilium. A small cystic zone was visualized in the left carpal navicular. A repeat examination of the calcium and phosphorus showed no essential change from the initial examination. The alkaline phosphatase at this time was 1.7 units per 100 cc, and on one occasion the calcium was 12.6 mg per 100 cc. The twenty-four-hour urinary-calcium excretion was 101 mg. On the eighth hospital day an operation was performed.

#### DIFFERENTIAL DIAGNOSIS

DR OLIVER COPE. The patient had a pathologic fracture in the midshaft of the right femur. The description of the physical examination gives no clue regarding the origin of the disease. Since the positive laboratory observations — cells in the urine, a slightly elevated white-cell count, a mild anemia, subnormal blood serum protein and an elevated blood serum calcium determination in one of presumably several determinations — are either inconsistent or bear no relation to bone disease, they must be dismissed as uninformative. The entire written record, therefore, is of no help in clarifying the diagnosis, and we must turn to the roentgenographic examination. Realizing the importance of the roentgenogram, Dr Castleman allowed me the privilege of reviewing the available films before starting this discussion.

Before examining the films, let me tell you how I approach such a problem — how I classify bone disease according to its distribution. The distribution of disease in bone may be divided into four categories: generalized, segmental, localized and warm bone involvement. Generalized bone disease occurs when the stimulus to bone disease is truly general, as in endocrine diseases and nutritional deficiencies. In endocrine diseases the hormonal disturbances are registered throughout the skeleton. The common hormonal diseases in this category are hyperparathyroidism, hyperthyroidism, adrenal cortical hyperfunction, anterior pituitary disturbances and perhaps acute gonadal disturbances. The

nutritional deficiencies have a generalized distribution because all regions of the skeleton are exposed equally to the deficiency. For example, vitamin D deficiency, giving rise to rickets in children and osteomalacia in adults, shows changes generalized in distribution. So also with vitamin C deficiency and protein deficiencies interfering with bone matrix.

In the segmental type of distribution the bone disease follows the distribution of a peripheral nerve or nerve root. The Albright syndrome, or fibrous dysplasia of bone, is the classic example in which the bone lesions are thus distributed. This disease has been termed disseminated, but though the lesions are often disseminated, the word is not critically descriptive.

Localized disease of bone may originate anywhere in the skeleton as a result of either primary osseous or primary marrow tumors. The primary osseous tumors are commoner in the younger age group and occur most frequently near the rapidly growing bone — that is, in close relation to an epiphysis. The primary marrow tumors are those arising in one of the various tissues encountered in bone marrow, such as the endothelioma of Ewing, the myelomas and hemangiomas. Since these tumors bear no true relation to bone tissue they are found anywhere in the bone, bearing no relation to epiphyses.

Warm bone disease is the type of distribution encountered when malignant tumors and lipid dystrophies, having a primary origin outside of bone, spread to the skeleton. The use of the word "warm" has a theoretic reason: that malignant tissue spreading to bone grows best in the warm areas. Metastatic lesions from cancers of the thyroid gland, breast, kidney and prostate are found less commonly in the bones of the distal extremities, which are less well covered with muscle and fat and are colder than the centrally located bones. In the metabolic disturbances, such as the Schüller-Christian syndrome, a similar warm bone distribution is found.

This is a peculiar case because although at first sign the distribution appears to be generalized (films of the entire skeleton are not available), the primary lesion, that of predominant interest, the right femur, can fit only in the category of localized bone disease. Let us look at the films. Dr Wyman, tell us where you see disease.

DR STANLEY M. WYMAN. As Dr Cope has said, all the films are not available. The presenting bone, the right femur, shows this rarefied bone-expanding lesion without significant reaction about its margins. There is a pathologic fracture through the center of this area of rarefaction. Lower in the same bone there are multiple, rather sharply defined areas of rarefaction. They are lesions that expand the cortex somewhat.

DR COPE. They are clearly punched out. I think you will agree that some of the areas in the acetabulum and skull are sharp and well defined.

discussing the pathological side because I have not the slightest idea what this boy suffered from. I can tell the anatomical findings quickly and briefly. There was an excess of fluid in the pericardium—70 cc—and a few fibrous adhesions. Microscopically a few lymphocytes were found in the epicardium. The heart was very much hypertrophied, being two and a half times the normal size. The valves showed a barely perceptible elevation here and there but no frank vegetations. The coronary arteries were normal. Microscopically the myocardium showed many small foci of absorption of muscle fibers of varying ages. One person who looked at the heart, knowing nothing of the age of the patient or the gross findings, said that it looked like coronary-artery disease. That was my first impression when I looked at it. The endocardium of the left ventricle was distinctly thickened, and overlying the endocardium at the apex of both left and right ventricles were numerous adherent, partially organized thrombi. So we had a source for embolism in both major and minor circulations. There was infarction of the lung. There was also a rather extensive focal atelectasis with overdistention of the respiratory bronchioles and complete collapse of alveoli in many areas. There were infarcts of the spleen and kidneys, but we could find nothing to explain the episodes of abdominal symptoms. We did not have permission to examine the brain, but without much question emboli were there also.

I have no idea how this case could be put together in any specific disease. We have what seems to be a primary extensive thrombosis within both ventricles, overlying thickened but not actually damaged endocardium. Nowhere in the valves, endocardium or myocardium do we have anything remotely suggestive of Aschoff bodies to permit a diagnosis of rheumatic infection, and nowhere in the sections did we find a vascular lesion. We have a slide here. Perhaps Dr. Farber can look at it and name the disease for us. The muscle cells are frankly hypertrophied for a child of this age. Here is one of the little patches of absorption where the muscle fibers have disappeared, with little reticulum and capillaries left. Most of these are old enough so that the muscle fibers have disappeared. There are one or two acute foci elsewhere between the columnae carneae where the endocardium goes into the myocardium. We found thrombi in varying stages of organization. In some places the muscle cells are markedly vacuolated, some degree of vacuolization is not uncommon, but this would be considerably more than normal.

In the liver there was extensive necrosis with congestion, and I am unable to say that it was on a degenerative or toxic basis. In many lobules two thirds of the liver cells were dead.

Can you offer any suggestions, Dr. Farber?

DR. FARBER: No, usually when I have entertained people here as a pseudoclinician, I comfort

myself by going back to the microscope. Here I have no such comfort. We have had examples of diffuse endocardial damage with emboli breaking off, without any suggestion from post-mortem examination concerning the exact nature of the underlying disease.

A PHYSICIAN: Nothing is said about a murmur.  
DR. WALLACE: No murmur was ever heard.

### CASE 34362

#### PRESENTATION OF CASE

A seventy-two-year-old widow was admitted to the hospital because of a fracture of the right femur.

Two weeks before admission the patient first noted pain in the right thigh when walking. Massages and local applications gave no relief, but she continued with her usual work of housekeeping. Two days previous to admission the right leg suddenly collapsed while she was walking. There was severe pain in the right thigh, and she was unable to walk. She was admitted to another hospital, where x-ray examination revealed a fracture of the right femoral shaft; she was then admitted to this hospital.

The patient had developed deafness at the approximate age of forty-five. A sister and a son had early deafness.

Physical examination revealed moderately severe deafness. The heart was slightly enlarged to the left. A loud, harsh, apical systolic murmur was widely transmitted. A thorough pelvic examination, though unsatisfactory, was essentially normal. There was tremendous swelling in the right midfemoral region, with crepitus, shortening and external rotation of the right leg. The hands showed mild rheumatoid changes at the metacarpophalangeal joints.

The temperature, pulse and respirations were normal. The blood pressure was 140 systolic, 80 diastolic.

The urine had a specific gravity of 1.022 and gave a + test for albumin, and the sediment contained 2 red cells, 20 pus cells, 10 epithelial cells and + bacteria per high-power field. It contained no Bence-Jones protein. The blood hemoglobin was 11 gm, and the white-cell count 13,300, with 80 per cent neutrophils, 11 per cent lymphocytes and 9 per cent monocytes. The nonprotein nitrogen was 29 mg, the calcium 9.9 mg, and the phosphorus 4 mg per 100 cc, the alkaline phosphatase was 4.4 units. The total protein was 5.3 gm per 100 cc, with 3.61 gm of albumin and 1.69 gm of globulin. A cytologic study of a vaginal smear was negative.

An x-ray film of the right femur showed a transverse fracture through the middle third of the shaft, with the distal fragment displaced posteriorly for a distance equal to the diameter of the bone and over-riding 6 cm. The fracture was through a large cystic area in the middle third of the shaft, and

# The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established 1828

Official Organ of

THE MASSACHUSETTS MEDICAL SOCIETY

and

THE NEW HAMPSHIRE MEDICAL SOCIETY

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND

PUBLISHED WEEKLY UNDER THE JURISDICTION OF THE

COMMITTEE ON PUBLICATIONS

Richard M. Smith M.D. Chairman

James P. O'Hare M.D.

Oliver Cope M.D.

Conrad Westelboelt M.D.

John Fallon M.D.

Joseph Garland M.D. Editor

ASSOCIATE EDITORS

Thomas H. Lannan M.D.

Donald Munro M.D.

Henry Jackson Jr. M.D.

Clara D. Davies EXECUTIVE EDITOR

Robert O. Leary ASSISTANT EDITOR

EDITORIAL BOARD

C. Guy Lane, M.D.

Henry R. Vicks, M.D.

Robert M. Green, M.D.

Dwight O'Hara, M.D.

Fletcher H. Colby, M.D.

Robert L. Goodale, M.D.

Chester M. Jones, M.D.

Harvey R. Morrison, M.D.

Maxwell Finland, M.D.

James M. Faulkner, M.D.

Carroll B. Larson, M.D.

Francis D. Moore, M.D.

C. Stuart Welch, M.D.

Vernon P. Williams, M.D.

Benjamin Castleman, M.D.

Hugh R. Leavell, M.D.

SUBSCRIPTION TERMS \$7.00 per year in advance, postage paid for the United States (medical students \$4.00 per year) Canada \$8.00 per year (Boston funds) \$9.50 per year for all foreign countries belonging to the Postal Union

MATERIAL should be received not later than noon on Thursday three weeks before date of publication

THE JOURNAL does not hold itself responsible for statements made by any contributor

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway Boston 15 Massachusetts Telephone KE 6-2094

NEW ENGLAND ADVERTISING REPRESENTATIVE Edwin B. Tyler 89 State Street Boston Massachusetts Telephone LA 3 5516

## ENGLAND ABANDONS COMPULSORY VACCINATION

THE Englishman, whose home is his castle, and who has for centuries stubbornly defended certain hard-won principles of personal freedom does not give up his rights without a struggle. A respecter of the law, he still may evade a law that does not please him and only extreme circumstances will force him to turn as he has done, to an authoritarian form of government.

The National Health Service Act provides a surprising example of the way in which such a government can take away with one hand and give with the other. Restricting many of the rights of the free-born Englishman in the practice of medicine it gives to the entire population (perhaps a sordid boon) freedom from compulsory vaccination against smallpox.

This surrender of compulsion in vaccination is not a complete right-about turn as the history of vaccination in England shows. Greenwood\* briefly tells the story.

For ninety-five years, with various modifications, vaccination of infants has been compulsory in England. In the early years of this period the provisions of the law changed little, and something over 60 per cent of infants were actually vaccinated, with the percentage increasing until, about sixty years ago, the law was observed in the cases of nearly 90 per cent of the infants born. Opposition to the Act then became firmer, and the vaccination rate dropped back nearly to the original 60 per cent. At about the turn of the century public vaccinators were required to visit the homes of infants, and the rate rose again to 70 per cent, dropping with further modification of the Act, to approximately 35 per cent, where it has remained ever since.

Now, in the land of Jenner's birth and within a few months of the two hundredth anniversary of that event and of the announcement of vaccination approximately the one hundred and fiftieth, compulsory vaccination has been entirely abandoned.

The decline in vaccination that has led up to this startling decision is not Dr Greenwood believes, a consequence of antivaccination propaganda, but has resulted from two facts. The first is that few Englishmen under sixty have had any experience with severe smallpox, and the second that vaccination has been known to have severe consequences. Postvaccinal encephalitis it is true, is extraordinarily rare, but it has occurred.

Compulsory vaccination, in Dr Greenwood's opinion, would be returned if it could be demonstrated that an epidemic of severe smallpox would inevitably result from its neglect. Such a promise, fortunately, cannot be made. British experience has shown on the contrary, that the introduction of classic smallpox into a poorly protected community does not automatically give rise to a major epidemic so long as means are at hand for the immediate vaccination of those willing to be vaccinated.

Endemic smallpox is thus invited, on the assumption that prompt vaccination will prevent sporadic

\*Greenwood M. End of compulsory vaccination. *Brit M J* 2 22-24 1948

DR WYMAN Yes, there are some in the ribs, pelvis and skull. The bones of the hands show no definite lesion. The left femur appears essentially normal, what I can see of it.

DR COPE It is the right femur and the left acetabulum that are affected.

DR WYMAN The left femoral shaft is normal. The interesting thing about the films is that the uninvolved bone appears fairly dense and of good normal texture, especially for a woman of seventy-two years. It is unfortunate that she has no teeth so that we cannot examine the lamina dura.

DR COPE Let us concentrate on the right femur and for the moment forget the other bones. There are multiple lesions, and all are in the lower half. There is nothing that I can see in the upper half. Is that right?

DR WYMAN Yes.

DR COPE This distribution immediately eliminates a metastatic tumor. If these lesions came from the thyroid gland, kidney or breast, the lesion should be concentrated in the upper half of the bone. On this distribution, therefore, I exclude renal and the other metastatic tumors. I cannot see that it follows the skeletal distribution of the Albright syndrome. The right femur is the major area of illness, and yet there is nothing in the right side of the pelvis. There are lesions in the left acetabulum but none in the left leg. Films of the arms to go with those of the hands are missing. As there is a questionable lesion in a carpal bone on the radial side, if there were lesions in the radius and in the ulna, it would be conclusive of the Albright syndrome.

It is hard to explain the appearance in the skull if you do not agree to a tumor that is metastasizing.

There is inconsistency in the pattern with which we are dealing. I cannot go any farther on the evidence available than to say that this was a disease primary in bone.

What kind of primary tumor was it? Was it an osteogenic sarcoma? It obviously was not, for there was no bone formation. The patient's age is also against such a tumor. Because of the clearly punched-out areas, I am going to take another long shot and say that it was not a primary osseous tumor, but a tumor arising in the bone marrow. Was it a hemangioma? Was it an endothelioma of Ewing? This tumor is also not usual in patients of this age. What other kind of tumor could it have been? There are a variety, of course that can arise.

DR BENJAMIN CASTLEMAN What did you have in mind so far as bone-marrow tumors are concerned? Do you mean tumors like lymphoma or myeloma?

DR COPE It could have been a myeloma. Multiple myeloma is ordinarily accompanied by a high total protein. This patient's total protein was 5.3 gm per 100 cc, which is low, and one cannot get a lead from the record.

DR BERNARD JACOBSON Why do you exclude metastatic carcinoma?

DR COPE The distribution in the bones is wrong, and there is no primary lesion.

DR JACOBSON Did she have a pyelogram?

DR COPE Yes, but a negative pyelogram does not exclude a hypernephroma. There ought to be more metastases around the pelvis and fewer metastases at the lower end of the femurs if it were hypernephroma or carcinoma of the thyroid gland or breast. Dr Castleman extracted myeloma out of me, and the skull picture is characteristic of myeloma. A few years ago we had a patient about whom everybody disagreed. The x-ray films of the skull were put on the screen and everybody took a shot at them. Dr Albright and I said multiple myeloma, Dr Sosman said hyperparathyroidism, and Dr Holmes suspected some kind of hemangiomatous tumor because of the connection of the punched-out areas in the skull with the venous sinuses. It turned out to be metastatic hypernephroma, so that one can be wrong on the basis of the x-ray films. In the final analysis dependence has to be placed on a biopsy of a lesion. I have tried to present to you how I personally attack such a problem. Yet I know on the evidence one cannot be flat-footed about making a diagnosis.

#### CLINICAL DIAGNOSIS

Metastatic carcinoma

#### DR COPE'S DIAGNOSIS

Primary bone-marrow tumor

#### ANATOMICAL DIAGNOSIS

*Multiple myeloma*

#### PATHOLOGICAL DISCUSSION

DR CASTLEMAN On the wards this was believed to be a metastatic tumor, myeloma was ruled out, as Dr Cope suggested, by the low serum protein and the absence of Bence-Jones protein. A biopsy, however, did show a definite plasma-cell myeloma.

DR COPE That fits with the configuration in the skeleton. We have had myeloma with a normal protein and a normal Bence-Jones, and Dr Aub pointed out to me that when a case is in remission and is not in an active phase of proliferation, the Bence-Jones and serum proteins may be normal. One could guess that this patient had had relatively inactive disease for some time. If she had adequate trauma to cause a fracture, myeloma would satisfactorily explain the whole picture.

DR JACOBSON I would not be so optimistic as Dr Cope about the inactivity of the disease. About 40 per cent of the cases of myeloma have normal serum proteins. About 99 per cent have elevated serum globulin. This patient's globulin was repeated and was low. She had a low formol-gel test. This is the first case of multiple myeloma that I know of in this hospital with a normal globulin.

definitely established. It has been pointed out elsewhere<sup>2</sup> that the long, unsettled and unsatisfactory experience with chaulmoogra oil dictates that considerable caution be exercised in ascribing antileprotic qualities to any drug. The final judgment must await the test of time, which the Carville workers place at five to ten years or possibly even longer.

These results in leprosy have important implications in the treatment of tuberculosis. It is of interest that the drugs that have proved effective in leprosy have been all but abandoned in the treatment of tuberculosis since the introduction of streptomycin. This was due mainly to the toxicity of these drugs and the relatively small benefit apparently derived from them. On the other hand, streptomycin was shown in brief trials to give a temporary improvement in leprosy for only a few weeks and later had no further beneficial effects at a time when the toxic effects of the drug began to occur. For that reason streptomycin has not been widely used in leprosy, which is in contrast to its relatively successful and widespread use in the treatment of tuberculosis. The results of sulfone therapy in the treatment of leprosy should lend encouragement to renewed and more persistent efforts to apply these or similar agents in the treatment of tuberculosis either alone or in conjunction with streptomycin or other effective antibiotics that may become available.

#### REFERENCES

1. Faget G. H. and Erickson P. T. Chemotherapy of leprosy. *J. A. M. A.* 136:451-457, 1948.
2. Editorial. Leprosy. *J. A. M. A.* 136:830, 1948.

#### PROFESSOR NEUBURGER IN AMERICA

PROFESSOR Max Neuburger, the world-renowned historian of medicine, who on December 8, 1948, will celebrate his eightieth birthday, has arrived in this country, where he plans to spend the years of his retirement. It is fitting that the medical profession send him greetings and take cognizance again of the illuminating contributions of this distinguished scholar.

In 1893 Neuburger received the doctorate of medicine from the University of Vienna, where he had been influenced by such teachers as Billroth,

Meynert, v. Brücke, Nothnagel, Fuchs and Politzer. The title of extra professor of the history of medicine was conferred upon him in 1904 and in 1912 he became titular professor. The University of Vienna honored him with the degree of Doctor of Philosophy in 1917. From 1917-1938 he was professor, founder and director of the Institute of Medicine and Historical Museum at the University of Vienna. Since 1939 he has been a member of the staff of the Wellcome Historical Medical Museum in London, England, and during these years he has published papers on the relations between British and German medicine.

Forty-two years ago, Neuburger's *Geschichte der Medizin* was published in Stuttgart. Through the interest of Sir William Osler the book was translated into English by Ernest Plavfair and was published in 1910 by the Oxford University Press. Osler expressed the thought that the work was particularly useful to English and American students.

Fielding Garrison called Neuburger the greatest philosophical historian of medicine, and Sigerist pointed out that Neuburger's book, monographs and articles were of full significance for our own day. These carefully weighed opinions were justified for at least two reasons: medical history as presented by Neuburger revealed itself as a pulsating living phenomenon supplementing thereby the then current approach, which focused attention upon the philologic analysis of historical texts, and developments in the history of medicine were now being treated by setting them into the background of general history and within the *Kulturgeschichte* with which they ordinarily blend.

Neuburger is unquestionably one of the pivotal figures in the history of medicine today. His writings exhibit high qualities of expansive, critical and well balanced thought. A few excerpts, which are applicable to present-day medical philosophy, from his masterful *History of Medicine* are pertinent.

The economic requirements of the human intellect necessitate a grouping of isolated facts from different points of view. The thirst for knowledge renders imperative a clearer insight into the laws governing natural phenomena. Biological research, cosmology and dialectics were all points on the circumference of a circle, the starting-point being taken at will.

It is neither doctrines nor knowledge which raise the Hippocratic creed to the highest pinnacle of Greek medi-

outbreaks of the disease from assuming major proportions England, in this respect, may now be compared to a city that abandons fireproof building construction because of its fire-fighting equipment that should, under normal conditions, hold in check those conflagrations that are likely to occur

## PROGRESS IN THE TREATMENT OF LEPROSY

THE recently published report of the United States Public Health Service workers on their latest results with the chemotherapy of leprosy<sup>1</sup> is the most encouraging of any thus far recorded and holds out high hopes for the eventual eradication of this ancient scourge. These results are the reward for perseverance and for painstaking efforts in the face of many disappointments that might easily have resulted in discouragement and the abandoning of the project.

Included in the report from the Leprosarium at Carville, Louisiana, are the results of therapy with the sulfone drug in 371 patients of whom 317 were treated with promin or diasone for varying periods up to six years. In the rest, the treatment was abandoned for various reasons but only in a very few cases was this due to failure to tolerate the drug. Severe toxic reactions were encountered, but in most cases it was possible to maintain therapy by adjusting the dose and method of administration. It was found, for example, that promin could not be tolerated in adequate doses when given by mouth. A change to intravenous injections permitted the continuation of therapy with favorable effects. It was usually necessary to start with a daily dose of 1 gm and then to increase the amount until 5 gm daily was given, and this gave the most consistently good results with a minimum of toxic effects.

The most frequent toxic manifestation encountered was a slow destruction of the erythrocytes. This complication could not be avoided, but its effect was counteracted by discontinuing treatment for one week after two weeks of daily intravenous injections. This resulted in fewer and milder types of toxic reactions and permitted a restoration of the blood cells and hemoglobin lost through the hemolytic action of the drug. Transfusions were not used,

and the administration of iron and liver extract was seldom found necessary. Diasone had the advantage of being less toxic than promin by oral administration, but otherwise it gave similar untoward effects. Dosage of this drug had to be increased gradually until the patient built up a tolerance, and most patients were eventually able to take 0.3 gm three times a day. With this drug, rest periods of two weeks every two months proved advisable, and liver extract and iron were sometimes needed to counteract the anemia.

That these efforts and the toxic effects encountered were justified is evidenced by the results. Only patients with lepromatous leprosy and mostly with far-advanced disease were subjected to the sulfone therapy, and the drug worked slowly, but the therapeutic effects were better than those obtained from any previous treatment tried at the Carville Leprosarium. Definite objective improvement seldom became manifest before six months of treatment, but thereafter it was progressive. The percentage of patients improved was in direct proportion to the duration and intensity of the treatment. After six months almost 25 per cent of the patients showed some improvement, after one year this percentage increased to 60, after two years to 75 and after three years to almost 100 per cent, and this was independent of the extent and stage of the disease when the treatment was undertaken. The percentage of bacterioscopically negative smears among treated patients was also in direct proportion to the duration of the treatment. During the first year, practically all the cases remained bacilliferous, but after four years of continuous intensive treatment the incidence of negative reports exceeded 50 per cent.

Of the entire group, 38 patients have been discharged with "arrested" disease, representing 12 per cent of all the patients treated with promin or diasone. During 1946, the number of patients discharged with arrested disease was more than double that of the annual average for the ten years prior to the institution of sulfone therapy and the number of deaths was less than half the average of the previous years.

Faget and Erickson<sup>1</sup> emphasize the fact that the ultimate value of sulfone therapy in leprosy is not

NOTICES (Concluded from page 382)

NOVEMBER 1-3 American Clinical and Climatological Association. Page 582 issue of April 15  
 NOVEMBER 3 and 4 Annual Meeting of National Committee for Mental Hygiene Inc. Page 282 issue of August 12  
 NOVEMBER 8-12 American Public Health Association Page 420 issue of March 18  
 NOVEMBER 10-13 Association of Military Surgeons of the United States Page 722 issue of May 15  
 NOVEMBER 20-23 American Academy of Pediatrics Annual Meeting Chalfonte-Haddon Hall Hotel Atlantic City New Jersey  
 DECEMBER 7-9 Southern Surgical Association Annual Meeting Page 543 issue of April 8  
 DECEMBER 9 and 10 New York State Society of Anesthesiologists Page 34 issue of July 1  
 FEBRUARY 4 1949 American Board of Obstetrics and Gynecology Inc. Page 244 issue of August 5  
 MARCH 28-APRIL 1 1949 American College of Physicians Page 158 issue of July 22  
 NOVEMBER 11-17 1949 Third Inter-American Congress of Radiology Page 158 issue of July 22

★ **A NEW SERVICE for  
YOUR ALLERGY PATIENTS**

- Gladown Pillows
- Rubber Pillows
- Rubber Mattresses
- Allergy-free Covers for Pillows
- Allergy-free Box Springs
- Rubber Carpets
- Allergy-free Insecticide
- Gladown Comforters

**FAST EFFICIENT MAIL ORDER SERVICE**  
 Brochures available for distribution to patients

**AMERICAN ALLERGY AIDS COMPANY**  
 240 BOYLSTON STREET BOSTON, MASS.  
 CO 6-3855

**TUFTS COLLEGE MEDICAL SCHOOL  
Postgraduate Division**

**SURGICAL ANATOMY** Nov 1-Dec 24 Various operative procedures and principal regional anatomy are studied. Supplementary lectures and demonstrations by surgeons. Dissections are performed by students on cadavers for prosection and demonstrations. Drs C Stuart Welch and John M McGowan in charge. Tuition \$260. Enrollment limited to 16. Candidates are selected on basis of previous surgical training and experience with priority given to surgical residents.

**GRADUATE COURSE IN MEDICINE** Oct 4 1948-June 30 1949. Formal graduate instruction includes didactic review two months of basic sciences practical work under supervision on wards and in laboratories ward rounds and conferences. An accredited course. Dr Robert P McCombs in charge. Tuition \$750. Enrollment limited.

**Courses for the General Practitioner**

**REVIEW OF RECENT ADVANCES IN MEDICINE** Oct 4-16. Emphasis on proved diagnostic and therapeutic methods. Daily case presentation. Given by Staff of New England Medical Center. Dr Robert P McCombs in charge. Tuition \$65.

**ELECTROCARDIOGRAPHY I** Oct 18-22 To familiarize the general practitioner with the interpretation of electrocardiograms in coronary rheumatic hypertensive and congenital heart disease and in the arrhythmias and rarer forms of heart disease such as myxoma pericarditis and pulmonary embolism. Dr Heinz Magendanz in charge. Tuition \$40.

**HEMATOLOGY I** Oct 25-30 The anemias (pernicious iron deficiency hemolytic) leukopenic disorders leukemia, hemorrhagic disorders polycythemia and lymphomas. Laboratory demonstrations and case presentations. Dr William Dameshek in charge. Tuition \$40.

For application forms and further information address

**POSTGRADUATE DIVISION**  
 30 Bennet Street Boston 11 Mass

**Valleyhead Hospital**

CONCORD, MASSACHUSETTS

For the treatment of psychoneuroses, alcoholism, mild mental disorders and chronic diseases. Pleasant pastoral setting near historic Concord. Accepted modern therapies used. Complete occupational and recreational facilities available including outdoor swimming pool and tennis court.

S GAGNON, M D  
 Superintendent

J BUTLER TOMPKINS, M D  
 Director of Clinical Psychiatry

J P THORNTON, M D  
 Consultant in Neuro-psychiatry

IRVING KAUFMAN, M D  
 Psychiatrist

Post Office, Box 151, Concord, Mass Tel Concord 1600

**Washingtonian Hospital**

41-43 WALTHAM STREET, BOSTON, MASS  
 Incorporated 1859

Conditioned Reflex, Psychotherapy, Semi-Hospitalization for Rehabilitation of Male Alcoholics  
 Treatment of Acute Intoxication and Alcoholic Psychoses Included  
 Outpatient Clinic and Social-Service Department for Male and Female Patients

JOSEPH THIMANN, M D, Medical Director

Visiting Psychiatric and Neurologic Staff  
 Consultants in Medicine, Surgery and the Other Specialties  
 Telephone HA 6-1750

**The Boston  
Children's Friend Society**

offers its services to physicians for the care of a limited number of unmarried mothers arranging for the adoption of their infants

Address communications to

GENERAL SECRETARY

BOSTON CHILDREN'S FRIEND SOCIETY  
 123 Marlborough Street, Boston 16, Massachusetts  
 Telephone KE 6-8070



Dr Wise soundly trained and well read

To a fellow practitioner said

Here's a word from the Wise —

Better firms advertise

In the New England Journal of Med

cine and even make it the well-spring of medical science for all time it is the conception of the medical vocation and the method of medical thought and action, true now as then

On the heels of the conqueror with his rude soldierly virtues follows the ruler with his love of luxury and his aspiration towards refinement of manners and customs. This historical law finally compelled even the empress of the earth, invincible Rome, to lay down her arms before a yet more powerful sovereign in the shape of Greek culture.

The essence of Galenism, as contrasted with Hippocratism, consists in giving the physician, through general principles, a reliable guide for his procedure in any individual case.

Honored throughout the world for his scholarly achievements Professor Neuburger may be heartened to learn that American students and physicians recognize the salutary lesson of his life in terms of modesty, patience and dignity. We sincerely wish him continued good health and the spirit and energy to pursue his invaluable labors.

#### BIBLIOGRAPHY

- Editorial Professor Max Neuburger *Brit M J* 1 1243 1948  
 Kagan, S. R. Professor Max Neuburger biography and bibliography *Bull Hist Med* 14 423-448 1943  
 Neuburger M. *Essays in the History of Medicine* Edited by Fielding H. Garrison. 227 pp. New York: Medical Life Press, 1930  
*Idem*. *History of Medicine*. Translated by Ernest Playfair. New York: Oxford University Press. Vol I 404 pp 1910 Vol II 135 pp 1923  
 Sigerist, H. F. Tribute to Max Neuburger on occasion of his seventy fifth birthday. December 8 1943. *Bull Hist Med* 14 417-421, 1943

#### STORROW HOUSE

THE Massachusetts General Hospital has announced the opening on August 9, 1948, of Storrow House, with ward, semi-private and private accommodations for convalescent patients. The conditions for admittance are reasonable patients must be ambulatory to the extent of being able to go to meals and they must be persons who are strictly convalescent or simply in need of rest. No terminal or mental patients or alcohol or drug addicts are to be accepted.

Storrow House, a stately mansion situated on a hilltop in Lincoln, Massachusetts, within twenty miles of Boston, was the country home of the late Mrs. James J. Storrow. Fulfilling the wishes of his mother, her son, James J. Storrow, Jr., has presented the house and estate to the Hospital for the purposes outlined above. It is a source of gratification to the recipients of her generosity that Mrs. Storrow's benefactions have continued in this manner after her death.

#### MASSACHUSETTS MEDICAL SOCIETY

##### DEATH

PRATT — William P. Pratt, M.D., of Quincy, died on August 15. He was in his seventy-second year. Dr. Pratt received his degree from Tufts College Medical School in 1907. He was a member of the staff of Quincy City Hospital.

An aunt and three-step-daughters survive.

##### NOTICES

#### AMERICAN SOCIETY OF ANESTHESIOLOGISTS, INC.

The American Society of Anesthesiologists will hold a joint meeting with the Ohio Society of Anesthesiologists October 1 and 2, 1948, at the Hotel Commodore-Perry, Toledo, Ohio.

#### OREGON STATE MEDICAL SOCIETY

The annual meeting of the Oregon State Medical Society will be held in Medford from September 15 to 18 (secretary, Werner E. Zeller, M.D., Medical Dental Building, Portland 2, Oregon).

#### VERMONT STATE MEDICAL SOCIETY

The annual meeting of the Vermont State Medical Society will be held in Burlington from September 15 to 17 (secretary, T. H. Harwood, M.D., 128 Merchants Row, Rutland, Vermont).

#### SOCIETY MEETINGS AND CONFERENCES

##### CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, SEPTEMBER 9

- FRIDAY, SEPTEMBER 10  
 \*10:00 a.m. - 12:00 p.m. Medical Staff Rounds. Peter Bent Brigham Hospital.  
 12:00 p.m. - 1:00 p.m. Clinicopathological Conference (Boston Floating Hospital). Joseph H. Pratt Diagnostic Hospital.  
 TUESDAY, SEPTEMBER 14  
 \*12:15 - 1:15 p.m. Clinicoröntgenological Conference. Peter Bent Brigham Hospital.  
 \*1:30 - 2:30 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children. Massachusetts General Hospital.  
 WEDNESDAY, SEPTEMBER 15  
 \*12:00 p.m. - 1:00 p.m. Clinical Conference (Children's Hospital). Amphitheater. Peter Bent Brigham Hospital.

\*Open to the medical profession.

- SEPTEMBER 7-11 American Congress of Physical Medicine. Page 582. Issue of April 15.  
 SEPTEMBER 7-11 American Occupational Therapy Association. Page xv. Issue of July 8.  
 SEPTEMBER 9 Some of the Advances in Surgery. Dr. Frank H. Leber. Pentucket Association of Physicians. 8:30 p.m. Haverhill.  
 SEPTEMBER 13-15 American Academy of Pediatrics. Olympic Hotel, Seattle, Washington.  
 SEPTEMBER 14 New England Society of Anesthesiologists. Page 316. Issue of August 19.  
 SEPTEMBER 16-18 Vermont State Medical Society. Annual Meeting. Burlington.  
 SEPTEMBER 20-23 American Hospital Association. Page 310. Issue of February 26.  
 SEPTEMBER 22 New England Conference of Industrial Physicians and Surgeons. Page 244. Issue of August 5.  
 SEPTEMBER 29 Mississippi Valley Medical Editors Association. Page 170. Issue of January 29.  
 OCTOBER 1 and 2 American Society of Anesthesiologists, Inc. Notice above.  
 OCTOBER 6-9 American Board of Ophthalmology. Page 170. Issue of January 29.  
 OCTOBER 18-22 American College of Surgeons. Page 34. Issue of July 1.  
 OCTOBER 27 New England Obstetrical and Gynecological Society. Hotel Somerset, Boston.  
 Annual Meeting. (Notices concluded on page viii).

# The New England Journal of Medicine

Copyright, 1948 by the Massachusetts Medical Society

Volume 239

SEPTEMBER 9, 1948

Number 11

## TRANSTRACHEAL ANESTHESIA FOR BRONCHOSCOPY

DWIGHT E. HARKEN, M.D.,\* AND ARNOLD M. SALZBERG, M.D.†

BOSTON, MASSACHUSETTS, AND PATERSON, NEW JERSEY

**B**RONCHOSCOPY contributes greatly to the diagnosis and treatment of intrathoracic disease. It is at once apparent that proper anesthesia serves the interest of both the bronchoscopist and the patient.

In a search for the most satisfactory anesthetic technic, the various methods of administering topical agents have been explored, the gamut of general anesthetics has been run, and a series of bronchoscopic and esophagosopic examinations have been conducted under bilateral vagus-nerve block. The technic described below appears to us to serve best the patient and bronchoscopist. The safety of this method is adequately established by experience with more than 1000 patients given tracheobronchial anesthetics.

For many years in the clinic of the late Tudor Edwards at the Brompton Hospital in England, it has been the custom to inject 5 minims of 20 per cent cocaine solution by means of a needle through the skin and cricothyroid membrane into the trachea.<sup>1</sup> This has been used both in bronchography and bronchoscopy. The technic that we have evolved is based on this maneuver but appears to us to have three advantages. The first advantage is derived from a large quantity of dilute agent that gives more complete surface coverage. The second depends on the administration of this agent in two injections, thus producing anesthesia of the main bronchi as well as the trachea. The final advantage accrues from the fact that the patient is in the dorsal decubitus position during the injection.

The simple equipment is illustrated in Figure 1.

### PROCEDURE

The preoperative medication consists of 0.09 gm. of pentobarbital sodium by mouth one and a half hours before bronchoscopy and 0.06 gm. of codeine sulfate by mouth one hour before the procedure.

\*Assistant professor of surgery, Tufts College Medical School, visiting surgeon in thoracic surgery, Boston City Hospital, Mount Auburn Hospital and Malden Hospital; consultant in thoracic surgery, Veterans Administration Hospital, Rutland Heights, Massachusetts, and Chelsea Naval Hospital.

†Senior intern in surgery, Medical College of Virginia Hospital, Richmond, Virginia; formerly resident in surgery, Veterans Administration Hospital, Rutland Heights, Massachusetts.

Ten or fifteen minutes before the intratracheal anesthetic is administered, the lips, mouth and pharynx of the patient are sprayed with 2 per cent pontocaine hydrochloride (dimethylaminoethyl-p-N-butylaminobenzoate) by means of an ordinary atomizer. This means that approximately 3 minims of 2 per cent solution is administered in three

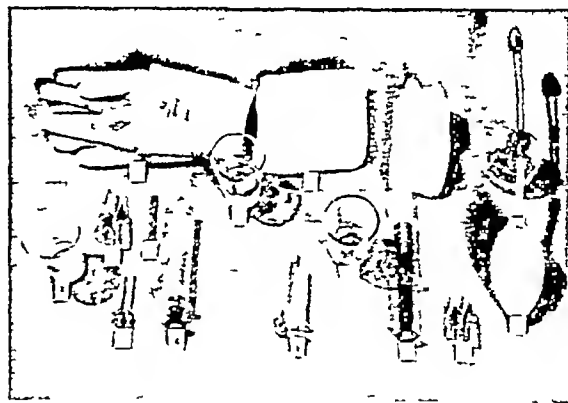
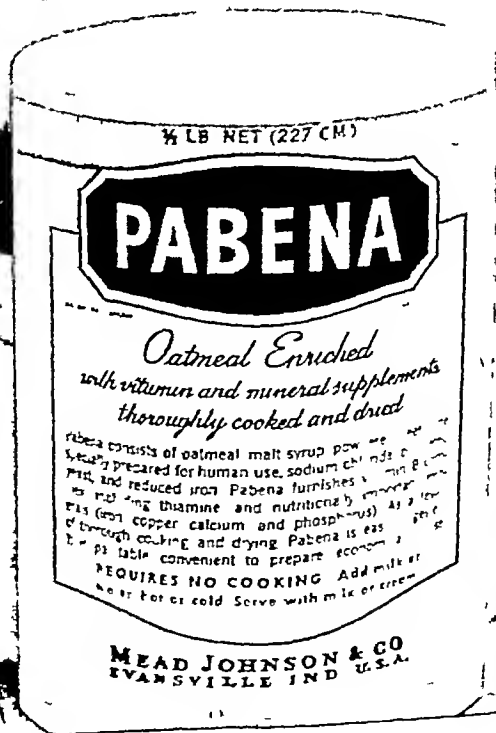


FIGURE 1. Equipment Used for Transtracheal Anesthesia. (1) Gloves. (2) Saline medicine glass. (3) Ampoules of pontocaine. (4) File. (5) Two 18-gauge needles. (6) Syringe for pontocaine. (7) Alcohol medicine glass. (8) Gauze squares. (9) Syringe for procaine with hypodermic needle. (10) Procaine medicine glass. (11) Syringe for sodium phenobarbital. (12) Ampoules of epinephrine and caffeine sodium benzoate. (13) Pontocaine atomizer.

sprays to the zones indicated. The patient is instructed to inspire deeply as the nebulizer is directed toward the back of the tongue and oropharynx.

Next, under aseptic technic with the patient on his back and the head hyperextended the anterior aspect of the neck is cleansed with 70 per cent alcohol. The cricothyroid membrane is identified with the gloved finger in the midline, between the cricoid and thyroid cartilages (Fig. 2). The skin and subcutaneous tissues are infiltrated with 2-cc of 2 per cent procaine hydrochloride. Two 2-cc ampoules of sterile pontocaine hydrochloride,

COPYRIGHT 1937  
MEAD JOHNSON & CO  
EVANSVILLE, IND., U.S.A.



1/2 LB NET (227 GM)

**PABENA**

*Oatmeal Enriched  
with vitamin and mineral supplements  
thoroughly cooked and dried*

Pabena consists of oatmeal malt syrup powder, vitamins A, B, and C, and reduced iron. Pabena furnishes a complete and balanced diet. It is rich in iron, copper, calcium, and phosphorus. As a result of thorough cooking and drying Pabena is easy to digest and is a most palatable convenient to prepare economical food.

**REQUIRES NO COOKING** Add milk or water for cold. Serve with milk or cream.

**MEAD JOHNSON & CO**  
EVANSVILLE IND. U.S.A.

# The New England Journal of Medicine

Copyright 1948 by the Massachusetts Medical Society

Volume 239

SEPTEMBER 9, 1948

Number 11

## TRANSTRACHEAL ANESTHESIA FOR BRONCHOSCOPY

DWIGHT E. HARKEN, M.D.,\* AND ARNOLD M. SALZBERG, M.D.†

BOSTON, MASSACHUSETTS, AND PATERSON, NEW JERSEY

**B**RONCHOSCOPY contributes greatly to the diagnosis and treatment of intrathoracic disease. It is at once apparent that proper anesthesia serves the interest of both the bronchoscopist and the patient.

In a search for the most satisfactory anesthetic technic, the various methods of administering topical agents have been explored, the gamut of general anesthetics has been run, and a series of bronchoscopic and esophagoscopy examinations have been conducted under bilateral vagus-nerve block. The technic described below appears to us to serve best the patient and bronchoscopist. The safety of this method is adequately established by experience with more than 1000 patients given tracheobronchial anesthetics.

For many years in the clinic of the late Tudor Edwards at the Brompton Hospital in England, it has been the custom to inject 5 minims of 20 per cent cocaine solution by means of a needle through the skin and cricothyroid membrane into the trachea.<sup>1</sup> This has been used both in bronchography and bronchoscopy. The technic that we have evolved is based on this maneuver but appears to us to have three advantages. The first advantage is derived from a large quantity of dilute agent that gives more complete surface coverage. The second depends on the administration of this agent in two injections, thus producing anesthesia of the main bronchi as well as the trachea. The final advantage accrues from the fact that the patient is in the dorsal decubitus position during the injection.

The simple equipment is illustrated in Figure 1.

### PROCEDURE

The preoperative medication consists of 0.09 gm of pentobarbital sodium by mouth one and a half hours before bronchoscopy and 0.06 gm of codeine sulfate by mouth one hour before the procedure.

\*Assistant professor of surgery, Tufts College Medical School, visiting surgeon in thoracic surgery, Boston City Hospital, Mount Auburn Hospital and Malden Hospital; consultant in thoracic surgery, Veterans Administration Hospital, Rutland Heights, Massachusetts, and Chelsea Naval Hospital.

†Senior intern in surgery, Medical College of Virginia Hospital, Richmond, Virginia; formerly resident in surgery, Veterans Administration Hospital, Rutland Heights, Massachusetts.

Ten or fifteen minutes before the intratracheal anesthetic is administered, the lips, mouth and pharynx of the patient are sprayed with 2 per cent pontocaine hydrochloride (dimethylaminoethyl-p-N-butylaminobenzoate) by means of an ordinary atomizer. This means that approximately 3 minims of 2 per cent solution is administered in three

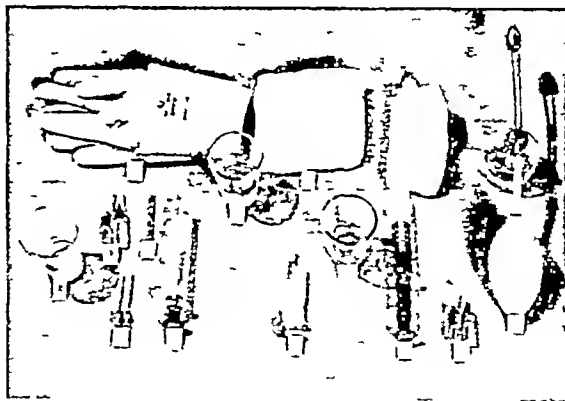


FIGURE 1. Equipment Used for Transtracheal Anesthesia. (1) Gloves. (2) Saline medicine glass. (3) Ampoules of pontocaine. (4) File. (5) Two 18-gauge needles. (6) Syringe for pontocaine. (7) Alcohol medicine glass. (8) Gauze squares. (9) Syringe for procaine with hypodermic needle. (10) Procaine medicine glass. (11) Syringe for sodium phenobarbital. (12) Ampoules of epinephrine and caffeine sodium benzoate. (13) Pontocaine atomizer.

sprays to the zones indicated. The patient is instructed to inspire deeply as the nebulizer is directed toward the back of the tongue and oropharynx.

Next, under aseptic technic with the patient on his back and the head hyperextended, the anterior aspect of the neck is cleansed with 70 per cent alcohol. The cricothyroid membrane is identified with the gloved finger in the midline, between the cricoid and thyroid cartilages (Fig. 2). The skin and subcutaneous tissues are infiltrated with 2-cc of 2 per cent procaine hydrochloride. Two 2-cc ampoules of sterile pontocaine hydrochloride,

each containing 20 mg of the agent, are opened, and 3 cc of this solution is diluted with 6 cc of sterile isotonic saline solution. This provides 9 cc of a 0.3 per cent pontocaine solution and is aspirated into a 10-cc syringe, through an 18-gauge needle. The needle is then directed through the skin in the infiltrated zone, and through the cricothyroid membrane into the trachea. The intratracheal position of the tip of the needle is verified by the aspiration of air into the syringe. Half of the solution is then quickly injected into the trachea, and the needle is immediately withdrawn. An alcohol sponge is firmly pressed over the injection site, for the patient will immediately cough. With the firm

(4.5 cc) is instilled through the cricothyroid membrane. Again, the alcohol pressure sponge is placed over the injection site, the patient is raised to a sitting position, leaned toward the side of principal disease and again instructed to cough. Generally, it has been found that anesthesia is fairly complete throughout the trachea down to the carina, and the patient must be encouraged to cough and expectorate the agent. He is then returned to the dorsal decubitus position and is ready for the bronchoscopic procedure.

After bronchoscopy, the patient is allowed nothing by mouth for three hours lest he aspirate material into the anesthetized tracheobronchial tree.

### DISCUSSION

In view of the small quantity of pontocaine employed (30 mg), the danger of overdosage is probably more theoretical than real, however, sensitivity is possible, since a reaction to four drops of 0.5 per cent pontocaine solution has been reported. Pentobarbital sodium is used in the preoperative medication for prophylaxis against pontocaine reactions. Barbiturates appear to increase tolerance to the anesthetic agent, without reducing efficiency, and their employment before pontocaine anesthesia for bronchoscopy is advised. In addition, it has seemed well to have immediately available a quick-acting barbiturate for intravenous use—0.5 gm of sodium phenobarbital in a 10-cc solution seems adequate for this purpose.

The anesthetic agent is obtained in the form of ampoules of pontocaine hydrochloride, 1 per cent solution (20 mg in 2 cc), prepared for spinal anesthesia. Three cubic centimeters of this solution diluted with 6 cc of isotonic saline solution provides 9 cc of 0.3 per cent solution, which is adequate for tracheobronchial anesthesia. We believe that the large volume of dilute solution is highly advantageous, since it allows more complete surface coverage. Administration in two doses, as described above, is important, for coughing renders the first injection ineffective distal to the carina, however, the second injection gravitates to a lower level because of the prior anesthesia.

It will be noted that both injections are administered with the patient in the dorsal decubitus position. This position renders impossible an accident inherent in the intratracheal instillation of drugs in the upright or sitting position. When a drug is injected into the trachea with the patient sitting upright, regardless of the method, there is always the danger that the patient's position and particular anatomic configuration of the right lower bronchial tree will allow the direct gravitation of the drug to the dependent alveoli. The toxic manifestations of such an accident are similar to the intravenous injection of the drug. The administration of the anesthetic agent by the direct needle injection into

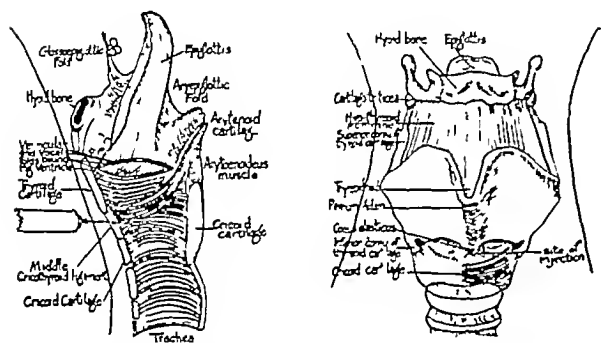


FIGURE 2 *Sagittal and Ventral Aspects of the Laryngeal Anatomy, to Illustrate the Site of Injection*

pressure maintained, the patient is at once instructed to sit up, and coughing is again encouraged. Tracheal secretions are coughed into an emesis basin. The patient is then returned to the dorsal decubitus position and allowed to remain at rest for approximately five minutes. This recess serves three purposes: it allows time for the agent to anesthetize the upper respiratory tract, an opportunity is afforded to explain the subjective symptoms of bronchoscopic anesthesia and examination (it is essential that the patient be reassured that although he has no sensation of air passing in and out of the trachea and pharynx he is actually breathing adequately), and finally, this interval provides an opportunity to watch the patient for drug toxicity or idiosyncrasy. As a safeguard against such a susceptibility 0.5 gm of sodium phenobarbital in 10 cc of water should be available in a syringe ready for intravenous administration. In addition, epinephrine and caffeine sodium benzoate should be at hand in the event of cardiac or respiratory failure. Of course, oxygen should be immediately available in the operating room. Actually, under the outlined conditions, the dangers are virtually negligible.

In a second tracheal injection similar to the first, the remainder of the dilute pontocaine solution

the trachea with the patient supine obviates this danger

A few simple comments about the equipment may be helpful. In Figure 1, two 18-gauge needles may be noted next to the saline medicine glass. The first needle is used for aspiration of 3 cc of 1 per cent pontocaine solution from the ampoules, its subsequent dilution and the first tracheal injection. After withdrawal from the trachea, this needle is discarded as contaminated, and the second needle is used for the second injection. When sterile pontocaine has not been obtainable, we have used 1.5 cc of the conventional pontocaine 2 per cent topical solution, diluted, of course, to 9 cc. This necessitates the inclusion of a third needle for aspiration and dilution of the unsterile solution. Otherwise, the routine is similar, however, if one is to use an unsterile solution, great care must be exercised to avoid leak or injection of this solution in the needle tract between the skin and tracheal lumen.

Though there are theoretical complications, discussed below, the actual complications in the course of more than 1000 cases of tracheal anesthesia have been limited to 3 patients, who had superficial cellulitis of the soft tissues about the site of injection. One resolved spontaneously, and the others required 1-cm skin incisions for drainage. These minor complications occurred more than five years ago, before adequate attention was given to pressure on the injection site and to the prevention of subcutaneous emphysema produced by air leak through the needle tract on coughing.

There are, of course, a number of possible dangers inherent in the technic described above. Often, our colleagues have asked about the dangers of infection spreading in the fascial planes. This has not occurred, and experience seems to justify our

lack of concern over this complication. Another conceivable complication—namely, that of injecting the solution under the tracheal mucosa—does give us some concern. This might produce obstruction to the airway and must be carefully avoided by verification of the position of the point of the needle, by the aspiration of air before injection and by the immediate removal of the needle after the solution has been quickly injected. There have been no tuberculous sinuses even though the method has been extensively used in open cases of tuberculosis. However, we should not elect to use this method in the presence of extensive tuberculous disease of the larynx and upper trachea. There has been no bleeding from an aberrant thyroid isthmus.

Finally, the applications or limitations of this form of anesthesia in bronchoscopy for foreign-body removal are contingent upon the position of the foreign body itself.

#### SUMMARY

A method of administering a dilute pontocaine solution for bronchoscopic anesthesia via the cricothyroid membrane directly into the trachea through a needle is described.

Technical details and the rationale of the maneuvers are outlined.

Theoretical and actual dangers are given consideration. The safety of the method is supported by experience in more than 1000 patients.

The value to patient and physician of a safe anesthetic technic that minimizes the discomfort of bronchoscopy is stressed.

#### REFERENCES

- 1 Magill I. W. Discussion on anaesthesia in endoscopy. *J Laryng & Otol* 54:425 1939.
- 2 Pfeiffer R. L. Hypersensitivity to pontocaine: report of case. *Arch Ophth* 18:62-64 1937.

## COEXISTING TUBERCULOUS AND MENINGOCOCCAL MENINGITIS\*

## Report of a Case

CAPTAIN EDGAR ALSOP RILEY, M C, A U S †

**M**ENINGITIS due to a simultaneous mixed infection is relatively rare. Neal<sup>1</sup> reviewed 3178 cases of meningitis and found that 26, or 0.8 per cent, were due to mixed infections. Unfortunately she did not break down these 26 cases into the different bacterial combinations that were present. Tripoli<sup>2</sup> studied 468 cases of bacterial meningitis and found 2 cases of mixed infection, an incidence of approximately 0.4 per cent. In a more recent study Hertzog<sup>3</sup> reviewed 377 cases of fatal meningitis with special reference to the bacterial diagnoses and collected 5 cases of mixed infection, or an incidence of 1.3 per cent.

Cases of tuberculous meningitis combined with a suppurative acute bacterial meningitis are even more unusual. Lemieux et al.,<sup>4</sup> in a review of the literature between 1900 and 1944, found only 20 reported cases of an associated meningococcal tuberculous meningeal infection. In the present review, an additional number of mixed cases of tuberculous meningococcal meningitis were discovered in the literature that had apparently not been found by those authors. Pipirs,<sup>5</sup> cited by Key,<sup>6</sup> studied 46 cases of mixed meningeal infection reported between 1896 and 1927 and found that the tubercle bacillus predominated as the primary organism. Cunningham<sup>7</sup> quotes Chalier and Guichard<sup>8</sup> as reporting in 1931 about 50 cases of combined tuberculous and meningococcal meningitis.

Regardless of the exact number of cases of combined tuberculous and suppurative infections of the meninges that have been reported, it was thought that the combination was unusual enough to justify presentation of the following case of a combined tuberculous and meningococcal meningitis.

## CASE REPORT

A 26-year-old man was admitted to the medical service on January 30, 1945, with the diagnosis of nasopharyngitis. About 4 days previously the patient had mentioned to a friend that he was suffering from a severe headache. At sick call on the following day he was seen by a medical officer, who believed that he had an upper respiratory infection, prescribed aspirin and returned him to duty. On January 28, the patient had again gone to sick call because of persistent headache and because he felt too sick to do duty. He was afebrile. The medical officer again believed that this soldier was suffering from nasopharyngitis and recommended symptomatic therapy. On the following day, however, the patient was admitted to the hospital complaining bitterly of a severe headache, which seemed to be localized to the base of the skull. He was rational, but was so acutely ill that a thorough history was not attempted. He admitted vomiting twice.

Physical examination revealed a well developed, well nourished man who was co-operative and rational. There was marked rigidity of the neck, the patient complained

bitterly when his head was flexed upon his neck. Neurologic examination revealed positive Kernig and Brudzinski signs, with a bilateral negative Babinski reflex. The remainder of the physical examination was negative.

The temperature was 98.8°F, the pulse 80, and the respirations 18.

A lumbar puncture was immediately performed, and several cubic centimeters of slightly cloudy fluid were removed for examination. A manometer was not available at the time for accurate determination of the spinal-fluid pressure, but it appeared abnormally high. Examination of the fluid revealed 774 white cells per cubic millimeter, with 54 per cent neutrophils and 46 per cent lymphocytes. The total protein was 270 mg per 100 cc. Sugar was not found in the sample. A diagnostic stain of the spinal fluid was made, and two gram-negative diplococci organisms suggestive of *Neisseria* were seen. Spinal-fluid culture was carried out, and at the end of 24 hours a luxuriant growth of *Neisseria intracellulare* was present. A malarial smear was taken, since the patient had seen service in Sicily and Italy, but was negative.

The patient was immediately started on a therapeutic course of sodium sulfadiazine intravenously and fluids parenterally. During the day he was rational but complained of nausea and had frequent episodes of projectile vomiting.

On the morning of the following day the temperature was 101.6°F, the respirations 16, and the pulse 54. On that afternoon, intravenous administration of sulfadiazine was discontinued, and he was put on a dosage schedule of 1 gm. of sulfadiazine orally accompanied by 2 gm. of sodium bicarbonate every 4 hours. At 8:00 p.m. the temperature was still 101.6°F, and 20,000 units of penicillin intramuscularly was ordered every 3 hours. During the day the patient appeared rather irritable and mentally hazy and continued to complain of a stiff neck.

On the morning of the following day the temperature was 99.6°F, but by noon it had climbed to 101.2°F. A lumbar puncture was done and several cubic centimeters of cloudy fluid under elevated pressure were removed. Examination of the fluid disclosed 441 white cells per cubic millimeter, but no differential count was obtained. A smear for organisms was negative, as was a culture at the end of 24 hours. The temperature dropped to 99°F by evening, but again climbed and at 3:00 a.m. on February 3 was 102°F. During the night he was incoherent and experienced a severe chill.

During the entire next day, the patient was mentally confused. He developed increasingly pronounced signs of meningeal irritation and during the morning had a severe clonic convulsion involving the right side of his body. During this attack, his pupils failed to react to light or accommodation and his left eye rotated inward. His temperature continued to climb and by midnight had reached 103.6°F.

On February 4 he continued to be restless and incoherent and had to be catheterized every 8 hours. Intravenous administration of fluids was maintained throughout the day.

On the following day the patient appeared much worse, developed Cheyne-Stokes respirations and was comatose throughout the morning. Doses of aminophylline and caffeine sodium benzoate relieved his respirations considerably. A lumbar puncture was done, and several cubic centimeters of opalescent fluid were removed. Examination of the fluid revealed 441 white cells per cubic millimeter, with 4 per cent neutrophils and 96 per cent lymphocytes. The sugar was 136 mg per 100 cc, and the chloride 473 mg per 100 cc. After the fluid had stood for 10 minutes, a delicate fibrin pellicle formed, but search of a stained smear revealed no acid-fast organisms, and a 24-hour culture for pathogens was negative. At the time this lumbar puncture was done, 10,000 units of penicillin was injected intrathecally, but after a report of the spinal fluid was obtained, it was considered useless to continue intrathecal medication on subsequent taps, and penicillin was discontinued. An x-ray film of the chest taken at the bedside showed some generalized increase in density of the left lower lobe.

\*From the Medical Service, Letterman General Hospital, San Francisco, California.  
†Assistant resident on Chest Service, Bellevue Hospital, New York City.

During February 6 the patient's condition remained about the same. He showed occasional moments of rationality but by afternoon had lapsed into complete stupor. Neurologic survey revealed loss of deep and superficial reflexes bilaterally with a positive bilateral Babinski sign. The Kernig and Brudzinski signs continued to be present. The pupils failed to react to light or accommodation, and the left eye continued to rotate inward. During the day he received fluids, sulfadiazine, oxygen and caffeine sodium benzoate intravenously. Examination of the blood showed a red-cell count of 4,410,000 and a white-cell count of 13,000, with 78 per cent neutrophils, 12 per cent lymphocytes and 5 per cent monocytes.

During the following day the patient remained comatose. Because of the high, fluctuating temperature a malaria smear was done and was found to be positive for *Plasmodium vivax*. A lumbar puncture during the day revealed 230 white cells per cubic millimeter, with 99 per cent lymphocytes. A very definite, fine fibrin pellicle formed within an hour of standing. Since quinine or atabrine for intravenous or intramuscular use was not available at that time, the patient was given 0.4 gm of atabrine that evening by rectum. On the next day quinine dihydrochloride was obtained, and large doses were given intravenously and intramuscularly every 6 hours. By 6:30 p.m. on February 9 the patient's condition became terminal, and his temperature continued to rise during the night, reaching 107.4°F by 4:00 a.m. At 6:00 a.m. on February 10 he ceased to breathe.

At autopsy the body was that of a fairly well developed man, revealing marked rigor mortis. The pupils were round and slightly unequal. When the pleural cavity was entered the lungs retracted, and no excess pleural fluid was observed. The lungs showed no pertinent disease on either gross or microscopic examination, and no tuberculosis was found. Examination of the spleen was essentially negative, and despite multiple sectioning, no lesions were noted. Examination of the liver was also negative.

On examination of the brain the external appearance of the dura showed no abnormalities. It was incised and reflected, revealing a very markedly congested vessel over both cerebral hemispheres. In addition, there was a small amount of yellow material about the blood vessels, and occasional small white foci, approximately 1 mm in diameter, were seen in the pia arachnoid. The brain was marked in the usual manner. It was of the usual size and shape, but slightly decreased in weight, which was 1280 gm. Over the base of the brain, there was a gelatinous, cloudy exudate, which was very abundant and which became yellow, opaque and purulent about the optic chiasm. This exudative process also clouded the leptomeninges covering the cerebellum. The multiple white, minute foci noted over the cerebral hemispheres were very numerous about the base of the brain and over the cerebellum. When the leptomeninges were dissected free, it was noted that they seemed to be contained within the meninges. Multiple coronal sections throughout the brain revealed some dilatation of the lateral and third ventricles. There was also a slight thinning of the cerebral cortex, however, there was no evidence of molding of the cerebellum about the brain stem. The superior portion of the caudate nucleus on the left contained red, softened areas measuring 0.8 cm in diameter. The superior portion of the temporal lobe on the right contained a very soft area immediately adjacent to the sylvian fissure. The meninges were thickened in this area, and the superior portion of the temporal lobe was adherent to the undersurface of the parietal lobe. There was no yellow discoloration about the border of the region, and no evidence of hemorrhage into it. The tissue in this region was white, soft and friable, and no sharp line of demarcation delimited this area from the surrounding brain tissue. In a number of areas throughout the brain, small congested vessels were visible, and petechiae were suggested. There was no evidence of gross hemorrhage or necrosis in the thalamus or brain stem.

On microscopic examination of the brain many of the blood vessels of the leptomeninges were surrounded by a cuff of chronic inflammatory cells, chiefly lymphocytes and mononuclear cells. There was a fairly diffuse infiltration of the leptomeninges by chronic inflammatory cells. In some areas, often perivascularly, there were foci of caseous necrosis. Tubercle-like lesions were noted with large numbers of epithelioid cells and scattered, multinucleated Langhans' giant cells. Acid-fast stains of these areas revealed scattered

acid-fast bacilli identical morphologically with tubercle bacilli. The chronic inflammatory infiltrate was also noted about the vessels in the Virchow-Robin spaces and in some areas deep within the brain substance. There was a fairly generalized congestion of the blood vessels of the brain, and in some areas, perivascular extravasation of red cells was present. The pineal body was surrounded by a similar inflammatory process. In a rare area, the peripheral substance of the brain was involved in a caseous necrosis for a short distance beneath the pia mater. However, the appearance was that of an extension of the meningeal process into the brain rather than vice versa. No true tuberculoma was noted. The softened area described grossly in the temporal lobe microscopically was composed of brain containing foci of hemorrhage and fragmentation of the brain substance with a few scattered polymorphonuclear leukocytes. The choroid plexus contained numerous small, round, calcific bodies, and a few of the vessels were surrounded by a cuff of lymphocytes. However, no marked inflammatory involvement or caseous necrosis was noted similar to that seen in the meninges. Occasional ganglion cells showed evidence of mild degenerative changes, with swelling and rounding of the cytoplasmic borders. There was a congestion and generalized slight increase in the glial cells throughout the brain.

Culture of the heart's blood revealed no growth.

A gram stain of the right lower lobe of the lung disclosed no organisms. On culture a nonhemolytic *Staphylococcus aureus* and a *Streptococcus viridans* were observed.

No malaria parasites were seen on a smear of the spleen.

A smear of the brain abscess demonstrated no organisms. Culture showed an alkaligenes bacillus, gram-positive cocci in chains and groups were overgrown by the gram-negative bacilli. On guinea-pig inoculation acid-fast bacilli were recovered from an inguinal lymph node and spleen.

On March 20 an autopsy of a guinea pig inoculated 38 days previously was positive for lesions typical of tuberculosis. Smears from the lesions showed the presence of acid-fast bacilli.

## DISCUSSION

This case was of unusual interest. What at the onset appeared to be an uncomplicated case of meningococcal meningitis terminated fatally with a tuberculous infection of the meninges and was further complicated by the recrudescence of a malarial infection that the patient had undoubtedly contracted during his service in Sicily and Italy. Because of the comparative rarity of a combined tuberculous and suppurative meningeal infection, it was thought of interest to review the literature. The cases reported in the medical literature since 1911 are presented in Table I.

A review of this table shows that most of these case reports are from the foreign literature. The case presented above is the first reported from American sources, and is approximately the thirty-fourth case of its type in the literature. Since meningococcal meningitis has been found in many series to be the most common bacterial type of meningitis, it is not surprising that cases of tuberculous meningococcal meningitis predominate.

The record in this case reveals considerable similarity with those in the other reported cases. The patient entered the hospital with the classic signs and symptoms of meningitis. Although, unfortunately, there is no record of any bacterial cultures taken from the nasopharynx, it can probably be assumed that this was the initial focus from which dissemination to the meninges occurred. The

spinal-fluid findings were certainly compatible with a meningococcal meningitis, and it is possible that at the time of onset the patient had a pure meningococcal infection. In retrospect however, there is one finding that might be significant in view of the patient's subsequent course. This is the fact that despite the acuteness of the infection, only 54 per cent of the white cells were neutrophils. This is almost the same ratio of lymphocytes to neutrophils as was found by Fiddes<sup>34</sup> in a case of

TABLE 1 *Cases of Combined Tuberculous and Suppurative Meningeal Infection Reported in the Literature*

NO OF CASES	BACTERIOLOGIC FINDINGS	AUTHOR
1	Tubercle bacillus and meningococcus	Guinou and Gruet <sup>1</sup>
1	Tubercle bacillus and meningococcus	Dupéré <sup>2</sup>
2	Tubercle bacillus and meningococcus	Bériel and Durand <sup>3</sup>
1	Tubercle bacillus and meningococcus	Ganducbeau <sup>4</sup>
1	Tubercle bacillus and meningococcus	Loubet et al. <sup>5</sup>
2	Tubercle bacillus and meningococcus	Sauton and Maillet <sup>6</sup>
1	Tubercle bacillus and meningococcus	Claude et al. <sup>18</sup>
1	Tubercle bacillus and pneumococcus	Devie et al. <sup>19</sup>
2	Tubercle bacillus and (?)	Vialard <sup>20</sup>
1	Tubercle bacillus and meningococcus	Achard et al. <sup>21</sup>
2	Tubercle bacillus and (?)	Colombe and Foulkes <sup>22</sup>
1	Tubercle bacillus and tetragenus organism	Todesco <sup>23</sup>
1	Tubercle bacillus and meningococcus	Aguirre and Bettinotti <sup>24</sup>
1	Tubercle bacillus and pneumococcus	Achard and Horowitz <sup>25</sup>
1	Tubercle bacillus and meningococcus	Imbert <sup>26</sup>
1	Tubercle bacillus and meningococcus	Mikulowski <sup>27</sup>
1	Tubercle bacillus and pneumococcus	Achard <sup>28</sup>
1	Tubercle bacillus and pneumococcus	von Cölke <sup>29</sup>
1	Tubercle bacillus and meningococcus	Schumau <sup>30</sup>
1	Tubercle bacillus and meningococcus	Grysz et al. <sup>31</sup>
1	Tubercle bacillus and meningococcus	Carlous <sup>32</sup>
1	Tubercle bacillus and meningococcus	Foa <sup>33</sup>
1	Tubercle bacillus and meningococcus	Moritz <sup>34</sup>
1	Tubercle bacillus and Friedländer bacillus	Moritz <sup>35</sup>
1	Tubercle bacillus and meningococcus	Cislaghi <sup>36</sup>
1	Tubercle bacillus and meningococcus	Fiddes <sup>34</sup>
1	Tubercle bacillus and meningococcus	Baur <sup>37</sup>
1	Tubercle bacillus and meningococcus	Todesco <sup>38</sup>
1	Tubercle bacillus and meningococcus	Lemieux et al. <sup>39</sup>

mixed tuberculous meningococcal meningitis in a fourteen-month-old baby. That this relative lymphocytosis in the face of a suppurative meningeal infection may be of significance is further strengthened by the findings of Claude et al.<sup>18</sup> These authors reviewed the literature and stated that in most cases an acute polymorphonuclear response in the spinal fluid is replaced by a lymphocytosis. Moritz,<sup>31</sup> in the report of a case of mixed tuberculous and Friedländer meningitis, also points out that the duality of the infection may alter the spinal-fluid findings. However, without some clinical findings to support the diagnosis of a tuberculous meningitis, it would be misleading in many cases to place too much emphasis on these findings alone.

After the institution of sulfadiazine therapy supplemented later by penicillin, the patient failed

to respond clinically but continued a downhill course, despite the fact that, after three days of sulfadiazine therapy, smear and culture of specimens of the spinal fluid were negative for the meningococcus. It was not until after the patient had shown progressive mental deterioration and central-nervous-system damage that another lumbar puncture revealed the pathognomonic fibrin pellicle and the characteristic cell count and chemical findings of a tuberculous meningitis.

As in the majority of other reported cases of combined tuberculous and suppurative meningitis, the failure of the patient to respond to specific therapy was the clue that led to the suspicion that perhaps this was a double infection. Certainly, with no obvious manifestations of an active tuberculous process elsewhere in the body, there was no reason to suspect a tuberculous infection earlier. Many of the available case reports emphasize the fact that the diagnosis of a mixed infection can only be made bacteriologically and that the suppurative phase does not alter the progressive characteristic course of the tuberculous infection or establish any marked deviation from the usual clinical pattern. Since there is apparently no characteristic clinical picture of the mixed type of infection, it is possible that a certain number of such cases are missed, owing to the fact that complete bacteriologic studies are not always carried out because the possibility of a combined infection is not considered.

The central-nervous-system pathological findings in this case were characteristic of a pure tuberculous meningitis. In almost all the other reported cases in which chronologically the tuberculous phase appears to have been superimposed upon the suppurative phase, the pathological findings have been those of a tuberculous infection alone. These findings certainly suggest that the tuberculous invasion is secondary to the suppurative phase, although Moritz<sup>31</sup> believes that the pathological findings of the two types of meningitis are not sufficiently distinct to enable any conclusions to be drawn regarding the primary infection. That the pathological changes secondary to the acute suppurative phase may be masked by the changes resulting from the tuberculous infection is suggested in the findings of a case of mixed tuberculous pneumococcal meningitis reported by Achard and Horowitz.<sup>22</sup> At post-mortem examination of the brain, a typical basal meningitis most marked in the region of the fourth ventricle was present. The arachnoid was thickened, opaque and milky in appearance, areas of caseation were present in the floor of the fourth ventricle, and no findings characteristic of a suppurative meningitis were observed. However, both pneumococci and tubercle bacilli were cultured from spinal fluid taken from the fourth ventricle, and both organisms were found by smear and culture in adjacent areas of

caseation The case reported by Fiddes<sup>44</sup> is interesting in that two distinct types of exudate were present

On the ventral surface of the cerebellum and stretching forward to the pons was a thick greenish-yellow purulent exudate. Covering the midbrain and crura cerebri and running into the cerebral sulci along the vessels was a much thinner, whitish exudate, containing many miliary tubercles especially about the vessels of the Sylvian fissure. There was a great excess of spinal fluid in the ventricles. The brain was fixed and when examined later, both lateral ventricles were greatly dilated and many miliary tuberculomata were seen in their walls

The two different types of exudate described certainly suggest the combined effects of a suppurative and nonsuppurative type of pathologic process. In the findings in the case presented above, however, there was nothing to suggest the presence of a suppurative process, and to quote from the comments made by Colonel Harold L. Stewart, the pathologist, "the histologic findings and demonstration of acid-fast organisms leave little doubt regarding the type of meningitis, at least in the terminal phase."

The pathogenetic problems presented by this case are extremely interesting. Until the publication of the paper by Rich and McCordock<sup>47</sup> from Johns Hopkins in 1933, tuberculous meningitis was generally considered to be the result of hematogenous dissemination of the tubercle bacilli to the meninges. The reason for this was the high incidence of tuberculous meningitis found in association with cases of disseminated hematogenous tuberculosis. Rich and McCordock, however, believed that several factors lent doubt to the hematogenous theory explaining the pathogenesis of tuberculosis of the meninges. Because of these objections, they considered the rupture of a caseous tuberculous focus into the subarachnoid space to be a better explanation of the pathogenesis of tuberculous meningitis. This caseous focus might be in the adjacent vertebra, in the meninges themselves or in the brain or spinal cord. By very meticulous sectioning of the brains and spinal cords of 82 cases of tuberculous meningitis, the authors were able to demonstrate caseous foci in 77 cases and in the 5 cases in which foci were not demonstrated, the examinations were not complete. This work of Rich and McCordock has been repeated and confirmed by other workers. MacGregor and Green,<sup>48</sup> for example, in examining 88 brains and spinal cords from cases of tuberculous meningitis found caseous foci in 74 brains and evidence of tuberculosis of the spine in 4 other cases making a total of 78 cases, or 88.6 per cent. In 59 of these cases, or 67 per cent, it was proved conclusively that the origin of the meningitis was from these caseous foci, and in a further 6 cases it was found highly probable, making a total of 74 per cent. In only 4 cases in this series were caseous choroid tubercles present, and the authors regarded these

choroid-plexus foci as part of the diffuse meningitis and of no pathogenetic significance.

Although the work of MacGregor and Green tends to support the conclusions reached by Rich and McCordock, their findings have not always been substantiated. Ragins,<sup>49</sup> for example, studied 39 cases of tuberculous meningitis and found that in 32 cases (82 per cent) the meningitis resulted from direct hematogenous spread from some focus of visceral tuberculosis found at autopsy. In another series of cases, Engel<sup>50</sup> studied 15 cases of tuberculous meningitis superimposed upon generalized miliary tuberculosis and failed to discover in a single case caseous foci that could be considered the source of the meningeal infection. In all cases the choroid plexi were involved microscopically with an acute tuberculous process with tubercle bacilli present in every case. The author reached the conclusion that infection from the choroid plexus was a more important factor in the pathogenesis than the rupture of a caseous focus into the subarachnoid space.

In the case reported above, the source of the tuberculous meningitis remains a mystery. No visceral focus of tuberculosis was found in any of the organs examined. It was suggested by Colonel Stewart that perhaps some small tuberculoma had been overlooked in the sections of the brain examined and this remains the best possibility. Both Rich and McCordock and MacGregor and Green mention the ease with which a small tuberculoma may be overlooked unless particular care is taken during the sectioning. The former group emphasize the fact that the brain sections should not be more than 3 mm in thickness and that special technics must be employed in many cases to demonstrate tuberculomas that are fresh and not yet encapsulated. In this case no mention was made of the number or thickness of the sections examined or the technic employed.

There were several other possible sites in this case for caseous foci that might have ruptured into the subarachnoid space, but in none of them is the possibility anything but remote. There was no evidence of any active caseous foci in the choroid plexi. It has been mentioned that a vertebral lesion may be the source of a tuberculous meningitis, and in this particular case there is no mention that this possibility was completely excluded by x-ray or pathological examination. However, it is unlikely that such a focus existed since the patient had no complaints suggestive of a vertebral lesion. Crowe<sup>51</sup> has demonstrated that a tuberculous otitis media can be the source of direct meningeal invasion in tuberculous meningitis, but this patient had no complaints referable to his ears and examination of the ear, nose and throat upon admission had been negative. There is one other possibility that was not wholly precluded since a complete examination of the spinal cord was not

performed a spinal-cord tuberculoma that had ruptured into the subarachnoid space, causing a meningitis

Single or multiple tuberculomas of the spinal cord are not common. By 1943 only 93 cases had been reported in the literature.<sup>42</sup> The most comprehensive review of the subject of spinal-cord tuberculomas was published by Thalhimer and Hassin<sup>43</sup> in 1922. These authors collected 67 cases and reported abstracts on 58. As might have been expected, almost every case presented symptoms suggestive of an expanding spinal-cord lesion that, in the majority of cases, was diagnosed clinically as a spinal-cord tumor. The cases of spinal-cord tuberculoma examined at autopsy often revealed microscopical and gross evidence of a localized tuberculous meningitis about the nerve roots, with extension of the caseous process up to and sometimes into the subarachnoid space. In the case reported above, however, because of the lack of any symptoms referable to the spine and especially because of the failure to find any active tuberculous focus elsewhere that could have acted as a feeding lesion, a spinal-cord tuberculoma producing meningitis is unlikely.

The relation between the suppurative and the tuberculous phases of this patient's illness is an interesting one. Certain writers, such as Claude and his co-workers,<sup>15</sup> considered the association coincidental. Moritz<sup>21</sup> believed that the tuberculous infection was primary, even though the tubercle bacillus did not appear in the spinal fluid until the day before death and although the Friedländer bacillus was found after the first lumbar puncture. Lemieux et al.<sup>4</sup> also regarded the suppurative phase of the dual infection as secondary.

Other authors, however, have thought differently. In a case of mixed meningococcal and tuberculous meningitis reported by Schuman<sup>27</sup> in a six-year-old boy who, three weeks before the onset of meningitis, had had an attack of measles, it was believed that the measles had activated a dormant tuberculous lesion of the lung, with a resultant meningitis. In another case of a combined tuberculous meningococcal meningitis reported by Grysez and his associates,<sup>28</sup> the meningococcal infection was considered to have activated a latent tuberculous focus. From the clinical and pathological evidence in this case, this mechanism seems the most likely explanation.

Baum and Amberson,<sup>44</sup> in a study of cases of pulmonary tuberculosis existing concomitantly with bronchiectasis, lung abscess and pneumonia, have demonstrated conclusively that a latent focus can be activated by a suppurative process. "Suppurative disease has been found repeatedly to be responsible for the activation of a tuberculous process, the mechanism most likely being destruction of the capsule with consequent liberation of the tubercle bacillus." If such a mechanism can be

held responsible for the activation of a pulmonary focus, the same mechanism can be held responsible for the activation of a subarachnoid focus, too small to have been demonstrated on sections. The problem of the exacerbation of the old malarial infection is perhaps even more obscure than the problems of pathogenesis raised by the dual meningeal infection.

## SUMMARY

An additional case of coexisting tuberculous and meningococcal meningitis is reported, and the pertinent literature is reviewed.

The pathogenesis of the inter-relation between tuberculous and suppurative meningitis is discussed.

It is hoped that further cases will be reported as they appear.

## REFERENCES

1. Neal J. B. Meningococcal meningitis in children. *J A M A* 105: 568-571 1935.
2. Tripoli C. J. Bacterial meningitis: comparative study of various therapeutic measures. *J A M A* 116: 171-177 1936.
3. Hertzog A. J. Study of 377 cases of fatal meningitis with special reference to bacteriologic diagnosis. *Am J Clin. Path.* 15: 571-574 1945.
4. Lemieux R., Morin E. and Nadeau H. Infection meningée tuberculeuse et meningococcique. *Laval med* 9: 295-307 1944.
5. Pipirs, I. S. Mischinfektion der Meningen durch Tuberkelbakterien und andere pathogene Keime. *Ztschr f. Kinderh.* 50: 161-166 1930.
6. Key R. W. Outie meningitis with dual infection of spinal fluid: report of case. *U S Nav M Bull* 39: 555-558 1941.
7. Cunningham A. A. Mixed meningococcal and streptococcal meningitis. *Lancet* 1: 198 1937.
8. Chaler J., and Guichard A. De l'association du pneumocoque et du meningococcus dans les méningites cerebro-spinales. *Prespe med* pp 2343-2350 1931.
9. Guinon L. and Grenet, H. Méningite à meningocoques et à bacilles de Koch associés. *Bull Soc de pédiat de Paris* 13: 296-303 1911.
10. Duperie R. Gomme tuberculeuses hypodermiques multiples chez un nourrisson. Méningite aiguë terminale à meningocoques et à bacilles de Koch. *Arch de med d enf* 15: 599-609 1912.
11. Benel L. and Durand J. Meningite tuberculeuse avec association de meningococcus. *Lyon méd* 121: 913-919 1913.
12. Gauducheau R. Meningite associée à meningocoques et à bacilles de Koch. *Gaz. med de Nantes* 31: 261-265, 1913.
13. Loubet, et al. Meningite à meningocoques avec association de bacilles de Koch. *Arch de med d enf* 17: 591-600 1914.
14. Saunton P. and Maille J. Meningite meningococcique et tuberculose. *Bull et mem Soc med d'hôp de Paris* 40: 103-112 1916.
15. Claude H. Schaeffer H. and Bernard S. Sur la coexistence des meningocoques et du bacille de Koch dans une méningite cerebro-spinale. *Bull et mem Soc med d'hôp de Paris* 43: 863-869 1919.
16. Devic, A. et al. Meningite tuberculeuse terminée par une méningite à pneumocoque. *Lyon méd* 131: 921-924 1922.
17. Vialard. Sur deux cas de méningite tuberculeuse granuleuse associée. *Bull et mem Soc med d'hôp de Paris* 47: 1630-1638 1923.
18. Achard C., Bloch S. and Marchal G. Meningite aiguë avec association tuberculo-meningococcique. *Bull et mem Soc med d'hôp de Paris* 48: 446-449 1924.
19. Colombe J. and Fouilles D. Deux observations de méningite tuberculeuse avec infection associée. *Arch de med d enf* 21: 477-486 1924.
20. Todisco J. Case of meningitis due to tubercle bacillus and diplococcus closely allied to *Micrococcus tetragenes*. *Lancet* 1: 538 1927.
21. Cibils Aguirre R. and Bettinotti S. I. Meningitis asociada tuberculosa y meningococcica. *Arch argent de pediat* 1: 611-613 1930.
22. Achard C. and Horowitz, A. Un cas de méningite associée tuberculopneumococcique. *Bull et mem Soc med d'hôp de Paris* 47: 24-28 1931.
23. Imbert, P. Sur infection d'une méningite tuberculeuse cliniquement latente, par le meningococcus. *Lyon méd* 147: 41 1931.
24. Mikolowski W. Infection meningée mixte à diplocoque de Weichselbaum et à bacille de Koch. *Arch de med d enf* 34: 671-674 1931.
25. Achard, C. Meningite tuberculo-pneumococcique. *Rev gén de clin. et de thérap* 45: 529-533 1931.
26. von Cötte L. Über einen interessanten Fall von Säuglingsmeningitis. *Ztschr f. Kinderh* 54: 140-143 1932.
27. Schuman M. Meningococcus meningitis followed by tuberculous meningitis. *M J & Rec* 137: 8-10 1933.

- 28 Gryszek, et al. Meningite aigüe tuberculo-meningococcique au terme d'un état infectieux d'allure septicémique de longue durée. *Presse med* 42 1162 1934
- 29 Carloni G. Meningitis mista tuberculosa e meningococcica. *Chir pediat* 16 610-626 1934
- 30 Foa A. Infezione meningea mista cerebro-spinale e tuberculosa. *Ped d med prat* 10 65-68 1935
- 31 Moritz D. Mischinfektion der Hirnhäute mit dem Koch- und dem Friedländer'schen Pneumo-Bazillen. *Arch f Kinderk* 109 21-24 1936
- 32 Idem. Mixed infection of meninges with tubercle bacilli and Friedländer's bacilli. *Oron ketil* 81 60, 1937
- 33 Cislaghi F. Meningitis mista tuberculosa e meningococcica. *Pediatrics* 48:585-598 1940
- 34 Fiddes J. Combined forms of meningitis mixed infection of meninges by tubercle bacilli and meningococcus. *Arch Dis Child* 16 140-144 1941
- 35 Baer O. Ein Fall von Meningitis epidemica bei gleichzeitigem Nachweis von Tbc-Bazillen im Liquor. *Münchener med Wochenschr* 88 47 1941
- 36 Todesco J. M. Case of cerebro-spinal meningitis followed by tuberculosis meningitis. *M Press* 207 127 1942
- 37 Rich A. R. and McCordock, H. A. Pathogenesis of tuberculous meningitis. *Bull. Johns Hopkins Hosp* 52:5 37 1933
- 38 MacGregor A. R. and Green C. A. Tuberculosis of central nervous system with special reference to tuberculous meningitis. *J Path & Bact* 45 613-645 1937
- 39 Ragins A. B. Pathogenesis of tuberculous lepto-meningitis. *J Lab & Clin Med* 21 1217-1227 1936
- 40 Engel S. Choroid plexus in origin of tuberculous meningitis. *J Path & Bact* 56 115-121 1944
- 41 Crowe, S. J. Pathologic changes in meningitis of internal ear. *Arch Otolaryng* 11:557-568 1930
- 42 Amyot R. and Vasquez, J. Tuberculome intra médullaire. *Union med du Canada* 72 652-656 1943
- 43 Thalhimer W. and Hassin G. B. Clinico-pathologic notes on solitary tubercle of spinal cord. *J Nerv & Ment Dis* 55 161-195 1922
- 44 Baum O. S. and Amberson J. B. Jr. Nontuberculous pulmonary infections complicating pulmonary tuberculosis. *Am Rev Tuberc* 45 243-279 1942

## PROPHYLAXIS AGAINST ALLERGY

### A Pediatric Program

MAURICE H. SHULMAN, M.D.

BOSTON

THE pediatrician holds a unique position in the field of allergy. To him falls the opportunity of dealing with the patient before the first manifestations of allergy. Therefore, whatever can be achieved in the way of preventive allergy lies within his sphere.

Allergy is defined as an altered reactivity of tissues following the introduction of foreign protein by inhalation, injection or ingestion. The difficulties of taking prophylactic measures in the field of allergy are inherent in its definition. In general, it is only after the occurrence of clinical symptoms that steps are taken to eliminate the offending allergens when possible, or to protect the patient by hyposensitization when indicated. Logically, many symptoms might be avoided by elimination or by guarded exposure prior to sensitization. Present knowledge is such that much foresight can be exercised.

In the evolution of the literature dealing with allergy, many equivocal and some contradictory findings appear. Many data, however, have been well established. Together with advances in clinical experience, this knowledge provides at least the foundation of a plan for prophylaxis.

The inheritance of the tendency to develop allergy is now generally accepted. Repeated observations of most clinicians, regardless of the variation in their figures, force the conclusion that the children of allergic adults will constitute the greatest number of allergic persons in the next generation. It is the purpose of this paper to outline a regime for this group of potentially allergic children by which the danger of sensitization to certain potent allergens may be minimized.

### HEREDITY OF ALLERGY

Vaughan<sup>1</sup> has summarized and evaluated the numerous statistical studies concerning the heredity of allergy. His figures indicate that about 10 per cent of the general population suffer from major allergy and that another 50 per cent have minor allergy. There is an antecedent family history of allergy in from 50 to 70 per cent of allergic patients whereas only 7 per cent of nonallergic people give a family history of allergy. Differences in methods of statistical classification employed by the various writers apparently account for the variation in their figures.

Table 1 illustrates this variation.

Vaughan concludes that there is a hereditary factor in allergy. He estimates that about 75 per cent

TABLE 1 *Types of Allergy in Relation to Positive Family History\**

ALLERGIC MANIFESTATION	POSITIVE FAMILY HISTORY %
Asthma (in children)	40-70
Asthma (in adults)	40-60
Migraine	75-85
Food allergy	68
Eczema	28-76
Urticaria	25-50

\*Adapted from Vaughan<sup>1</sup>

of all children with bilateral allergic inheritance and about 50 per cent of those with unilateral inheritance will eventually develop some type of allergic manifestation. The heavier the inheritance, the greater the number of allergic symptoms and the earlier they will appear in each offspring.

Since the earliest indication of this potentiality lies in the parental history, the importance of determining the presence or absence of allergy in the parents of the newborn by carefully taken case histories becomes evident. The program for the care and feeding of such infants during their first year of life can be guided by such information. Although all children of allergic parents need not become allergic themselves, their potentialities must certainly be reckoned with as a group.

### MECHANISM OF SENSITIZATION

The mechanism of sensitization depends on the type of allergy involved. The inhalants, as the name suggests, occur in the environment of the patient or in the atmosphere, creating sensitization through the respiratory tract. Pollens, ubiquitous and probably uncontrollable, fall into this category. Other inhalants, such as feathers and animal dander, are controllable. Allergens found in food cause symptoms upon ingestion, and these symptoms are alleviated by diet.

The presence of the allergic tendency, whether inherited or acquired, does not result in clinical allergy unless sensitization occurs by exposure to potent allergens. A large part of allergic treatment consists of elimination of offending allergens from the environment or the diet. This clinical procedure has given excellent results. Is it not wiser, then, to avoid exposure, thereby substituting prevention for the need of a cure?

The factor of food allergens is most important at the earliest period of life. Fortunately for this group, the dietary intake is most readily regulated at this time. Adequate infant feeding has two major requirements: normal growth must be maintained, and minimum vitamin and mineral requirements must be fulfilled. These two basic requirements can be met, while, at the same time, the exposure to potent allergens is lessened.

Food allergy has been recognized for many years, but it was not until 1916 that Schloss and Worthen<sup>2</sup> gave the first hint of its mechanics. In their classic paper they proved that foreign proteins are absorbed in unchanged form through the gastrointestinal tracts of normal infants and to a greater degree in those suffering from debility or any form of gastroenteritis. In 1920 Schloss<sup>3</sup> described the hyperacute type of sensitivity to food as evidenced by urticaria, asthma and symptoms of shock. The diagnosis of this condition is commonly made by the parents because of its obvious cause and effect relation. The symptoms are so distressing that the detection of the offending food is never a problem. Another type of sensitivity that brought on gastrointestinal disturbances with vomiting and diarrhea or skin manifestations such as eczema was described by the same author. In 1925 DuBois, Schloss and Anderson<sup>4</sup> reported that enteral absorption of antigenic protein by normal or marasmic infants led

not only to the appearance of a specific precipitin in the blood but also, in many cases, to cutaneous sensitivity. This fundamental work has been repeated by Wilson and Walzer<sup>5</sup> and other investigators.

Schloss and his co-workers<sup>6</sup> stated that the mechanism whereby the body is protected from the continued absorption of appreciable amounts of foreign protein was unknown. This statement still holds true today. They advanced three possible explanations, which continue to be of great interest by some means the gastrointestinal wall becomes impermeable to each newly introduced protein after it has been ingested for a certain length of time, an alteration in the digestive enzymes takes place so that they ultimately become capable of producing complete denaturation, and finally, even though foreign protein is absorbed as such, it may be neutralized by some hitherto unrecognized immune reactions. It has been observed by Rackemann<sup>7</sup> and others<sup>8</sup> that children frequently manifest the first symptoms of hypersensitivity to antigenic substances a few days or weeks after initial exposure. This interval coincides with the development of the antibodies as observed by Schloss and his co-workers<sup>6</sup>. In the average infant this immunologic process is passed over without incident. In the infant with the inherited tendency to hypersensitivity, Schloss and his associates<sup>6</sup> have reasoned that this mechanism may be altered so that the clinical manifestations of allergy result.

### BASIC FOODS IN INFANT FEEDING

The basic foods in infant feeding are milk, egg, wheat, orange juice and fish oil. These foods are added to the diet at varying ages, depending on the fashion of the moment and, to a lesser degree, on the school of thought to which the practicing pediatrician subscribes. Allergists<sup>9</sup> have found these five foods to be the most common sources of allergic manifestations in infants and young children. Laboratory workers have used the same allergens to prove the absorption of undigested protein through the gastrointestinal tract. Thus, there is the rare circumstance of five basic foods, ever-present in infant feeding, that are potent allergens and are readily absorbed unchanged through the mucous membrane of the gastrointestinal tract.

In summary, a large number of infants are potentially allergic by reason of heredity. Five basic food requirements of the infant diet are potent allergens, and these proteins are absorbed unchanged through the gastrointestinal tract. Is it not logical, then, to diminish the potency of these allergens by introducing them into the diet in a denatured form or to avoid them whenever possible?

Milk holds a unique position in the infant diet, unparalleled by any one food in adult life. Hill<sup>10</sup> pointed out that the infant takes enormous quantities of milk in proportion to his weight. He

asserted that nature never intended the infant diet to have so high a protein content as that furnished by cow's milk and that the infant's digestive function is not adapted to this milk.

There are two proteins present in milk the more common offender, as Hill and Pratt<sup>11</sup> have pointed out, is lactalbumin, the second is casein. Anderson, Schloss and Stuart<sup>12</sup> demonstrated the close biologic relation between goat, cow and human casein. This explains why casein-sensitive patients do not benefit when the milk ingested is changed from one type to another. Lewis and Hayden,<sup>13</sup> in 1930, reported a diminution of antigenic properties in heated milk. Ratner<sup>14</sup> supported this view by pointing out the diminished antigenicity of evaporated cow's milk, owing to the prolonged heat applied in evaporation. Because of its method of manufacture, this does not hold true of powdered milk.

Egg allergy in infants and children is relatively common and important. As early as 1907, Gelbke<sup>15</sup> reported marked clinical response to the ingestion of egg. The cases reported were of the immediate, dramatic type, the symptoms developing instantaneously from the slightest contact with egg. This high degree of sensitivity does not represent the most frequent type of reaction. The slow, masked type of reaction is more common. In Vaughan's<sup>1</sup> experience, corroborated by Hill and others, egg appears to cause cutaneous manifestations more frequently than other symptoms.

There are a few cases on record in which egg sensitization appears to have been hereditary. This situation is evidenced by the occurrence of symptoms on the first exposure to this food. These cases are the exception rather than the rule.

Although egg white is the most frequent source of trouble, the egg yolk cannot be considered blameless. Egg white is the most difficult of all proteins to digest completely. Walzer<sup>16</sup> has found that incompletely digested egg protein circulates normally in the blood of some infants after feedings.

There are at least three aspects to the problem of egg as an allergen. Foremost is the prevailing custom of early introduction of egg into the diet of infants. Undigested egg protein circulating in the blood makes sensitization much easier in the potentially allergic infant. The second is the inability to denaturize egg by heat or any other known procedure. The third, and equally important, is the frequency with which egg is used in the preparation of other foods.

Wheat is also an ubiquitous allergen. Less potent than egg, it is also ingested in large quantities at an early age by most infants. Of 63 prepared cereals and infants' foods that contain wheat, 39 convey by their trade names no suggestion of the presence of wheat. Whether or not the allergenicity of wheat is diminished by heat in its preparation is still a disputed point. It is sufficient to say that the early ingestion of wheat together with the failure to recog-

nize its presence in many prepared foods makes this allergen an active one in the infant. Rarely does wheat cause the type of acute symptom complex associated with a potent allergen such as egg.

Fish as an allergen in infancy may seem paradoxical since fish is not often included in infant feeding. When, however, one considers that thirty species of fish are recognized and allowable as the source of *USP* cod-liver oil, its importance becomes evident.

Clinically, fish may cause either an acute or a delayed type of reaction. In the hypersensitive patient the odor of fish may cause asthma. Denaturation here is again difficult. Clinically complete avoidance has been the most expedient course. Since cod-liver oil, or at any rate, vitamins A and D are added to the infant diet at a very early age, care must be exercised in handling this potent allergen.

Another essential in all infant feeding is vitamin C. This is usually added to the diet at an early age in the form of orange juice. Sensitivity to orange juice does occur. Even the artificial coloring added to most oranges has been known to cause allergy. Denaturation by heat is impractical because it destroys the vitamin C content.

#### PROPHYLACTIC TREATMENT OF THE POTENTIALLY ALLERGIC INFANT

The prophylactic treatment of the potentially allergic infant must begin at birth. Every child in this category must be carefully watched for the first sign of an allergic manifestation. Before any symptoms develop, the following procedures are recommended to avoid, whenever possible, exposure to active allergens.

The period necessary for the development of symptoms after the introduction of a new food is not definitely known. The work of Schloss et al,<sup>4</sup> Rackemann<sup>7</sup> and Hill,<sup>10</sup> in addition to personal experience, has prompted the adoption of an arbitrary time of fourteen to twenty-one days as a trial period. Immediate symptoms are detected readily, and such a trial period allows sufficient time for cumulative effect to become apparent.

When the trial period has been passed safely, a food may be considered nonallergenic for the patient under consideration. The next danger lies in the continual daily or even twice daily ingestion of the accepted food. This hazard may be overcome by rotation of diet. For example, if cereal is given daily, there should be a rotation of cereals: wheat one day, rice the next day and oats the following day. Vegetables and meat should also be rotated.

The pediatrician's first concern for any newborn infant is a formula on which the infant can thrive. Evaporated milk is the first choice whenever breast feeding is not feasible. The low antigenicity of the lactalbumin in evaporated milk has been firmly established. Care should be exercised to determine that cow's milk is not first given as a matter of hos-

Since the earliest indication of this potentiality lies in the parental history, the importance of determining the presence or absence of allergy in the parents of the newborn by carefully taken case histories becomes evident. The program for the care and feeding of such infants during their first year of life can be guided by such information. Although all children of allergic parents need not become allergic themselves, their potentialities must certainly be reckoned with as a group.

### MECHANISM OF SENSITIZATION

The mechanism of sensitization depends on the type of allergy involved. The inhalants, as the name suggests, occur in the environment of the patient or in the atmosphere, creating sensitization through the respiratory tract. Pollens, ubiquitous and probably uncontrollable, fall into this category. Other inhalants, such as feathers and animal dander, are controllable. Allergens found in food cause symptoms upon ingestion, and these symptoms are alleviated by diet.

The presence of the allergic tendency, whether inherited or acquired, does not result in clinical allergy unless sensitization occurs by exposure to potent allergens. A large part of allergic treatment consists of elimination of offending allergens from the environment or the diet. This clinical procedure has given excellent results. Is it not wiser, then, to avoid exposure, thereby substituting prevention for the need of a cure?

The factor of food allergens is most important at the earliest period of life. Fortunately for this group, the dietary intake is most readily regulated at this time. Adequate infant feeding has two major requirements: normal growth must be maintained, and minimum vitamin and mineral requirements must be fulfilled. These two basic requirements can be met, while, at the same time, the exposure to potent allergens is lessened.

Food allergy has been recognized for many years, but it was not until 1916 that Schloss and Worthen<sup>2</sup> gave the first hint of its mechanics. In their classic paper they proved that foreign proteins are absorbed in unchanged form through the gastrointestinal tracts of normal infants and to a greater degree in those suffering from debility or any form of gastroenteritis. In 1920 Schloss<sup>3</sup> described the hyperacute type of sensitivity to food as evidenced by urticaria, asthma and symptoms of shock. The diagnosis of this condition is commonly made by the parents because of its obvious cause and effect relation. The symptoms are so distressing that the detection of the offending food is never a problem. Another type of sensitivity that brought on gastrointestinal disturbances with vomiting and diarrhea or skin manifestations such as eczema was described by the same author. In 1925 DuBois, Schloss and Anderson<sup>4</sup> reported that enteral absorption of antigenic protein by normal or marasmic infants led

not only to the appearance of a specific precipitin in the blood but also, in many cases, to cutaneous sensitivity. This fundamental work has been repeated by Wilson and Walzer<sup>5</sup> and other investigators.

Schloss and his co-workers<sup>6</sup> stated that the mechanism whereby the body is protected from the continued absorption of appreciable amounts of foreign protein was unknown. This statement still holds true today. They advanced three possible explanations, which continue to be of great interest by some means the gastrointestinal wall becomes impermeable to each newly introduced protein after it has been ingested for a certain length of time, an alteration in the digestive enzymes takes place so that they ultimately become capable of producing complete denaturation, and finally, even though foreign protein is absorbed as such, it may be neutralized by some hitherto unrecognized immune reactions. It has been observed by Rackemann<sup>7</sup> and others<sup>8</sup> that children frequently manifest the first symptoms of hypersensitivity to antigenic substances a few days or weeks after initial exposure. This interval coincides with the development of the antibodies as observed by Schloss and his co-workers<sup>6</sup>. In the average infant this immunologic process is passed over without incident. In the infant with the inherited tendency to hypersensitivity, Schloss and his associates<sup>6</sup> have reasoned that this mechanism may be altered so that the clinical manifestations of allergy result.

### BASIC FOODS IN INFANT FEEDING

The basic foods in infant feeding are milk, egg, wheat, orange juice and fish oil. These foods are added to the diet at varying ages, depending on the fashion of the moment and, to a lesser degree, on the school of thought to which the practicing pediatrician subscribes. Allergists<sup>9</sup> have found these five foods to be the most common sources of allergic manifestations in infants and young children. Laboratory workers have used the same allergens to prove the absorption of undigested protein through the gastrointestinal tract. Thus, there is the rare circumstance of five basic foods, ever-present in infant feeding, that are potent allergens and are readily absorbed unchanged through the mucous membrane of the gastrointestinal tract.

In summary, a large number of infants are potentially allergic by reason of heredity. Five basic food requirements of the infant diet are potent allergens, and these proteins are absorbed unchanged through the gastrointestinal tract. Is it not logical, then, to diminish the potency of these allergens by introducing them into the diet in a denatured form or to avoid them whenever possible?

Milk holds a unique position in the infant diet, unparalleled by any one food in adult life. Hill<sup>10</sup> pointed out that the infant takes enormous quantities of milk in proportion to his weight. He

The problem of pollen sensitivity, which is common in early life, may be raised at this point. The unequivocal answer to this question must be that nothing can be done to prevent such sensitization. It seems likely, however, that environmental or dietary factors are often operative first in destroying the allergic balance of the potentially allergic infant.

### DISCUSSION

This article offers no statistics supporting its proposed program. Any valid statistical study would require large numbers of patients observed over many years. Since the study of inheritance is so complicated, reports of individual cases successfully avoiding allergic manifestations can neither refute nor support the aim of the proposed regime for allergic prophylaxis.

The maintenance of allergic balance is considered very important in the potentially allergic person. Often a minor sensitization is believed to set off an extensive chain of symptoms. In infancy every precaution that may defer the upset of this balance should be taken.

A program such as that set forth is readily carried out. It calls for no major deviation from generally accepted practice in infant care. All that is necessary is a knowledge of the infant's inherited allergic tendencies, together with an awareness of the relative allergic potencies of each of the major foods and inhalants.

If prophylaxis fails in this group, a new awareness of the sources and onset of allergy will make detection of offending substances much simpler.

### SUMMARY

An attempt is made to define the potentially allergic infant and to review the current information about the mechanisms involved in the development of allergy. In the practice of allergy, many cases

are studied that require the removal of offending foods as well as other allergens. Their elimination is generally advised only after symptoms have developed. Clinical experience has shown the importance of five major food allergens. On the basis of the information provided by the literature and clinical knowledge, a program is outlined for the control of environment and of food intake that has as its aim the prevention of allergic symptoms in infants. This program is presented as an aid to those taking care of children and employs no radical deviation from the accepted procedures of pediatric care.

416 Marlborough Street

### REFERENCES

- 1 Vangban W T. *Practice of Allergy*. 1082 pp. St. Louis: Missouri C. V. Mosby Co. 1939. Pp. 74-84.
- 2 Schloss O M and Worthen T W. Permeability of gastro-enteric tract of infants to undigested protein. *Am J Dis Child* 11:542-360 1916.
- 3 Schloss O M. Allergy in infants and children. *Am J Dis Child*, 19:453 1920.
- 4 DuBois R O, Schloss O M and Anderson A F. Development of cutaneous hypersensitivity following intestinal absorption of antigenic protein. *Proc Soc Exptl Biol & Med* 23:176-180 1925.
- 5 Wilson S J and Walzer M. Absorption of undigested proteins in human beings; absorption of unaltered egg protein in infants and in children. *Am J Dis Child* 50:49-54 1955.
- 6 Lippard V W, Schloss O M and Johnson P A. Immune reactions induced in infants by intestinal absorption of incompletely digested cow's milk protein. *Am J Dis Child* 51:562-574 1956.
- 7 Rackemann F M. Can hypersensitivity be acquired? *J A M A* 84:489-491 1925.
- 8 Simon F A and Rackemann F M. Development of hypersensitivity in man. *J Allergy* 5:459 1934.
- 9 Rowe A H. Bronchial asthma in children and young adults. *Am J Dis Child* 31:1-27 1926.
- 10 Hill L W. Critical review immunologically altered skin reactivity in nonatopic persons. *J Allergy* 11:170-177 1940.
- 11 Hill L W and Pratt H N. Sensitivity of casein in infantile eczema confirmed by biologic variation of testing extract. *J Allergy* 12:143-153 1941.
- 12 Anderson A F, Schloss O M and Stuart H C. Biologic relationship between cow's goats and human caseins. *Am J Dis Child* 44:1178-1186 1952.
- 13 Lewis J H and Hayden H C. Effect of heat on antigenic properties of milk. *Am J Dis Child* 44:1211-1220 1952.
- 14 Rainer B. Treatment of milk allergy and its basic principles. *J A M A* 105:934-939 1935.
- 15 Gelbke. Fall von erblicher Idiosynkrasie. *Münchener med Wochenschr* 54:49 1907.
- 16 Walzer M. Studies in absorption of undigested proteins in human beings: simple direct method of studying absorption of undigested protein. *J Immunol* 14:143-174 1927.
- 17 Randolph T G. Food allergy. *M Clin North America* 32:245-263 1948.

pital routine. This may lead to sensitization later. If allergic symptoms do appear on an evaporated-milk formula, it is safe to assume that milk casein is the offender and no type of animal milk will improve the condition. In these cases, which fortunately are rare, soy-bean milk should be substituted. Once evaporated milk has been instituted and no symptoms occur, it should be continued as the only type of milk given for the entire first year of life. At the termination of this period, absorption of undigested protein through the intestinal tract is less likely to occur.

An essential ingredient in every infant's formula is the added carbohydrate. Corn syrup in the form of Karo is commonly used for this purpose. Randolph<sup>17</sup> suggests that corn in all forms is a potent allergen. More work may be necessary to confirm this finding, but its probable allergenicity can be avoided with ease. Dexin, a product of Burroughs and Wellcome, does not contain corn sugar but has been found excellent in infant feeding. Such a simple substitution is worthy of trial.

Between the ages of one and four weeks it is essential to add vitamins A, D and C to the average infant's diet. In the group of potentially allergic children, this should be done by the use of ascorbic acid for vitamin C and provitol or any other synthetic for vitamins A and D. By these simple expedients one can avoid exposure to fish oil or natural orange juice. Here, too, avoidance should be continued at least until the infant has reached one year of age.

The proper age for the introduction of solid foods into the infant diet has long been a disputed point. In view of the ease with which undigested protein is assimilated through the gastrointestinal tract of the infant, caution should be exercised. Three or four months of age seems a proper time, albeit an arbitrary one.

As important as the age of introduction of solid food is the type of food selected for each increase in the infant diet. Since the infants under discussion are readily sensitized by any type, it is imperative to introduce one simple food at a time. For some years it has been the custom to start with prepared cereals such as pablum and cerevim. Unfortunately these cereals represent combinations of cereals that are not indicated by their trade names. Should sensitization occur, identification of the offending allergen becomes very difficult. Pablum, for example, contains farina, oat meal, wheat germ, yellow corn meal, powdered beef bone, powdered alfalfa leaf and powdered yeast. Cerevim contains whole-wheat meal, oatmeal, wheat germ, powdered skimmed cow's milk, yellow corn meal, dried brewer's yeast, barley and malt.

I prefer the introduction of cereals in the form of rice, the least antigenic of all the cereals. Wheat may be introduced, but in a pure form, such as

cream of wheat. Then, if allergic symptoms occur, identification of the offender is facilitated.

Egg may then be introduced as hard-boiled yolk. If no reaction takes place after two to four weeks of daily ingestion, one may safely assume that no sensitization has occurred, and proceed to add egg white in small quantities.

At about the age of six months, vegetables may be introduced. There is a growing tendency to use combinations of vegetables at the start. This procedure should be avoided. Single vegetables added at an interval of two to four weeks will simplify the identification of a sensitizing agent. After a sufficient number of vegetables have been tolerated, the infant is ready to be given vegetable soups, but in offering such mixtures, one must avoid the use of commercial soups that often contain "fillers" such as barley.

Beef juice may be introduced at about eight or nine months of age. If well tolerated in the allergic sense, one different well cooked meat may be added at each monthly change of diet.

Although in the potentially allergic infant, food is of prime importance in precipitating allergic manifestations, environmental factors cannot be exonerated. Fortunately, the environment of infants can be controlled. Care must be exercised from the moment the infant is brought home from the hospital and precautionary measures must be taken in the establishment of allergic cleanliness in the nursery. The infant's mattress should be covered with a dust-proof covering. Better yet is the use of the newer foam-rubber mattress. Feather pillows should be avoided. The new glass-fiber pillow is a good substitute. No feather puffs or comforters should be permitted in the room. Wall-to-wall carpeting with ozite padding is inadvisable in the nursery. Linoleum, which can be kept free of dust, is ideal. Washable glass curtains can be substituted for heavy draperies.

No insect sprays or pyrethrum compounds should be used in the nursery. There is no point in exposing potentially allergic infants to heavy doses of pyrethrum, which is closely related to ragweed pollen.

No wooly stuffed toys should be introduced for these children to play with. These toys are commonly stuffed with cotton lint or kapok, both of which are potent allergens.

The hygiene of an infant requires the frequent use of baby powder. It is a simple matter to provide a nonallergic dusting powder. Highly scented baby oil should also be avoided. Shampoo lotions as allergens are well recognized, and such lotions need not be employed. A simple castile soap will serve adequately.

Domestic-animal contacts in the home are one of the commonest sources of early sensitivity. If the introduction of dogs, cats, birds or rabbits into the homes of such infants is avoided, a great deal of difficulty in later life may be averted.

in which the tip of the tube actually perforated the small intestine. It appears that little can be done to prevent perforation except the discontinuance of the procedure as soon as possible.

When it is thought that the tube is no longer necessary it is good policy to stop suction a reasonable length of time before the actual withdrawal.<sup>1</sup> Leigh, Nelson and Swenson<sup>2</sup> believe that a tube should either reach a definite obstruction or proceed as far as the cecum in all cases before it is removed.

The following brief case report describes an unusual development encountered during the withdrawal of a Miller-Abbott tube.

Mrs. E. F. (B. I. H. 92980), a 72-year-old woman, was admitted to the hospital on February 28, 1947, after she had sustained an incomplete intertrochanteric fracture of the femur. Buck's extension apparatus was applied, and the patient did well until March 6, when she began to suffer from ileus. Nausea, vomiting and mild distention led to the use of a Miller-Abbott tube, which relieved her distress. On March 9 withdrawal of the tube was attempted, and during this maneuver the patient developed serious respiratory difficulty, and became moderately cyanotic. The tube seemed to be fixed when the markers indicated that about 120 cm. was still to be withdrawn. The pharynx was inspected, and three lengths of tubing could be seen lying against the posterior wall. One of the lengths was grasped and the knotted mass of tubing shown in Figure 1 was extracted from the nasopharynx.

### DISCUSSION

In this case the tube was used as a therapeutic measure primarily, intrinsic intestinal disease merely

being kept in mind. There was no reason strongly to suspect either mechanical obstruction or physiologic obstruction other than on the basis of a benign ileus. Because there was clinical evidence that the tip was past the pylorus (almost pure bile in the drain bottle soon after it was passed) and because almost immediately the tube was successful in relieving the patient's distress, no x-ray examination was carried out. The tube was passed on the assumption that it was in the small intestine.

Only in retrospect is the value of knowing everything possible about the tube demonstrated. The knot should certainly have been discovered had routine x-ray or fluoroscopic study been carried out. Because this complication is preventable and can be circumvented by anticipation when discovered this case is reported. A similar incident could occur with any of the modifications of the original Miller-Abbott tube.

### REFERENCES

1. Blodgett, J. B. Technique for satisfactory use of Miller-Abbott tube. *Am. J. Surg.* 53:271-279, 1941.
2. Leigh, O. C., Jr., Nelson, J. A., and Swenson, P. C. Miller-Abbott tube as adjunct to surgery of small intestinal obstructions. *Am. Surg.* 111:186-212, 1940.
3. Wangenstein, O. H., and Paine, J. R. Treatment of acute intestinal obstruction by suction with duodenal tube. *J. A. M. A.* 101:1532-1539, 1933.
4. Cantor, M. O., Kennedy, C. S., and Reynolds, R. P. Use and abuse of intestinal decompression tube. *Am. J. Surg.* 73:437-449, 1947.
5. Caruolo, J. E. Unpublished data.
6. Abbott, W. O. Indications for use of Miller-Abbott tube. *Ann. Ent. J. Med.* 225:641-646, 1941.
7. Berger, L., and Aches, S. Perforation of small intestine by Miller-Abbott tube. *Surgery* 22:648-656, 1947.

## PRIMARY ATTACK OF VIVAX MALARIA OCCURRING TWENTY-SEVEN MONTHS AFTER INFECTION\*

WILLIAM S. JORDAN, JR., M.D.†

CLEVELAND, OHIO

TROPICAL diseases, particularly malaria, have assumed greatly increased diagnostic and therapeutic importance in this country with the return of servicemen from endemic areas.<sup>1-4</sup> Studies of the natural course of relapsing vivax malaria<sup>5, 6</sup> have led to the prediction that cases of this disease, acquired in the Southwest Pacific, would continue to appear for at least three years after the return of the last serviceman.<sup>4-7</sup> In addition, the use of quinacrine (atabrine) for the suppression of malaria has delayed the onset of the primary attack for months, whereas the normal intrinsic incubation period is eight to seventeen days.<sup>8</sup> Discontinuance of suppressive therapy in infected subjects is usually followed by symptoms within two to ten weeks, but occasionally the first clinical symptoms of malaria may be delayed for months.

Reviews of the Army and Navy experience have indicated that the longest interval thus far observed in such cases from last exposure to onset of the primary attack has been eighteen months.<sup>7, 9</sup>

This report records the occurrence of the first symptoms of vivax malaria in an ex-serviceman twenty-seven months after his return from an endemic area.

### CASE REPORT\*

A 28-year-old married salesman entered the hospital on December 6, 1947, complaining of chills and fever. Five days prior to admission, he had awakened with a mild, generalized headache, stiffness in his neck muscles and slight malaise. The headache and malaise increased during the day, and by evening he felt alternately chilly and feverish. On the following morning he felt better, but his symptoms returned that afternoon and his temperature reached 102.2°F. Three days before entry, he was given penicillin orally because of persistent symptoms and a temperature of 103.1°F. On the next afternoon, his headache became severe, and he experienced a shaking chill of 2 hours' duration during which his temperature rose to 104.9°F, and he became delirious. Drenching sweats followed, and

\*From the Departments of Preventive Medicine and Medicine, School of Medicine, Western Reserve University and the University Hospitals.

†Teaching fellow, Departments of Preventive Medicine and Medicine, School of Medicine, Western Reserve University and the University Hospitals.

\*This case is reported through the kindness of Dr. Harley A. Williams.

## AN UNUSUAL COMPLICATION OF MILLER-ABBOTT INTUBATION

## Report of a Case

LIEUTENANT JOSEPH E CARUOLO, M C, A U S

**I**NTUBATION of the small intestine has become an invaluable diagnostic and therapeutic measure, so fundamental that when indicated it is used routinely and not extraordinarily. Too often, however, a procedure seems to attract attention proportional only to its novelty. All are concerned with what an intestinal decompression tube is doing for the patient, but few are concerned with what is being done for the tube so long as it appears to be functioning.

There is much literature on intubation. It teaches that the procedure should be used with deliberation at all times. This report stresses care in its

fully before it is passed. It must be clean, deodorized, without leaks and, above all, patent. The Miller-Abbott balloon should have sufficient slack to prevent curling of the tip after it is inflated.<sup>1</sup> Whenever mercury is used the operator must be certain that it will not escape. A report, including 2 cases of mercury free within the gastrointestinal tract, shows that mercury is not absorbed and, therefore, not toxic. It is unreasonable, however, to elaborate devices designed to aid in the passage of the tube and at the same time to permit the escape of their essential element.<sup>4</sup>

Several measures that are sometimes indicated better prepare the patient. Small doses of morphine and atropine about half an hour before intubation have two functions. Apprehension is often reduced to a desirable minimum. It has been suggested moreover that fear and excitement not only deprive the patient of co-operation but also tend to produce hypertonicity of gastric cardia and the pylorus, two most important obstacles a tube must overcome. For patients with small nasal passages and for those who are hypersensitive, a solution of ephedrine and pontocaine will provide extra room and will lessen sensation.<sup>4</sup> None but experienced personnel should attempt to pass a tube of any sort, or more precisely, no one who does not appreciate his limitations should be allowed to pass a tube. Recently a well meaning attendant decided to pass a tube that the patient had dislodged. She admitted that there was considerable coughing and gagging but could not believe that this caused the patient to lose his voice for two months. An ear, nose and throat specialist described the vocal cords as edematous without any other signs of trauma. It is quite conceivable that at the time it occurred the incident could have led to serious respiratory embarrassment.<sup>5</sup>

Once in the stomach the tube should be passed *pari passu* with its progress through the pylorus, never faster, for curled tubing in the stomach serves no purpose except that of creating the complication reported below. It is agreed that x-ray examination and fluoroscopy are the only infallible indicators of the position of the tube. The thick mucinous secretions of the stomach, which tend to bog the advance of the tube, can partially be neutralized by allowing clear fluids by mouth temporarily. Electrolytes thus washed away must be replaced quantitatively. The literature contains innumerable discussions of this relation.<sup>6</sup> Frequent irrigations of the tube are always indicated.

A most serious complication has been reported recently by Berger and Achs,<sup>7</sup> who describe a case

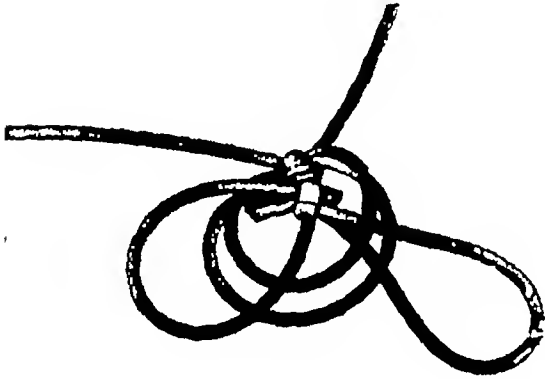


FIGURE 1 *Knotted Mass of Tubing Extracted from the Nasopharynx*

use routinely, especially when it is decided that the tube be removed. It is not intended fully to discuss the subject.

Complications arising from ill advised use of intubation are obviously the most serious. In strangulation, for example, when the tube is considered more than an adjunct, disaster is inevitable. Here, intubation can serve only to mask the gravity of the situation.<sup>1</sup> Temporizing in cases of excellent functioning of the tube without clinical improvement of the patient is treating the tube and not the patient. Conversely, a tube that refuses to function in a patient who is definitely getting better carries no weight for intervention.<sup>2</sup> A further contraindication is the treatment of obstruction of the large intestine with distention of a segment of bowel defined by the point of obstruction and the ileocecal valve.<sup>3</sup> While generalized distention is abating a closed segment is maintained under localized distention because of the unilateral flow permitted by the valve.

The preparation of the tube for the patient is a primary consideration. It must be inspected care-

in which the tip of the tube actually perforated the small intestine. It appears that little can be done to prevent perforation except the discontinuance of the procedure as soon as possible.

When it is thought that the tube is no longer necessary it is good policy to stop suction a reasonable length of time before the actual withdrawal.<sup>1</sup> Leigh, Nelson and Swenson<sup>2</sup> believe that a tube should either reach a definite obstruction or proceed as far as the cecum in all cases before it is removed.

The following brief case report describes an unusual development encountered during the withdrawal of a Miller-Abbott tube.

Mrs. E. F. (B. I. H. 92980), a 72-year-old woman, was admitted to the hospital on February 28, 1947, after she had sustained an incomplete intertrochanteric fracture of the femur. Buck's extension apparatus was applied, and the patient did well until March 6, when she began to suffer from ileus. Nausea, vomiting and mild distention led to the use of a Miller-Abbott tube, which relieved her distress. On March 9 withdrawal of the tube was attempted, and during this maneuver the patient developed serious respiratory difficulty, and became moderately cyanotic. The tube seemed to be fixed when the markers indicated that about 120 cm. was still to be withdrawn. The pharynx was inspected, and three lengths of tubing could be seen lying against the posterior wall. One of the lengths was grasped and the knotted mass of tubing shown in Figure 1 was extracted from the nasopharynx.

### DISCUSSION

In this case the tube was used as a therapeutic measure primarily, intrinsic intestinal disease merely

being kept in mind. There was no reason strongly to suspect either mechanical obstruction or physiologic obstruction other than on the basis of a benign ileus. Because there was clinical evidence that the tip was past the pylorus (almost pure bile in the drain bottle soon after it was passed) and because almost immediately the tube was successful in relieving the patient's distress, no x-ray examination was carried out. The tube was passed on the assumption that it was in the small intestine.

Only in retrospect is the value of knowing everything possible about the tube demonstrated. The knot should certainly have been discovered had routine x-ray or fluoroscopic study been carried out. Because this complication is preventable and can be circumvented by anticipation when discovered this case is reported. A similar incident could occur with any of the modifications of the original Miller-Abbott tube.

### REFERENCES

1. Blodgett, J. B. Technique for satisfactory use of Miller-Abbott tube. *Am. J. Surg.* 53:271-279, 1941.
2. Leigh, O. C., Jr., Nelson, J. A. and Swenson, P. C. Miller-Abbott tube as adjunct to surgery of small intestinal obstructions. *Ann. Surg.* 111:186-212, 1940.
3. Wangenstein, O. H. and Paine, J. R. Treatment of acute intestinal obstruction by suction with duodenal tube. *J. A. M. A.* 101:1532-1539, 1933.
4. Cantor, M. O., Kennedy, C. S. and Reynolds, R. P. Use and abuse of intestinal decompression tube. *Am. J. Surg.* 73:437-449, 1947.
5. Carnolo, J. E. Unpublished data.
6. Abbott, W. O. Indications for use of Miller-Abbott tube. *New Eng. J. Med.* 225:641-646, 1941.
7. Berger, L. and Acbs, S. Perforation of small intestine by Miller-Abbott tube. *Surgery* 22:648-656, 1947.

## PRIMARY ATTACK OF VIVAX MALARIA OCCURRING TWENTY-SEVEN MONTHS AFTER INFECTION\*

WILLIAM S. JORDAN, JR., M.D.†

CLEVELAND, OHIO

**T**ROPICAL diseases, particularly malaria, have assumed greatly increased diagnostic and therapeutic importance in this country with the return of servicemen from endemic areas.<sup>1-4</sup> Studies of the natural course of relapsing vivax malaria<sup>5, 6</sup> have led to the prediction that cases of this disease, acquired in the Southwest Pacific, would continue to appear for at least three years after the return of the last serviceman.<sup>4-7</sup> In addition, the use of quinacrine (atabrine) for the suppression of malaria has delayed the onset of the primary attack for months, whereas the normal intrinsic incubation period is eight to seventeen days.<sup>8</sup> Discontinuance of suppressive therapy in infected subjects is usually followed by symptoms within two to ten weeks, but occasionally the first clinical symptoms of malaria may be delayed for months.

Reviews of the Army and Navy experience have indicated that the longest interval thus far observed in such cases from last exposure to onset of the primary attack has been eighteen months.<sup>7, 9</sup>

This report records the occurrence of the first symptoms of vivax malaria in an ex-serviceman twenty-seven months after his return from an endemic area.

### CASE REPORT\*

A 28-year-old married salesman entered the hospital on December 6, 1947, complaining of chills and fever. Five days prior to admission, he had awakened with a mild, generalized headache, stiffness in his neck muscles and slight malaise. The headache and malaise increased during the day, and by evening he felt alternately chilly and feverish. On the following morning he felt better, but his symptoms returned that afternoon and his temperature reached 102.2°F. Three days before entry, he was given penicillin orally because of persistent symptoms and a temperature of 103.1°F. On the next afternoon, his headache became severe, and he experienced a shaking chill of 2 hours' duration during which his temperature rose to 104.9°F, and he became delirious. Drenching sweats followed, and

\*From the Departments of Preventive Medicine and Medicine, School of Medicine, Western Reserve University and the University Hospitals.

†Teaching fellow, Departments of Preventive Medicine and Medicine, School of Medicine, Western Reserve University and the University Hospitals.

\*This case is reported through the kindness of Dr. Harley A. Williams.

by the morning of the day prior to admission his temperature was normal and he was essentially asymptomatic. Another severe chill accompanied by prostration and delirium occurred the next day and he was hospitalized.

The past history included 2 years of military service, 1943-1945, in New Guinea and the Philippines. During this time the patient had had no illness requiring hospitalization and no symptoms suggestive of malaria. He took suppressive quinacrine daily until his return to the United States in September, 1945. He remained in Northern Ohio and had suffered only minor respiratory illnesses since that date.

Physical examination showed a well developed and well nourished, acutely ill man, who was rational, but weak and drowsy. Slight conjunctival injection and a firm, nontender spleen palpable 3 cm below the costal margin were the only abnormal physical findings.

The temperature was 103.1°F by rectum, the pulse 106, and the respirations 24. The blood pressure was 110/66.

Examination of the blood showed a red-cell count of 4,800,000, with a hemoglobin of 12 gm per 100 cc, and a white-cell count of 8800, with a normal differential. Routine urinalyses showed no abnormalities. An aerobic blood culture was sterile. Cultures of the throat and sputum failed to detect pneumococci, beta-hemolytic streptococci or staphylococci. An anteroposterior roentgenogram of the chest was interpreted as showing accentuation of hilar markings but no definite infiltration. Examination of thin blood smears at the time of admission showed no malarial parasites. A thick film was not made until the next morning, when the temperature was normal. This and subsequent smears were negative.

Without therapy, the patient's temperature fell to normal within 12 hours and he remained afebrile and asymptomatic until discharge on the 5th hospital day. Despite the failure to demonstrate the parasites, his clinical picture was very suggestive of malaria. Moreover, it was learned that he had received 1.0 gm (15 gr) of quinine on the morning of admission. The diagnosis was confirmed when he was readmitted 6 days later because of recurrent chills and fever. His physical findings were unchanged, but many colonies of *Plasmodium vivax* were demonstrable in routine blood smears. Quinacrine therapy induced a prompt remission, and he was discharged free from symptoms.

### DISCUSSION

This case, with the long latent period, raises the question of a more recent exposure and illustrates the diagnostic difficulties that may be encountered in a patient with malaria. Since rare cases of malaria apparently acquired in the Cleveland area have been observed,<sup>10</sup> it is possible that this patient's infection was contracted locally. Against this possibility is the time of year, December, the known previous exposure in a highly endemic area and the size of the spleen. Such splenomegaly suggests, according to Boyd,<sup>1</sup> reactivation of a latent infection.

The onset of fever, which was at first sustained but later remittent in the tertian pattern, resembles that seen in the first attack of natural malaria<sup>8</sup> or that observed in many delayed primary attacks.<sup>6-9</sup>

Early administration of only a small amount of quinine was sufficient to halt the paroxysms temporarily, confuse the clinical picture and delay diagnosis. Use of a sulfonamide might have produced the same result.<sup>11</sup>

Although the usual incubation period of unmodified malaria is approximately eight to seventeen days, longer natural latent periods have frequently been observed. Shute<sup>12</sup> recently reviewed the problem of latency and long-term relapses in malaria and reported an average latent period

of two hundred and eighty-two days in 9 cases under natural conditions. He pointed out cases, particularly those reported from the Netherlands, of attacks in early spring from infection acquired the previous summer or autumn. Students of the disease are familiar with the occurrence of the first malarial attack upon arrival in a cooler climate, and protracted latent periods of ten months are mentioned.<sup>13</sup> No account was found of a primary attack occurring as long as twenty-seven months after the last exposure.

It seems reasonable to attribute this alteration in the incubation period of the disease to quinacrine. Wartime experience showed that the mechanism of quinacrine protection in vivax malaria is not destruction of the infective organism but reduction of parasitemia to a level insufficient for the production of clinical symptoms.<sup>4</sup> Delayed primary attacks indicate prolonged survival of the postulated fixed-tissue or exoerythrocytic stage of the parasite, or a degree of immunity that, until altered, is able to suppress the parasitemia to subclinical levels. The present concept that malarial immunity is dependent on the occurrence of frequent relapses<sup>6</sup> tends to eliminate this factor in the case reported above.

Baker and Platt<sup>14</sup> reported a study of troops heavily infected with malaria on Guadalcanal and subsequently maintained on quinacrine suppression for eighteen months after their transfer to non-malarious areas. A greatly reduced relapse rate was noted during a three-month period of observation following withdrawal of quinacrine. Subject to the limitations of this period of observation, the authors concluded that "not only is the high malaria rate in heavily seeded troops temporarily controlled by atabrine suppressive medication but a highly significant amount of clinical vivax malaria is permanently abolished." It is difficult, as they suggest, to know whether to ascribe such apparent cures to the medication or merely to the passage of time with the development of immunity. The patient in the case reported above did not develop clinical malaria until more than four years after his first possible exposure and more than two years after his last exposure. Two years of suppressive quinacrine therapy during exposure did not prevent the eventual occurrence of overt disease.

Noe, Greene and Cheney<sup>6</sup> observed that patients, previously on suppressive quinacrine therapy, who have their first attack of malaria in this country show a tendency to run the complete two-year to three-year relapsing course of the disease. Should this patient show a similar tendency, and particularly if he is treated only with quinacrine, he might well suffer a malarial relapse as long as four or five years after his last exposure in the Southwest Pacific. This implies that physicians must continue to consider the possibility of malaria in febrile illnesses in veterans. The future experience of the

armed forces and the Veterans Administration will be of help in clarifying this problem, just as use of the new antimalarial drugs<sup>15, 16</sup> offers hope of its eventual solution

### SUMMARY

A primary attack of vivax malaria occurring in an ex-serviceman twenty-seven months after his last exposure in an endemic area is reported

Such prolonged latent periods have not been reported in natural malaria. Primary attacks occurring eighteen months after discontinuance of quinacrine suppression have been observed, and the effect of this drug is suggested as a possible explanation for the delayed attack in this patient. If this, or similar cases, show a tendency to further relapses, it would indicate that a small number of malaria relapses may continue to occur for four to five years after the return of the last serviceman from endemic areas in the Southwest Pacific

2109 Adelbert Road

### REFERENCES

- 1 Boyd M F Present day problems of malaria infections *J A M A* 124 1179-1187 1944

- 2 Coggeshall, L. T. Malaria and filariasis in returning servicemen *Am J Trop Med* 25 177-184 1945
- 3 Faast, E. C. Clinical and public health aspects of malaria in United States from historical perspective *Am J Trop Med* 25 185-201 1945
- 4 Saper J J Malaria problem today: influence of wartime experience and research *J A M A* 132 623 627 1946
- 5 Gordon H H et al. Clinical features of relapsing Plasmodium vivax malaria in soldiers evacuated from South Pacific area. *Arch Int Med* 75 159 167 1945
- 6 Noe W L Jr, Greene C C Jr and Cheney G. Natural course of chronic Southwest Pacific malaria. *Am J M Sc* 211 215-219 1946
- 7 Bianco A A, Sanders G M, Levine A S and Cohn R. Long term observation of Plasmodium vivax malaria in returned servicemen. *U S Nav M Bull* 47 352 367 and 550-567 1947
- 8 Boyd M F Infection in intermediate host, symptomatology, general consideration. In *A Symposium on Human Malaria Publication No 15* 398 pp. Washington D C. American Association for the Advancement of Science 1941. Pp 163-182
- 9 London I M, Kane C A, Schroeder E F and Most H. Delayed primary attack of vivax malaria. *New Eng J Med* 235 406-410 1946
- 10 Hayman J M Jr. Personal communication
- 11 Page S G Jr and McCall J V Jr. Delay in diagnosing malaria after sulfadiazine therapy. 2 case reports. *South M J* 39 728-731 1946
- 12 Shute P G. Latency and long term relapses in benign tertian malaria. *Tr Roy Soc Trop Med & Hyg* 40 189 200 1946
- 13 Strong R P. *Stitt's Diagnosis, Prevention and Treatment of Tropical Diseases*. Seventh edition. 871 pp. Philadelphia: The Blakiston Company 1944
- 14 Baker B M and Platt D. Vivax relapse following continued atabrine suppressive medication: observations on malaria in infantry regiment. *Bull Johns Hopkins Hosp* 81 295 304 1947
- 15 Most H et al. Combined quinine plasmoquin treatment of vivax malaria: effect on relapse rate. *Am J M Sc* 212:550-560 1946
- 16 Saunders G M. Treatment of malaria. *J Missouri M A* 44 89 94 1947

## MEDICAL PROGRESS

### PROCTOLOGY

E PARKER HAYDEN, M D \*

BOSTON

IN a comprehensive bibliography prepared for the 1947 meeting of the American Proctologic Society numerous articles on nonmalignant and malignant lesions of the colon and rectum, published during 1946, were carefully listed and indexed, and some of them abstracted in greater or less detail. With perhaps an equal number in the literature of 1947, it is apparent that a complete review of them is a task too extensive for inclusion in this rather short article. Spectacular advances in this field are the exception, — not the rule, — and yet articles of value and interest, contributed both by those who limit their work to proctology and by those who do not, have appeared from time to time.

The American Proctologic Society, organized in 1899 and holding yearly meetings since that time, has always published its papers in a series of bound volumes entitled *Transactions of the American Proctologic Society*, until this year. The February, 1948, issue of the *American Journal of Surgery* was devoted exclusively to publication of the papers read at the 1947 meeting of the society.

\*Associate visiting surgeon, Massachusetts General Hospital

At this meeting, a paper by Courtney,<sup>1</sup> was given the Hermance award as being the best original paper presented on that occasion. Courtney reported the results of a study carried out in the anatomic laboratories of the Graduate School of the University of Pennsylvania under supervision of Professor Batson of the Anatomy Department, in an effort further to clarify the classification and mode of extension of perirectal abscesses. Eight cadavers were dissected in detail, and 40 cadavers were inspected while being dissected by others, both from above and below, and with the aid of sagittal, parasagittal and coronal sections.

Heretofore there have been described, and accepted as accurate, three deep spaces, — the retrorectal and the right and left pelvirectal spaces, — abscesses of which are recognized.

As a result of this study Courtney has identified a fourth deep space, to which he has given the name "posterior levator space." This space is formed by a division, close to the rectum, of the levator muscle attachment into a superior and inferior layer which produces a V-shaped flare with attachments at

different levels to the longitudinal muscle fibers of the rectum, thus creating a space, bounded by the longitudinal muscle of the rectum medially, by the superior and inferior muscle bundles of the levator above and below, and extending around the posterior surface of the rectum from side to side, decreasing in size and depth as the pubis is approached, and with its greatest size near the posterior midline.

Infection of this space arises by upward extension from one of the posterior crypts, and is characterized by formation of a deep abscess, not palpable externally but felt as a rounded swelling on intra-rectal palpation in the posterior midline.

Courtney advises incision in the midline posterior to the anus, spreading the fibers of the sphincter as they converge toward the coccyx. If the abscess has spread laterally a counterincision can be made lateral to the sphincter and as far forward as necessary.

#### PARASYMPATHETIC SUPPLY OF THE DISTAL COLON

On the basis of a dissection of 9 infant and 9 adult bodies, Lannon and Weller<sup>2</sup> found variations in parasympathetic distribution in practically every body, and in the two sides of any one body. On the left,

sympathetic fibers usually arise from the anterior aspect of the second and third sacral nerves within 1 cm. of their exit from the anterior sacral foramina. Well defined fibers pass anteriorly as the nervi erigentes, and from three to six moderately thick strands pass medially, upward and anteriorly, to the distal colon. The nerves are creamy white, and a tiny red blood vessel can be seen on the surface of the nerve—an identifying characteristic. Difficulty was encountered in tracing the fibers through the dense pelvic fascia, but it was possible to identify them in some of the dissections as giving off some fibers to the rectum just after piercing the fascia, the remainder passing down with the superior hemorrhoidal artery.

There was also found to be a connection of some fibers on the left with the inferior hypogastric plexus. At the level of the promontory the fibers leave the artery and pass across the left common iliac artery and upward into the mesentery of the bowel, where some fibers could be traced to the bowel itself as high as the midportion of the descending colon. They do not enter the bowel with the vessels, but independently.

On the right side the plan is similar in general except that the nerves tend to lie at a distance from the superior hemorrhoidal artery and in closer association with the inferior hypogastric plexus.

The authors believe that they have demonstrated several points of clinical interest—that in resections of the rectum and pelvic colon the parasympathetic vessels are bound to be destroyed—a fact that has always been considered to be true. On the other hand a periarterial stripping of the inferior mesen-

teric artery and presacral neurectomy should not interfere with the parasympathetic supply to any part of the colon, but in a high colonic resection the part of the colon lying above the point of resection and below the distal point of vagal parasympathetic supply will be deprived of its parasympathetic supply.

#### ANORECTAL AND URINARY DYSFUNCTION

McCrae<sup>3</sup> discusses the intimate relation between anorectal and urinary dysfunctions on the basis of the common blood supply and innervation of the two areas. The bladder and the anorectum both originate from the fetal cloaca in their embryologic stage. Each is supplied with blood from the hypogastric artery by its various branches, though the rectum also receives some of its blood by way of the superior hemorrhoidal artery from the inferior mesenteric.

Each organ is likewise innervated by the somatic, sympathetic and parasympathetic systems. Somatic supply is by way of the pudendal nerve from the second, third and fourth sacral vessels. It is through this nerve that the voluntary impulses of urination are carried. Another branch of the pudendal, the inferior hemorrhoidal nerve, supplies the anal region. The pudendal nerve is both motor and sensory and on this fact is best explained the retention of urine following hemorrhoidectomy and other anal procedures, owing to a reflex contraction of the external vesical sphincter following trauma to the perineal branch of the pudendal nerve.

#### PERFORATIONS OF THE COLON

Andresen<sup>4</sup> has gathered some interesting facts regarding perforations of the bowel during proctoscopy. His figures are based on 215 replies to questionnaires sent to 340 members of the American Gastro-Enterological Association and the American Proctologic Society. From 34 of these replies he received reports of 46 cases of perforation, which he has analyzed.

Onset with sudden pain occurred in only 2 patients (55 per cent).

Diagnosis was made by direct observation through the proctoscope in 25 cases (54 per cent).

In the 46 cases 21 patients had no other disease of sigmoid or rectum. There were 13 carcinomas, 5 others with diverticula in the sigmoid, 3 with ulcerative colitis, 2 with polyps, 1 with lymphopathia venereum, and 1 with hemorrhoids only. Nineteen patients, or 41 per cent, died, including the 3 patients who were not operated on.

Immediate operation showed a mortality of 8 per cent, and when operation was delayed one to six hours the mortality was 32 per cent, from six to twelve hours, 50 per cent, and over twelve hours 75 per cent.

The best results were obtained in 8 cases in which colostomy was performed, 2 with suture and 6

without suture of the perforation Only 1 of the 8 patients died In 23 cases in which the perforation was closed, but colostomy not done, there were 6 deaths Of 22 patients not operated upon, in the two series of cases, there were 13 deaths (59 per cent) Nine recovered

The over-all mortality in the 94 cases was 47 per cent Andresen emphasizes the importance of passing a proctoscope only under direct vision, and discontinuing the attempt if poor preparation, bleeding, spasm and so forth make it impossible to obtain a good view

I should like to urge, in addition to these precautions, that proctoscopic examinations not be made on patients under anesthesia, and in lithotomy position, if they can be avoided More information can be obtained, and with less risk, if proctoscopy is performed with the patient in the inverted, or in the knee-shoulder position, prior to anesthesia

Davis<sup>5</sup> reports 3 cases in which an enema tube, inserted through a colostomy stoma, perforated the sigmoid and permitted the enema fluid to enter the peritoneal cavity In 1 case immediate pain brought the patient to operation within 6 hours, and in the second case after three days, with signs of peritonitis, whereas the third patient was operated upon after three weeks with drainage of an abscess All recovered

This is an unusual occurrence though it has also happened in 2 of my patients who were taking their own enemas In 1, who had had for some time a colostomy for lymphopathia venerea with extensive rectal involvement, the perforation produced sudden pain with ensuing tenderness at one side of the stoma, but no fluid had been introduced and operation was never necessary, the small cavity, demonstrated by barium enema a little later, eventually obliterating itself My second patient came into the hospital with fever, distention and cramps, suggesting small-bowel obstruction After some decompression had been obtained with a Miller-Abbott tube, pus could be seen coming from the colostomy in small amount, the abscess having drained itself into the bowel In this case a colostomy was constructed at a higher point in the colon

#### PILONIDAL CYST AND SINUSES

Pilonidal-sinus problems seem to fall within the scope of this review by virtue of the proximity of the lesions to the anus and the natural gravitation of many of these patients to the offices and clinics of surgeons doing proctologic work Throughout the war, efforts were directed toward developing improved methods of reducing the healing period following operation, mostly by the use of primary closure in one form or another Many ways of accomplishing this have been described, and series of cases published, with more or less follow-up data, since Lahey described his method of sliding a flap of

skin, fat and fascia to the midline to fill in this poorly healing area

Pope<sup>6</sup> has reported a considerable experience at the Chelsea Naval Hospital with an operation that he devised, the principal feature of which is the sliding of a single mobilized section of gluteus muscle across the midline to obliterate the defect following excision of cyst and sinuses In 92 cases out of a series of 130, this operation was used, whereas 38 others were closed by primary suture without use of the sliding muscle graft Follow-up data were reserved for a subsequent article, but the results, so far as could be observed during the extended hospitalization often given to Army and Navy personnel, were very good

Success in achieving primary healing in pilonidal cyst excisions depends upon bacteriologic cleanliness of the lesion at time of operation, careful hemostasis and tissue handling, obliteration of dead space in the suturing process, and careful post-operative treatment, including chemotherapy

It is obvious, therefore, that good results will depend upon proper selection of patients, the use of a procedure best suited to the individual case, and upon the ability of the individual surgeon to carry through on the technical procedure and aftercare The open method still remains the most certain to produce a permanent healing

#### FISTULA

The old idea that most anal fistulas are tuberculous is once again refuted by a study that Jackman and Buie<sup>7</sup> carried out in 600 patients with anal fistula Of these only 11.5 per cent showed evidence of tuberculosis anywhere in the body, and in only 7 or 8 per cent was the fistula itself proved to be tuberculous There was no case of tuberculous fistula in a person who did not have tuberculosis elsewhere in the body These authors consider the guinea-pig inoculation with material from the fistula to be the best test of the nature of the fistula, though they admit that contamination of the area could occur from higher up in cases in which the histology of the fistula is negative for tuberculosis

Skir<sup>8</sup> has studied various reports in the literature, totaling 50 cases, in which carcinoma was considered to have developed from a previously existing fistula From this group he has selected 14 in which the fistula was known to have been present for at least ten years prior to the diagnosis of cancer, thereby strengthening the likelihood that the cancer really did supervene on the fistula To this group of 14 he adds 3 from the Brooklyn Hospital These 3 patients were elderly people, 2 of them Negroes, all with long histories of fistula — ten, thirty and fifty-five years of intermittent discharging sinus — and all presenting a similar picture that of a fungating, ulcerating tumor protruding from the fistulous buttock, through the skin of which it had ulcerated The pathological reports were

different levels to the longitudinal muscle fibers of the rectum, thus creating a space, bounded by the longitudinal muscle of the rectum medially, by the superior and inferior muscle bundles of the levator above and below, and extending around the posterior surface of the rectum from side to side, decreasing in size and depth as the pubis is approached, and with its greatest size near the posterior midline

Infection of this space arises by upward extension from one of the posterior crypts, and is characterized by formation of a deep abscess, not palpable externally but felt as a rounded swelling on intra-rectal palpation in the posterior midline

Courtney advises incision in the midline posterior to the anus, spreading the fibers of the sphincter as they converge toward the coccyx. If the abscess has spread laterally a counterincision can be made lateral to the sphincter and as far forward as necessary

#### PARASYMPATHETIC SUPPLY OF THE DISTAL COLON

On the basis of a dissection of 9 infant and 9 adult bodies, Lannon and Weller<sup>2</sup> found variations in parasympathetic distribution in practically every body, and in the two sides of any one body. On the left, the pelvic autonomic fibers usually arise from the anterior aspect of the second and third sacral nerves within 1 cm. of their exit from the anterior sacral foramina. Well defined fibers pass anteriorly as the *nervi erigentes*, and from three to six moderately thick strands pass medially, upward and anteriorly, to the distal colon. The nerves are creamy white, and a tiny red blood vessel can be seen on the surface of the nerve—an identifying characteristic. Difficulty was encountered in tracing the fibers through the dense pelvic fascia, but it was possible to identify them in some of the dissections as giving off some fibers to the rectum just after piercing the fascia, the remainder passing down with the superior hemorrhoidal artery.

There was also found to be a connection of some fibers on the left with the inferior hypogastric plexus. At the level of the promontory the fibers leave the artery and pass across the left common iliac artery and upward into the mesentery of the bowel, where some fibers could be traced to the bowel itself as high as the midportion of the descending colon. They do not enter the bowel with the vessels, but independently.

On the right side the plan is similar in general except that the nerves tend to lie at a distance from the superior hemorrhoidal artery and in closer association with the inferior hypogastric plexus.

The authors believe that they have demonstrated several points of clinical interest—that in resections of the rectum and pelvic colon the parasympathetic vessels are bound to be destroyed—a fact that has always been considered to be true. On the other hand a periarterial stripping of the inferior mesen-

teric artery and presacral neurectomy should not interfere with the parasympathetic supply to any part of the colon, but in a high colonic resection the part of the colon lying above the point of resection and below the distal point of vagal parasympathetic supply will be deprived of its parasympathetic supply.

#### ANORECTAL AND URINARY DYSFUNCTION

McCrae<sup>3</sup> discusses the intimate relation between anorectal and urinary dysfunctions on the basis of the common blood supply and innervation of the two areas. The bladder and the anorectum both originate from the fetal cloaca in their embryologic stage. Each is supplied with blood from the hypogastric artery by its various branches, though the rectum also receives some of its blood by way of the superior hemorrhoidal artery from the inferior mesenteric.

Each organ is likewise innervated by the somatic, sympathetic and parasympathetic systems. Somatic supply is by way of the pudendal nerve from the second, third and fourth sacral vessels. It is through this nerve that the voluntary impulses of urination are carried. Another branch of the pudendal, the inferior hemorrhoidal nerve, supplies the anal region. The pudendal nerve is both motor and sensory and on this fact is best explained the retention of urine following hemorrhoidectomy and other anal procedures, owing to a reflex contraction of the external vesical sphincter following trauma to the perineal branch of the pudendal nerve.

#### PERFORATIONS OF THE COLON

Andresen<sup>4</sup> has gathered some interesting facts regarding perforations of the bowel during proctoscopy. His figures are based on 215 replies to questionnaires sent to 340 members of the American Gastro-Enterological Association and the American Proctologic Society. From 34 of these replies he received reports of 46 cases of perforation, which he has analyzed.

Onset with sudden pain occurred in only 26 patients (55 per cent).

Diagnosis was made by direct observation through the proctoscope in 25 cases (54 per cent).

In the 46 cases 21 patients had no other disease of sigmoid or rectum. There were 13 carcinomas, 5 others with diverticula in the sigmoid, 3 with ulcerative colitis, 2 with polyps, 1 with lymphopathia venereum, and 1 with hemorrhoids only. Nineteen patients, or 41 per cent, died, including the 3 patients who were not operated on.

Immediate operation showed a mortality of 8 per cent, and when operation was delayed one to six hours the mortality was 32 per cent, from six to twelve hours, 50 per cent, and over twelve hours 75 per cent.

The best results were obtained in 8 cases in which colostomy was performed, 2 with suture and 6

without suture of the perforation. Only 1 of the 8 patients died. In 23 cases in which the perforation was closed, but colostomy not done, there were 6 deaths. Of 22 patients not operated upon, in the two series of cases, there were 13 deaths (59 per cent). Nine recovered.

The over-all mortality in the 94 cases was 47 per cent. Andresen emphasizes the importance of passing a proctoscope only under direct vision, and discontinuing the attempt if poor preparation, bleeding, spasm and so forth make it impossible to obtain a good view.

I should like to urge, in addition to these precautions, that proctoscopic examinations not be made on patients under anesthesia, and in lithotomy position, if they can be avoided. More information can be obtained, and with less risk, if proctoscopy is performed with the patient in the inverted, or in the knee-shoulder position, prior to anesthesia.

Davis<sup>5</sup> reports 3 cases in which an enema tube, inserted through a colostomy stoma, perforated the sigmoid and permitted the enema fluid to enter the peritoneal cavity. In 1 case immediate pain brought the patient to operation within 6 hours, and in the second case after three days, with signs of peritonitis, whereas the third patient was operated upon after three weeks with drainage of an abscess. All recovered.

This is an unusual occurrence though it has also happened in 2 of my patients who were taking their own enemas. In 1, who had had for some time a colostomy for lymphopathia venerea with extensive rectal involvement, the perforation produced sudden pain with ensuing tenderness at one side of the stoma, but no fluid had been introduced and operation was never necessary; the small cavity, demonstrated by barium enema a little later, eventually obliterating itself. My second patient came into the hospital with fever, distention and cramps, suggesting small-bowel obstruction. After some decompression had been obtained with a Miller-Abbott tube, pus could be seen coming from the colostomy in small amount, the abscess having drained itself into the bowel. In this case a colostomy was constructed at a higher point in the colon.

#### PILONIDAL CYST AND SINUSES

Pilonidal-sinus problems seem to fall within the scope of this review by virtue of the proximity of the lesions to the anus and the natural gravitation of many of these patients to the offices and clinics of surgeons doing proctologic work. Throughout the war, efforts were directed toward developing improved methods of reducing the healing period following operation, mostly by the use of primary closure in one form or another. Many ways of accomplishing this have been described, and series of cases published, with more or less follow-up data, since Lahey described his method of sliding a flap of

skin, fat and fascia to the midline to fill in this poorly healing area.

Pope<sup>6</sup> has reported a considerable experience at the Chelsea Naval Hospital with an operation that he devised, the principal feature of which is the sliding of a single mobilized section of gluteus muscle across the midline to obliterate the defect following excision of cyst and sinuses. In 92 cases out of a series of 130, this operation was used, whereas 38 others were closed by primary suture without use of the sliding muscle graft. Follow-up data were reserved for a subsequent article, but the results, so far as could be observed during the extended hospitalization often given to Army and Navy personnel, were very good.

Success in achieving primary healing in pilonidal cyst excisions depends upon bacteriologic cleanliness of the lesion at time of operation, careful hemostasis and tissue handling, obliteration of dead space in the suturing process, and careful post-operative treatment, including chemotherapy.

It is obvious, therefore, that good results will depend upon proper selection of patients, the use of a procedure best suited to the individual case, and upon the ability of the individual surgeon to carry through on the technical procedure and aftercare. The open method still remains the most certain to produce a permanent healing.

#### FISTULA

The old idea that most anal fistulas are tuberculous is once again refuted by a study that Jackman and Buie<sup>7</sup> carried out in 600 patients with anal fistula. Of these only 11.5 per cent showed evidence of tuberculosis anywhere in the body and in only 7 or 8 per cent was the fistula itself proved to be tuberculous. There was no case of tuberculous fistula in a person who did not have tuberculosis elsewhere in the body. These authors consider the guinea-pig inoculation with material from the fistula to be the best test of the nature of the fistula, though they admit that contamination of the area could occur from higher up in cases in which the histology of the fistula is negative for tuberculosis.

Skir<sup>8</sup> has studied various reports in the literature, totaling 50 cases, in which carcinoma was considered to have developed from a previously existing fistula. From this group he has selected 14 in which the fistula was known to have been present for at least ten years prior to the diagnosis of cancer, thereby strengthening the likelihood that the cancer really did supervene on the fistula. To this group of 14 he adds 3 from the Brooklyn Hospital. These 3 patients were elderly people, 2 of them Negroes, all with long histories of fistula — ten, thirty and fifty-five years of intermittent discharging sinus — and all presenting a similar picture that of a fungating, ulcerating tumor protruding from the fistulous buttock, through the skin of which it had ulcerated. The pathological reports were

different levels to the longitudinal muscle fibers of the rectum, thus creating a space, bounded by the longitudinal muscle of the rectum medially, by the superior and inferior muscle bundles of the levator above and below, and extending around the posterior surface of the rectum from side to side, decreasing in size and depth as the pubis is approached, and with its greatest size near the posterior midline.

Infection of this space arises by upward extension from one of the posterior crypts, and is characterized by formation of a deep abscess, not palpable externally but felt as a rounded swelling on intra-rectal palpation in the posterior midline.

Courtney advises incision in the midline posterior to the anus, spreading the fibers of the sphincter as they converge toward the coccyx. If the abscess has spread laterally a counterincision can be made lateral to the sphincter and as far forward as necessary.

#### PARASYMPATHETIC SUPPLY OF THE DISTAL COLON

On the basis of a dissection of 9 infant and 9 adult bodies, Lannon and Weller<sup>2</sup> found variations in parasympathetic distribution in practically every body, and in the two sides of any one body. On the left, the pelvic autonomic fibers usually arise from the anterior aspect of the second and third sacral nerves within 1 cm. of their exit from the anterior sacral foramina. Well defined fibers pass anteriorly as the nervi erigentes, and from three to six moderately thick strands pass medially, upward and anteriorly, to the distal colon. The nerves are creamy white, and a tiny red blood vessel can be seen on the surface of the nerve—an identifying characteristic. Difficulty was encountered in tracing the fibers through the dense pelvic fascia, but it was possible to identify them in some of the dissections as giving off some fibers to the rectum just after piercing the fascia, the remainder passing down with the superior hemorrhoidal artery.

There was also found to be a connection of some fibers on the left with the inferior hypogastric plexus. At the level of the promontory the fibers leave the artery and pass across the left common iliac artery and upward into the mesentery of the bowel, where some fibers could be traced to the bowel itself as high as the midportion of the descending colon. They do not enter the bowel with the vessels, but independently.

On the right side the plan is similar in general except that the nerves tend to lie at a distance from the superior hemorrhoidal artery and in closer association with the inferior hypogastric plexus.

The authors believe that they have demonstrated several points of clinical interest—that in resections of the rectum and pelvic colon the parasympathetic vessels are bound to be destroyed—a fact that has always been considered to be true. On the other hand a periarterial stripping of the inferior mesen-

teric artery and presacral neurectomy should not interfere with the parasympathetic supply to any part of the colon, but in a high colonic resection the part of the colon lying above the point of resection and below the distal point of vagal parasympathetic supply will be deprived of its parasympathetic supply.

#### ANORECTAL AND URINARY DYSFUNCTION

McCrae<sup>3</sup> discusses the intimate relation between anorectal and urinary dysfunctions on the basis of the common blood supply and innervation of the two areas. The bladder and the anorectum both originate from the fetal cloaca in their embryologic stage. Each is supplied with blood from the hypogastric artery by its various branches, though the rectum also receives some of its blood by way of the superior hemorrhoidal artery from the inferior mesenteric.

Each organ is likewise innervated by the somatic, sympathetic and parasympathetic systems. Somatic supply is by way of the pudendal nerve from the second, third and fourth sacral vessels. It is through this nerve that the voluntary impulses of urination are carried. Another branch of the pudendal, the inferior hemorrhoidal nerve, supplies the anal region. The pudendal nerve is both motor and sensory and on this fact is best explained the retention of urine following hemorrhoidectomy and other anal procedures, owing to a reflex contraction of the external vesical sphincter following trauma to the perineal branch of the pudendal nerve.

#### PERFORATIONS OF THE COLON

Andresen<sup>4</sup> has gathered some interesting facts regarding perforations of the bowel during proctoscopy. His figures are based on 215 replies to questionnaires sent to 340 members of the American Gastro-Enterological Association and the American Proctologic Society. From 34 of these replies he received reports of 46 cases of perforation, which he has analyzed.

Onset with sudden pain occurred in only 26 patients (55 per cent).

Diagnosis was made by direct observation through the proctoscope in 25 cases (54 per cent).

In the 46 cases 21 patients had no other disease of sigmoid or rectum. There were 13 carcinomas, 5 others with diverticula in the sigmoid, 3 with ulcerative colitis, 2 with polyps, 1 with lymphopathia venereum, and 1 with hemorrhoids only. Nineteen patients, or 41 per cent, died, including the 3 patients who were not operated on.

Immediate operation showed a mortality of 8 per cent, and when operation was delayed one to six hours the mortality was 32 per cent, from six to twelve hours, 50 per cent, and over twelve hours 75 per cent.

The best results were obtained in 8 cases in which colostomy was performed, 2 with suture and 6

are then undercut. Complete closure of the wounds occurs in about a month, and Kallet advises digital dilations of the anus periodically.

The difference between this procedure and the old undercutting operation, as advocated by Ball, lies in the excision of skin that characterizes the former, whereas in the latter little or no skin is sacrificed.

Discussion of this paper brought forth varying reactions, including emphasis on the value of subcutaneous alcohol injection as a substitute for too radical excision of skin and mention of the value of including some degree of anal-canal surgery — removal of papillae and crypts, and partial incision of the anal ring to relieve tightness — in association with the external work. Kallet, in closing the discussion, strongly urged that no intra-anal cutting be done and emphasized that in most of these cases the anal canal is found to be quite normal. In the last statement I agree with him.

#### HEMOSTATIC AGENTS

Rosser<sup>12</sup> reported, as an experimental study in 141 anorectal operations, the use of gelatin sponge (gel foam), oxidized cotton or oxidized gauze as a packing in the wounds at time of operation. Fibrin foam was not tried because of its origin in human blood, which might make it less available. Rosser cites the experimental work of several authors indicating that gelatin sponge is nonirritating and gradually absorbable. He used it in 43 anorectal wounds and found that it usually disappeared in forty-eight hours, though in large surface wounds it remained four days.

Oxidized gauze and cotton were used in 98 cases, the best results being obtained with small pieces placed directly in the cuts. Hemostasis was aided, and the material liquefied readily so that it did not occlude drainage. Rosser used these materials in most of the common types of anal operations as well as in pilonidal wounds.

It is probably superfluous to add a word of emphasis, with which Rosser would be the first to agree, that the above devices are not a substitute, but only an adjunct to careful ligation of bleeding points, particularly arterial bleeders.

#### RELIEF OF PAIN

Mentzer<sup>13</sup> employed the oil anesthetic "anucaine" in 1510 cases, with satisfactory relief of postoperative pain and a decrease in the number of patients requiring catheterization. This particular preparation contains 0.5 per cent procaine, 1 per cent butesin, 5 per cent anesthesin, 5 per cent benzyl alcohol and as much sweet almond oil as necessary. The solution was injected through three points of entry, 2.5 cm. to the right and left of the anus and directly posterior to it, 2.5 to 5 cc. being placed in each lateral area and 5 cc. posteriorly. The solution was injected at three levels — subcutaneously

into the external sphincter and into the levator-muscle attachment. An average hospital stay of only four days and definite decrease in pain were attributed to the use of this preparation.

#### PROLAPSE OF THE RECTUM

Hayden<sup>14</sup> reviewed the experience at the Massachusetts General Hospital with the surgical treatment of complete rectal prolapse over a thirty-four-year period (1912 through 1946), with such follow-up data as could be obtained. During this period 60 patients were operated upon one or more times by 23 different surgeons, utilizing nine or ten different procedures in various combinations. The largest number of patients operated by one surgeon was 18, and the next largest 9, and so on down the line, illustrating the fact that anyone's experience is bound to be limited in this condition which is not encountered with great frequency. The Moschowitz operation (obliteration of the cul-de-sac of Douglas) was used alone or in combination with other procedures, in 43 cases. Other procedures consisted of fixation of uterus or of cervical stump, suspension of uterus or cervical stump, Mikulicz resection of sigmoid or simple fixation of sigmoid to left lateral pelvic wall, posterior fixation of rectum by various methods — Lockhart-Mummery, Tuttle and Maes-Rives — DeLorme, amputation of the prolapse by surgical excision or by compression ligature and finally, linear cauterization. Good and poor results were obtained by most of these methods, some of the best results being achieved by combined procedures. The Moschowitz operation, with or without modifications or additions, is based on a sound conception of the underlying disease, and good results may be expected, also, from use of the DeLorme operation and by excision of the prolapse.

Haves and Burr,<sup>15</sup> in reporting on 9 cases of complete rectal prolapse seen in a period of 9 years, have concluded that the procedure advocated by Graham in 1942, with a modification of their own, is an eminently satisfactory way of dealing with this condition. Graham's procedure includes an incision of the pelvic peritoneum and freeing of the rectum anteriorly and posteriorly as in abdominoperineal resection for cancer. The levators are then sutured together anteriorly. Haves and Burr modified this in 1 case by suturing the lateral ligaments across in front of the rectum, thus taking up their slack. Then, with the pelvic portion of the colon held taut, the excess peritoneum was infolded and sutured around the rectum, thus obliterating the previously deep cul-de-sac. A new bed for the sigmoid was then created by incising the lateral parietal peritoneum for 10 or 12 cm. and anchoring the taut sigmoid to the peritoneal edges raised from the deeper tissues.

Dunphy,<sup>16</sup> sharing the dissatisfaction of most surgeons about the treatment of complete prolapse, has utilized a combined abdominal and perineal

all "mucinous carcinoma" The fact that 2 of Skir's 3 patients were Negroes is also of interest because of the very low incidence of cancer of the rectum and anus in that race, as borne out by the experience of other men whose hospital clinics have a large Negro attendance

These reports are of value, and presumably the occasional development of carcinoma at the site of a chronic fistula of long duration may be considered to bear a relation to the chronic irritation of the long-continued infectious process If there is a direct relation these cases can be considered as demonstrating a good reason for dealing with fistulas reasonably promptly and eradicating them However, it seems unnecessary to resort to the fear of cancer as an argument in convincing people that their fistulas should be operated upon when the obvious inconvenience and discomfort of recurring abscesses and of intermittent or continuous drainage are sufficient reasons for instituting surgical treatment promptly

Kenney<sup>9</sup> reports his experience with a method of excision and suture of anal fistulas, carried out in 12 cases with healing in 11 and with no recurrences for follow-up periods extending from two to six months After a preoperative preparation with sulfanilamide and castor oil he carefully cuts around the external opening, after first passing a probe through the sinus, and then incises radially toward the anus but not into the tract and not across the mucocutaneous junction The sinus is dissected out, free of the muscle, after which the internal opening is encircled and the sinus removed The tissues are then infiltrated with penicillin solution, using 20 to 100 cc of a solution containing 2000 units per cubic centimeter and after careful hemostasis the wound is obliterated with fine cotton sutures in layers, the internal opening closed with fine chromic and the external opening with 80-gauge or 120-gauge cotton Patients leave the hospital in several days

This is a praiseworthy attempt to improve the technic of dealing with anal fistula and is in line with the advances made in primary union after pilonidal-sinus excisions It is perhaps only fair, however, to emphasize the difficulties encountered by many surgeons in attempts to obtain primary healing in the anal area, and it is probable that most surgeons will have a higher percentage of cures if they adhere to open incision and drainage operations

#### PRURITUS ANI

Attempts to relieve or cure pruritus of the anal region have embraced as wide a variety of therapeutic agents and methods as any pathologic condition, and yet no striking progress has been made in establishing its cause or in finding a permanent cure

Frankfeldt<sup>10</sup> calls attention to the well known fact that the majority of people with hemorrhoids, fissures, fistulas, incontinent sphincter, colitis and so forth do not complain of itching despite the fecal soiling, mucus and purulent discharge that often accompany these conditions Therefore, it seems to him logical to assume that two factors operate in people who have pruritus and a sensitization of the skin, and an irritant (allergen or antigen) With this premise he concludes that anal pruritus must be an *allergic manifestation*

A careful history, dealing with all sorts of factors that might contribute to the establishment of an allergy, is taken from each patient by means of an extensive questionnaire, and as a result Frankfeldt believes that he can classify the cases into five groups, allergic to food, fungus and bacteria, contact dermatitis, drugs and atopans

In mentioning the various substances to which an allergy might exist Frankfeldt presents a list so long that it is hard to see how anyone could escape having pruritus

He believes that histamine is in some way concerned with the problem and has employed the antihistaminic agent, pyribenzamine, in treatment, giving 50 to 150 mg after each meal and at 10 p m This plan was carried out in 90 patients with 85 to 100 per cent relief from itching in 57 Of the 57 he considered 26 to have a food allergy, 10 a fungus allergy, 12 contact dermatitis, 6 a drug allergy, and 3 an atopic dermatitis An ointment of 2 per cent pyribenzamine in a water-washable base was also used in 11 cases, with relief only in patients who had also experienced relief from oral administration of the drugs In 33 patients there was no relief

Instructions regarding hygienic measures were given to the patients in all cases

In discussion of this paper Belknap reported only 13 per cent good results in his experience with pyribenzamine, whereas Terrell emphasized the role of fungi as of prime importance

All in all proctologists are not much farther along toward a cure of pruritus ani than they were thirty years ago

Kallet<sup>11</sup> reports gratifying relief in 92 per cent of 100 cases of intractable pruritus ani subjected to a combined excision and under-cutting operation, which he calls "the clover-leaf operation" because of the appearance of the area following excision of three or four elliptical segments of perianal skin Patients selected for this procedure were all chronic cases with symptoms of long duration — up to twenty years Most of them had had various types of treatment — such as ointments, x-rays, injections and other rectal surgery The operation is best suited to patients with localized thickening, skin folds, lichenification and hypertrophy of the perianal skin

The incisions are made only up to the anal verge, not into it, and strips of skin about 0.6 cm wide are left between the elliptical incisions These bands

are then undercut. Complete closure of the wounds occurs in about a month, and Kallet advises digital dilatations of the anus periodically.

The difference between this procedure and the old undercutting operation, as advocated by Ball, lies in the excision of skin that characterizes the former, whereas in the latter little or no skin is sacrificed.

Discussion of this paper brought forth varying reactions, including emphasis on the value of subcutaneous alcohol injection as a substitute for too radical excision of skin and mention of the value of including some degree of anal-canal surgery — removal of papillae and crypts, and partial incision of the anal ring to relieve tightness — in association with the external work. Kallet, in closing the discussion, strongly urged that no intra-anal cutting be done and emphasized that in most of these cases the anal canal is found to be quite normal. In the last statement I agree with him.

#### HEMOSTATIC AGENTS

Rosser<sup>12</sup> reported, as an experimental study in 141 anorectal operations, the use of gelatin sponge (gel foam), oxidized cotton or oxidized gauze as a packing in the wounds at time of operation. Fibrin foam was not tried because of its origin in human blood, which might make it less available. Rosser cites the experimental work of several authors indicating that gelatin sponge is nonirritating and gradually absorbable. He used it in 43 anorectal wounds and found that it usually disappeared in forty-eight hours, though in large surface wounds it remained four days.

Oxidized gauze and cotton were used in 98 cases, the best results being obtained with small pieces placed directly in the cuts. Hemostasis was aided, and the material liquefied readily so that it did not occlude drainage. Rosser used these materials in most of the common types of anal operations as well as in pilonidal wounds.

It is probably superfluous to add a word of emphasis, with which Rosser would be the first to agree, that the above devices are not a substitute, but only an adjunct to careful ligation of bleeding points, particularly arterial bleeders.

#### RELIEF OF PAIN

Mentzer<sup>13</sup> employed the oil anesthetic "anucaine" in 1510 cases, with satisfactory relief of postoperative pain and a decrease in the number of patients requiring catheterization. This particular preparation contains 0.5 per cent procaine, 1 per cent butesin, 5 per cent anesthesin, 5 per cent benzyl alcohol and as much sweet almond oil as necessary. The solution was injected through three points of entry, 2.5 cm. to the right and left of the anus and directly posterior to it, 2.5 to 5 cc. being placed in each lateral area and 5 cc. posteriorly. The solution was injected at three levels — subcutaneously

into the external sphincter and into the levator-muscle attachment. An average hospital stay of only four days and definite decrease in pain were attributed to the use of this preparation.

#### PROLAPSE OF THE RECTUM

Hayden<sup>14</sup> reviewed the experience at the Massachusetts General Hospital with the surgical treatment of complete rectal prolapse over a thirty-four-year-period (1912 through 1946), with such follow-up data as could be obtained. During this period 60 patients were operated upon one or more times by 23 different surgeons, utilizing nine or ten different procedures in various combinations. The largest number of patients operated by one surgeon was 18, and the next largest 9, and so on down the line, illustrating the fact that anyone's experience is bound to be limited in this condition, which is not encountered with great frequency. The Moschowitz operation (obliteration of the cul-de-sac of Douglas) was used, alone or in combination with other procedures, in 43 cases. Other procedures consisted of fixation of uterus or of cervical stump, suspension of uterus or cervical stump, Mikulicz resection of sigmoid or simple fixation of sigmoid to left lateral pelvic wall, posterior fixation of rectum by various methods — Lockhart-Mummery, Tuttle and Maes-Rives — DeLorme, amputation of the prolapse by surgical excision or by compression ligature and, finally, linear cauterization. Good and poor results were obtained by most of these methods, some of the best results being achieved by combined procedures. The Moschowitz operation, with or without modifications or additions, is based on a sound conception of the underlying disease, and good results may be expected, also, from use of the DeLorme operation and by excision of the prolapse.

Haves and Burr,<sup>15</sup> in reporting on 9 cases of complete rectal prolapse seen in a period of 9 years, have concluded that the procedure advocated by Graham in 1942, with a modification of their own, is an eminently satisfactory way of dealing with this condition. Graham's procedure includes an incision of the pelvic peritoneum and freeing of the rectum anteriorly and posteriorly as in abdominoperineal resection for cancer. The levators are then sutured together anteriorly. Haves and Burr modified this in 1 case by suturing the lateral ligaments across in front of the rectum, thus taking up their slack. Then, with the pelvic portion of the colon held taut, the excess peritoneum was infolded and sutured around the rectum, thus obliterating the previously deep cul-de-sac. A new bed for the sigmoid was then created by incising the lateral parietal peritoneum for 10 or 12 cm. and anchoring the taut sigmoid to the peritoneal edges raised from the deeper tissues.

Dunphy,<sup>16</sup> sharing the dissatisfaction of most surgeons about the treatment of complete prolapse, has utilized a combined abdominal and perineal

operation in 4 patients, with satisfaction to the patients and to himself though the follow-up period had not exceeded a year and eight months in any of the 4 at the time he wrote the paper. The operation described combines the best features of several of the radical procedures previously in use and is done in two stages—the perineal part first. It embraces circular amputation of the external prolapse, excision of the peritoneal hernial sac so far as accessible from below, suture of the levators anteriorly, and reconstruction of the lumen of the bowel by a combination of interrupted and short continuous sutures, to eliminate or reduce the degree of narrowing at the suture line.

A week of preliminary preparation with sulfathaladine to diminish the bacterial flora in the bowel is advocated, and during this time, also, the patient is encouraged to build up sphincter tone by numerous voluntary contractions of the muscle—"a thousand times a day."

Some days later the abdomen is opened and the rectum mobilized as in the abdominoperineal resection for cancer, after which some deep sutures are placed laterally, including peritoneum and fascia and lateral ligaments. The cul-de-sac is then obliterated by pursestring sutures, as in the Moschcowitz operation, and the pelvic portion of the colon anchored to the lateral wall of the pelvis with interrupted silk sutures.

### COLITIS

Although the etiology of ulcerative colitis is still unknown, various experiments in the treatment of the disease continue to be reported in the literature. Gill<sup>17</sup> has utilized mucosa from the small intestine, particularly the jejunum, of pigs, on the theory that ulcerative colitis may be due to a deficiency of some constituent normally supplied by the mucosa of the small intestine. The mucosa is given in the form of a desiccated raw preparation, one ounce (equivalent to one pound of the original mucosa) being given daily.

Nasio<sup>18</sup> has utilized a colloidal preparation similar to the intestinal juices, giving it by the drip method. Alvarez<sup>19</sup> emphasizes the value of amino acid therapy in ulcerative colitis to make up for the loss of protein in the evacuations.

Kiefer and Jordan<sup>20</sup> presented before the American Proctologic Society an analysis of 430 cases of ulcerative colitis from the Lahey Clinic. Mention was made of the psychosomatic factor in this disease, of the unexplainable remissions and exacerbations and of its characteristic proctoscopic picture.

The proctologic complications occurring in this series consisted of perianal abscess in 12 per cent of cases, 14 strictures, 5 severe perianal skin infections and 25 cases of accompanying hemorrhoids or fissures. The authors also stated that hemorrhoidectomy had been performed in a good many

cases before they came to the clinic, presumably by surgeons who were not aware of the true diagnosis.

Adenocarcinoma developed in 7 per cent of the long-standing cases, possibly superimposed on true polyps that existed coincidentally.

In the 430 cases, the rectum alone was involved in 73, or 17 per cent. Involvement of rectum and part or all of the left portion of the colon occurred in 92 cases, or 21 per cent, and in 242 cases, or 56 per cent, the right portion of the colon was also involved. A fourth group—cases with segmental colitis and no rectal involvement—numbered 23, or 6 per cent. Medical measures in treatment were designed to control diarrhea, malnutrition, blood loss and anemia and sepsis. Emphasis was laid on the term "control" rather than "cure"—a distinction with which all agree in the management of this disease.

In the milder cases fever therapy, by means of gradually increasing doses of typhoid vaccine, has been used with gratifying results, and the elimination of causes of psychic trauma is desirable if possible.

Medical treatment in 34 cases with proctitis alone resulted in control of the disease that was good in 16, fair in 9 and poor in 9. Of 84 cases involving only the descending colon good control was obtained in 22, fair in 13 and poor in 28. In the group with generalized colitis (160 patients) the results were as follows: good control in 37, fair in 11 and poor in 77, whereas in the segmental group of 14 cases good control of the disease resulted in 5, fair in none and poor in 6.

With their experience of obtaining distinct improvement in most patients after ileostomy the authors believe that to delay this measure over a week in a patient with spiking temperature and evidence of increasing toxicity is a very risky postponement.

There were 32 "emergency" ileostomies performed, with 75 per cent mortality. For this reason every attempt is made to anticipate the need for ileostomy to avoid the necessity for an emergency procedure in a poor-risk patient. Elective ileostomy in 76 patients yielded a mortality of only 6.5 per cent.

Partial or complete colectomy was performed in 93 patients—a total of 146 different procedures—with an operative mortality of 8.2 per cent and a case mortality of 12.8 per cent.

The König-Rutzen bag is considered to be the best appliance for ileostomy control, since it is cemented to the skin and if properly applied can be made leak tight both day and night.

### POLYPS

Binkley and Sunderland<sup>21</sup> classify benign adenomas of the colon as areas of hyperplasia, adenomas and papillary adenomas—the second group

being most frequently encountered. Emphasis is laid on the uncertainty of pathological diagnosis in some cases owing to the fact that early malignant change in a small area may be easily overlooked. The importance of recognizing clinically the characteristics of malignant change is also stressed — the induration, ulceration and bleeding on slight trauma and the color of the lesion. Treatment varies with size and location of the lesion — surgical excision, removal with a snare or electrocoagulation. Radiation is reserved for the polyps that cannot be completely removed, and can be given either by external application of x-rays or by intrarectal application of radium to the surface of the lesion or in the form of gold radon seeds. Once in a while the rectum must be removed completely to eradicate a lesion, particularly if the base is suspicious of cancer.

Swinton<sup>22</sup> reported the presence of polyps in the colons of 311 of 1843 patients coming to autopsy at the New England Deaconess Hospital. In 42 of the 311 there were multiple lesions. Over 50 per cent were within reach of a 25-cm sigmoidoscope.

Of 22 cases reported in this paper, very early malignant change in the polyp but not involving the stalk was found in 12 cases, and a local removal was performed. All patients had had bleeding as a symptom. Two of these also had a later radical operation, but no cancer could be found in the specimens. Of the group, 10 had tumors in the colon — 8 in the sigmoid and 2 in the descending colon.

In 41 cases with polyps, removal was accomplished by the abdominal route. There was no evidence of malignant change in 31 of these. Bleeding

was a symptom in 38 of the 41 cases. One death occurred.

270 Commonwealth Avenue

## REFERENCES

- 1 Courtney, H. Posterior levator space abscess. *Am J Surg* 75:405-412, 1948.
- 2 Lannon, J. and Weller, E. Parasympathetic supply of distal colon. *Brit J Surg* 34:373-378, 1947.
- 3 McCrae, L. E. Management of vesical dysfunction in anorectal disease. *Tr Am Proct Soc* 1946. Pp 560-573.
- 4 Andresen, A. F. R. Perforations from proctoscopy. *Gastroenterology* 9:52-53, 1947.
- 5 Davis, C. Jr. Enema tube perforation of colon. *Ann Surg* 126:377-379, 1947.
- 6 Pope, C. E., and Hndson, H. W. Pilonidal sinns: review of 130 consecutive cases in which patients were treated by closure, new closed operative method and management. *Arch Surg* 52:680-700, 1946.
- 7 Jackman, R. J. and Buie, L. A. Tuberculosis and anal fistula. *J A M A* 130:630-632, 1946.
- 8 Skir, I. Mucinous carcinoma associated with fistulas of long standing. *Am J Surg* 75:285-289, 1948.
- 9 Kenney, J. M. Successful method for securing primary wound healing after resection of fistulae in ano: preliminary report. *Ann. Surg* 126:320-323, 1947.
- 10 Frankfeldt, F. M. Pyribenzamine: its role in the treatment of pruritus ani. *Am J Surg* 75:307-312, 1948.
- 11 Kallet, H. I. Clover leaf operation for pruritus ani. *Tr Am Proct Soc* 1946. Pp 470-477.
- 12 Rosser, C. New hemostatic dressings in anorectal surgery. *South M J* 39:921-925, 1946.
- 13 Mentzer, C. G. Evaluation of oil soluble anesthetics in proctologic surgery: based on series of 1510 cases. *South. M J* 40:186-189, 1947.
- 14 Hayden, E. P. Prolapse of rectum. *S. Clin. North America* 27:1062-1070, 1947.
- 15 Hayes, H. T. and Burr, H. B. Treatment of complete prolapse of rectum. *Am J Surg* 75:358-364, 1948.
- 16 Dnnphy, J. E. Combined perineal and abdominal operation for repair of rectal prolapse. *Surg Gynec & Obs.* 86:493-498, 1948.
- 17 Gill, A. M. Treatment of ulcerative colitis with intestinal mucosa. *Proc Roy Soc Med* 39:517-519, 1946.
- 18 Nasio, J. Continuous drip treatment for chronic ulcerative colitis: preliminary report. *Am J Digest Dis* 13:252-255, 1946.
- 19 Alvarez, W. C. Ulcerative colitis — panel discussion. *J A M A* 132:980, 1946.
- 20 Kiefer, E. D. and Jordan, S. M. Review of problem of chronic ulcerative colitis. *Tr Am Proct Soc* 1946. Pp 487-506.
- 21 Binkley, G. E. and Sniderland, D. A. Diagnosis and treatment of papillary adenomas of rectum. *Am J Surg* 75:365-368, 1948.
- 22 Swinton, N. W. Diagnosis and treatment of mucosal polyps of rectum and colon with early malignant change. *Am J Surg* 75:369-379, 1948.

operation in 4 patients, with satisfaction to the patients and to himself though the follow-up period had not exceeded a year and eight months in any of the 4 at the time he wrote the paper. The operation described combines the best features of several of the radical procedures previously in use and is done in two stages — the perineal part first. It embraces circular amputation of the external prolapse, excision of the peritoneal hernial sac so far as accessible from below, suture of the levators anteriorly, and reconstruction of the lumen of the bowel by a combination of interrupted and short continuous sutures, to eliminate or reduce the degree of narrowing at the suture line.

A week of preliminary preparation with sulfathaladine to diminish the bacterial flora in the bowel is advocated, and during this time, also, the patient is encouraged to build up sphincter tone by numerous voluntary contractions of the muscle — “a thousand times a day.”

Some days later the abdomen is opened and the rectum mobilized as in the abdominoperineal resection for cancer, after which some deep sutures are placed laterally, including peritoneum and fascia and lateral ligaments. The cul-de-sac is then obliterated by pursestring sutures, as in the Moschcowitz operation, and the pelvic portion of the colon anchored to the lateral wall of the pelvis with interrupted silk sutures.

### COLITIS

Although the etiology of ulcerative colitis is still unknown, various experiments in the treatment of the disease continue to be reported in the literature. Gill<sup>17</sup> has utilized mucosa from the small intestine, particularly the jejunum, of pigs, on the theory that ulcerative colitis may be due to a deficiency of some constituent normally supplied by the mucosa of the small intestine. The mucosa is given in the form of a desiccated raw preparation, one ounce (equivalent to one pound of the original mucosa) being given daily.

Nasio<sup>18</sup> has utilized a colloidal preparation similar to the intestinal juices, giving it by the drip method.

Alvarez<sup>19</sup> emphasizes the value of amino acid therapy in ulcerative colitis to make up for the loss of protein in the evacuations.

Kiefer and Jordan<sup>20</sup> presented before the American Proctologic Society an analysis of 430 cases of ulcerative colitis from the Lahey Clinic. Mention was made of the psychosomatic factor in this disease, of the unexplainable remissions and exacerbations and of its characteristic proctoscopic picture.

The proctologic complications occurring in this series consisted of perianal abscess in 12 per cent of cases, 14 strictures, 5 severe perianal skin infections and 25 cases of accompanying hemorrhoids or fissures. The authors also stated that hemorrhoidectomy had been performed in a good many

cases before they came to the clinic, presumably by surgeons who were not aware of the true diagnosis.

Adenocarcinoma developed in 7 per cent of the long-standing cases, possibly superimposed on true polyps that existed coincidentally.

In the 430 cases, the rectum alone was involved in 73, or 17 per cent. Involvement of rectum and part or all of the left portion of the colon occurred in 92 cases, or 21 per cent, and in 242 cases, or 56 per cent, the right portion of the colon was also involved. A fourth group — cases with segmental colitis and no rectal involvement — numbered 23, or 6 per cent. Medical measures in treatment were designed to control diarrhea, malnutrition, blood loss and anemia and sepsis. Emphasis was laid on the term “control” rather than “cure” — a distinction with which all agree in the management of this disease.

In the milder cases fever therapy, by means of gradually increasing doses of typhoid vaccine, has been used with gratifying results, and the elimination of causes of psychic trauma is desirable if possible.

Medical treatment in 34 cases with proctitis alone resulted in control of the disease that was good in 16, fair in 9 and poor in 9. Of 84 cases involving only the descending colon good control was obtained in 22, fair in 13 and poor in 28. In the group with generalized colitis (160 patients) the results were as follows: good control in 37, fair in 11 and poor in 77, whereas in the segmental group of 14 cases good control of the disease resulted in 5, fair in none and poor in 6.

With their experience of obtaining distinct improvement in most patients after ileostomy the authors believe that to delay this measure over a week in a patient with spiking temperature and evidence of increasing toxicity is a very risky postponement.

There were 32 “emergency” ileostomies performed, with 75 per cent mortality. For this reason every attempt is made to anticipate the need for ileostomy to avoid the necessity for an emergency procedure in a poor-risk patient. Elective ileostomy in 76 patients yielded a mortality of only 6.5 per cent.

Partial or complete colectomy was performed in 93 patients — a total of 146 different procedures — with an operative mortality of 8.2 per cent and a case mortality of 12.8 per cent.

The König-Rutzen bag is considered to be the best appliance for ileostomy control, since it is cemented to the skin and if properly applied can be made leak tight both day and night.

### POLYPS

Binkley and Sunderland<sup>21</sup> classify benign adenomas of the colon as areas of hyperplasia, adenomas and papillary adenomas — the second group

DR HALSTED The x-ray findings suggest gastritis, but the x-ray diagnosis of gastritis is not accurate. One can see apparent gastritis on x-ray examination and find a normal-appearing mucosa by gastroscopy, but the reverse is more generally true—that the x-ray film appears normal and gastroscopy demonstrates gastritis.

In summary, this man had a chief complaint of chronic epigastric distress for a year, with no anemia and no weight loss. There was evidence of bleeding by gastroscopy as well as by examination of fluid removed from the stomach by aspiration. Apparently he had a rather diffuse lesion that tended to involve the upper part of the stomach. This was first reported from another hospital four months before entry here. At that time he showed what was thought to be an ulcer crater in the center of the area.

From the evidence at hand it is not possible to make more than a guess at the diagnosis in this patient without surgical exploration. What are the differential possibilities? The commonest lesion that causes chronic epigastric distress at this age is peptic ulcer. I rule that out because of the achlorhydria, confirmed by two examinations and the history. Such rare lesions as tuberculosis and syphilis, which might involve the stomach, can also be discarded, since there was no evidence of these diseases elsewhere in the body. We come down to a tumor or gastritis. If it was a tumor, was it cancer or a lymphoblastoma type of tumor or possibly a benign tumor? Carcinoma is about a hundred times more common in the stomach than lymphosarcoma statistically. At this patient's age, however, it is only about fifteen times more common. Cancer of the stomach is more apt to be in the lower end, 50 per cent of cases involve the antrum and pylorus. This lesion apparently involved the upper portion of the stomach, which makes one suspect more strongly some other lesion than cancer. If he had carcinoma, with symptoms of a year's duration and with this rather extensive involvement as evidenced by gastroscopy, I should expect that he would have lost weight and be definitely anemic, neither weight loss nor anemia was mentioned, so that I should be in favor of tumor other than carcinoma, provided it was a tumor.

Could it have been gastritis? A severe hypertrophic ulcerating type of gastritis can produce this picture, both by x-ray and gastroscopic findings as well as clinically. I cannot interpret the gastroscopy, it is a subjective method of examination, and I have to rely on what the gastroscopist thought at the time. I do not imagine a biopsy was taken, there is no mention, although it is now possible to take biopsies through a new kind of flexible gastroscope. I do not know what Dr Benedict's results have been with that instrument. The achlorhydria is an important finding here. At the age of thirty, it is estimated to occur in 2

to 4 per cent of people normally. Thus the achlorhydria in a patient of thirty would almost surely be due to disease. Schindler<sup>1</sup> says that gastritis is not associated with achlorhydria as a rule, the hypertrophic type is generally associated with acid.

The suggestion of a mass that the gastroscopist reported—apparently a round mass protruding from the submucosa—may be important and suggests that this man had a tumor of the upper part of the stomach, not a carcinoma. Hodgkin's disease, restricted to the stomach and not involving other parts of the gastrointestinal tract or other parts of the body, is extremely rare. There were only 20 cases reported up to 1946. The same observation is true of leukemic infiltration of the stomach in an aleukemic phase of the disease. I would have to rule this out without any other evidence of the disease. There is nothing to suggest that this was an extragastric tumor, such as retroperitoneal sarcoma, which was compressing or invading the stomach. No mass was felt, and the x-ray report indicates that the lesion involved the stomach wall. Leiomyoma or leiomyosarcoma is usually an isolated tumor, although in rare cases it has been reported as a diffuse tumor involving the stomach. This type of tumor characteristically is without symptoms except for bouts of massive bleeding, with no digestive symptoms of pain and distress. Lymphosarcoma comprises about 40 per cent of gastric sarcomas. This may diffusely involve the stomach or may grow inward or outward as a discrete tumor.

I suppose, on statistical grounds alone, that carcinoma is perhaps the most likely diagnosis, but for the reasons I have given, I do not believe it was present. This could have been extensive hypertrophic gastritis or a lymphomatous or sarcomatous type of tumor. Gastritis is much more common, but because of the achlorhydria and the gastroscopic findings this case is more suggestive of a diffusely invading tumor, probably lymphosarcoma.

DR BENJAMIN CASTLEMAN Will you tell us what your opinion was before operation, Dr Allen?

DR ALLEN Dr Halsted has covered our line of reasoning very accurately. We were not sure that this man had a serious lesion of the stomach, but we felt that we had to explore him to find out whether there was tumor in the stomach or not. This was based to some extent on the achlorhydria and on the gastroscopic impression. We had had an almost identical picture in a patient who proved to have a lymphoma of the stomach. We have also had 2 other cases presenting the same picture but with acid in the stomach that proved to be due to giant gastritis. In these patients there was an enormous increase in the size of the rugae of the stomach.

I explored this patient with an open mind, thinking that I would have to rule out a serious surgical situation.

## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

EDITH E. PARRIS, *Assistant Editor*

### CASE 34371

#### PRESENTATION OF CASE

A thirty-year-old man was admitted to the hospital because of epigastric distress.

The patient had previously been well until one year prior to admission, when he began to notice epigastric distress following large meals. This became gradually more persistent and then became consistently associated with the noonday meal. X-ray studies done at another hospital four months before entry showed a filling defect on the greater-curvature side of the pars media of the stomach surrounded by exaggerated rugae and a suspicious ulcer crater in the center of the area. Three days later a repeat examination failed to show any filling defect but there were some hypertrophied rugae on the greater curvature. Further studies one month before admission again demonstrated a questionable gastric lesion and a total achlorhydria following an alcohol test meal. He was given dilute hydrochloric acid, but the symptoms continued. There was no relation of the distress to fatty or other particular foods, and alkalies afforded no relief. Neither did eating smaller meals bring any relief from the gastric distress. He gained several pounds over the several weeks before entry. There was no change in bowel habit.

The past history and a system review were non-contributory.

Physical examination revealed a well developed and well nourished man in no distress. Examination of the lungs, heart and abdomen was entirely negative.

The blood pressure was 120 systolic, 65 diastolic. Examination of the blood disclosed a white-cell count of 8000. The hemoglobin was 13.8 gm per 100 cc. The urine was normal. Gastric analysis after an alcohol test meal showed no free hydrochloric acid in the fasting, half-hour and one-hour specimens. All three were guaiac positive. A gastrointestinal series demonstrated a normal esophagus. The stomach was situated high and transversely. Unusually large rugal folds were present in the proximal half of the stomach. The mucosal pat-

tern of the distal portion of the stomach was not abnormal, although slight mucosal thickening was possibly present. The mucosa in the upper half appeared to be coated with foreign material, and the pattern was mottled. The walls of the stomach were pliable. The duodenal bulb was not remarkable.

Gastroscopy was done, and the gastroscope readily passed. The angulus was somewhat rigid, and no peristalsis was seen. There was not the usual response to air inflation. Only the proximal portion of the antrum was visualized, and the distal antrum and pylorus were not seen. Throughout the body of the stomach, particularly on the posterior wall and greater curvature, the rugae were very thick and tortuous. The wall of the stomach was also somewhat rigid and did not respond to air inflation. The mucosa was markedly hemorrhagic throughout the body of the stomach and bright-red blood apparently oozed from the posterior wall and greater curvature. A similar appearance was present to a lesser extent on the lesser curvature. At times there appeared to be an inconstant, round, submucosal mass on the greater curvature in the lower part of the body of the stomach.

Following these diagnostic procedures an operation was performed.

#### DIFFERENTIAL DIAGNOSIS

DR. JAMES A. HALSTED: I should like to ask Dr. Allen about this man's total weight loss. It is not clear.

DR. ARTHUR W. ALLEN: It is my impression that he had regained all the weight he had lost before he came to operation.

DR. HALSTED: In other words, he had a year's symptoms without any essential weight loss.

DR. ALLEN: He was certainly well nourished at the time of operation.

DR. HALSTED: Is there any record of a stool examination?

DR. ALLEN: The stools were guaiac negative.

DR. HALSTED: During gastroscopy, "there was not the usual response to air inflation." I believe that refers to the fact that with the usual response one might expect peristalsis to develop as a result of inflating the stomach. The fact that the pylorus was not seen is not surprising. In 50 per cent of gastroscopies one cannot see the pylorus.

Are the x-ray films available?

DR. JAMES McCORT: This examination shows the widening of the rugal folds, which appears mainly in the fundus of the stomach, extending down into the body of the stomach. According to the fluoroscopist's note, he was able to discover no rigidity or loss of pliability by palpation.

DR. HALSTED: The lower end is normal?

DR. McCORT: The rugal pattern in the lower end of the stomach is not altered.

## DIFFERENTIAL DIAGNOSIS

DR EARLE M. CHAPMAN I think we should start out by seeing the x-ray films

DR STANLEY M. WYMAN The mass described is well seen in the right-upper-lung field in the posteroanterior view, lying far posteriorly, and not very well seen in the lateral film. The heart shadow is definitely enlarged, probably chiefly left ventricular, and the aorta is tortuous as described. The pulmonary vascular shadows are, I think, slightly increased in prominence, suggesting some vascular engorgement. There is no evidence of rib erosion and no evidence of involvement of the chest wall itself.

DR CHAPMAN The pyelograms were done to exclude kidney tumor, I assume.

DR WYMAN The kidneys seem to be normal. The calyceal pattern shows no abnormality. The bladder shadow is not included on the film. This is the opaque material in both buttocks.

DR CHAPMAN There is no osteoporosis?

DR WYMAN Nothing significant.

DR CHAPMAN It seems to me that we are faced squarely with a differential diagnosis of a circumscribed, well outlined mass in the right-upper-lung field, not eroding bone, and not connected with the vascular system. In my simplicity, I would say that it boils down to a differential diagnosis between one of two diseases: gumma or malignant tumor of some type. From the clinical course and what happened to the patient I assume that the previous group of physicians in charge of him considered that the chance of a malignant tumor was greater than that of syphilis and advised operation. However, my reasoning, now that it is all over, is somewhat different. I think the weight of evidence rather favors syphilis of the lung and not a malignant lesion. Of course it could have been a malignant melanoma. We know that metastases occur years after the eye is originally enucleated. I think that we have to accept the other clinical signs and evidence of active syphilis. I would point out also that certain negative signs favor this as well. The absence of symptoms in this man, notably the lack of symptoms referable to the lungs, and the fact that cytologic smears failed to show cancer cells are against cancer. As you know syphilis of the lung is extraordinarily rare. We seldom see it here. In a large autopsy series, 2800 I believe, Osler\*

found only 12 cases of syphilis of the lung. It is not too uncommon in the congenital form in the infant, but in adults it is rare. Cases have been described that fall into three categories: syphilitic pneumonitis with a stenosing lesion of the bronchus, a fibrosing lesion within the lung that can simulate tuberculosis often to the point of cavity formation and the single gummatous form that may or may not have cavitation within it from necrosis. I cannot help feeling that this patient had syphilis, which was not thoroughly treated, that he had syphilitic heart disease, with aortic regurgitation and syphilitic aortitis, and that this lesion in the chest could perfectly well have been syphilis.

The physician obviously was looking for other sources. Hypernephroma is a possibility. I remember a patient who had a lymphoma removed four or five years before he came back with a single lesion in the lung. He did not have syphilis. I decided it was metastatic, the original lesion had been removed previously. He did nicely for a month but finally died with metastases in the brain.

I wonder why the clinicians did not try anti-syphilitic treatment. If it had been syphilis, it should have responded to iodides, arsphenamine or mercury. I do not know whether this was a recent case, but it seems that such a program of treatment should have been tried before operation.

A PHYSICIAN Do you think it could have been a tuberculoma, in which case the iodides would not be used?

DR CHAPMAN No, I do not. I thought of tuberculosis, but the patient had no fever, no elevated white-cell count, and no mention of the tuberculin test, and I cannot believe that it entered the minds of those taking care of him. I think they thought so strongly of its being a malignant tumor that they went ahead and removed it. But I think in view of the evidence of syphilis in the heart that it could have been a late manifestation of the disease. I do not know how I can arrive at a better diagnosis than one of those two. I cannot believe that it was pulmonary infarction. He had injection treatment for "calf pains." Did he have thromboembolic disease throwing off an embolus? I have never seen an infarct in a lung look like that, so I exclude embolic disease in the lung. Failure of progression of symptoms is against the diagnosis of cancer.

\*Osler W. *Principles and Practice of Medicine*. Fifteenth edition. 1498 pp. New York and London: D. Appleton-Century Co. 1944. P. 407.

## CLINICAL DIAGNOSIS

Gastric tumor

DR HALSTED'S DIAGNOSIS

Lymphosarcoma of stomach

## ANATOMICAL DIAGNOSIS

*Chronic gastritis, superficial type, superimposed on hypertrophic type*

## PATHOLOGICAL DISCUSSION

DR ALLEN At operation the stomach was, as you can see, very high and difficult to palpate. This man was quite fat. Not being satisfied with palpation of the stomach from the outside, I opened the anterior wall of the stomach and put one hand inside the stomach and with my other hand outside I could feel the entire stomach throughout and be sure that the patient had no tumor. He did have huge rugae, and we took out a section, perhaps not so high as we would have liked but high enough we thought to include a portion that would be diagnostic. The stomach was then closed, and the abdomen closed — just a biopsy was done.

DR CASTLEMAN The microscopical sections showed a definite and characteristic chronic gastritis. Normally the glands in the fundic portion of the stomach are composed of cells whose nucleus is basally situated, the rest of the cell being filled with large amounts of mucin. Also, in the normal stomach there is a variably cellular infiltration of plasma cells, lymphocytes and eosinophils between and in the glands in the neck zone of the mucosa. Some years ago Drs Benedict and Mallory<sup>2</sup> reviewed our gastric material and determined about how much cellular infiltration in the various parts of the stomach was within physiologic limits.

In this particular case, instead of the normal type of epithelium, the glands had lost their mucin secretion, the cells were smaller, and the cytoplasm was dense. Function was obviously disturbed. There was an intense cellular infiltration, polymorphonuclears predominating, involving the upper part of the mucosa, much more than is seen normally. This form of gastritis is called superficial gastritis, and it may be superimposed on the hypertrophic or atrophic form. I believe that this is an example of acute and chronic gastritis of the superficial type superimposed on the hypertrophic form.

DR HALSTED According to Schindler<sup>1</sup> the superficial type of gastritis is much more commonly associated with achlorhydria than the chronic hypertrophic gastritis, that is probably the explanation of the achlorhydria in this case.

## REFERENCES

- 1 Schindler R. *Gastritis* 462 pp. New York: Grune & Stratton 1947 132.
- 2 Benedict E B and Mallory T B. Correlation of gastroscopic and pathological findings in gastritis. *Surf. Gynec. & Obst.* 76: 129-135 1943.

## CASE 34372

## PRESENTATION OF CASE

A seventy-year-old retired merchant entered the hospital on his physician's advice following x-ray studies revealing a mass in the right lung.

For the past fourteen years the patient had had frequent checkups for a cardiac condition, although his only symptom was slight exertional dyspnea. He had noticed no edema, orthopnea or weakness, but had been told a few years previously that his blood pressure was low. One year previous to admission a routine chest x-ray film revealed a mass in the right lung. Five months later x-ray study showed essentially the same picture, but in an examination two months prior to admission a slight change in the mass was noted and he was referred here. During the past year he had been asymptomatic, with no weight loss, chest pain, fever or remarkable upper respiratory infection. During this time cytologic smears of the sputum were twice reported negative.

Fifteen years prior to admission an enucleation of the left eye had been done for a malignant melanoma. About ten years prior to entry he had received injections for "calf pains."

Physical examination revealed a heart enlarged to the upper limit of normal. A long systolic and a short diastolic murmur, not widely transmitted, were heard in the aortic area. The peripheral pulses were of the Corrigan type.

The blood pressure was 200 systolic, 65 diastolic. Examination of the blood disclosed a hemoglobin of 15.8 gm and a white-cell count of 7600, with 61 per cent neutrophils, 26 per cent lymphocytes, 6 per cent monocytes and 4 per cent eosinophils. A urinalysis was negative. The serum nonprotein nitrogen was 33 mg, and the protein 7 gm per 100 cc. A cytologic smear of the sputum was negative. Blood Hinton and Wassermann tests were positive.

X-ray films of the chest showed a slightly lobulated mass of homogeneous increased density within the posterior segment of the right upper lobe overlying the right fifth, sixth and seventh ribs posteriorly. The mass was approximately 5 cm in diameter, although it lay against the posterior wall; there was no evidence of erosion. The heart was somewhat prominent in the region of the left ventricle, and the aorta was tortuous. There were areas of calcification in the mediastinum. Intravenous pyelogram showed prompt excretion in fair concentration, outlining grossly normal-appearing calyces, pelves and ureters. The bladder shadow was not remarkable. There was opaque material in both buttocks. The bones of the pelvis and lumbar spine were not remarkable. An electrocardiogram was consistent with left ventricular strain and hypertrophy.

On the eighth hospital day an operation was performed.

## DIFFERENTIAL DIAGNOSIS

DR EARLE M. CHAPMAN I think we should start out by seeing the x-ray films

DR STANLEY M. WYMAN The mass described is well seen in the right-upper-lung field in the posteroanterior view, lying far posteriorly, and not very well seen in the lateral film. The heart shadow is definitely enlarged, probably chiefly left ventricular, and the aorta is tortuous as described. The pulmonary vascular shadows are, I think, slightly increased in prominence, suggesting some vascular engorgement. There is no evidence of rib erosion and no evidence of involvement of the chest wall itself.

DR CHAPMAN The pyelograms were done to exclude kidney tumor, I assume.

DR WYMAN The kidneys seem to be normal. The calyceal pattern shows no abnormality. The bladder shadow is not included on the film. This is the opaque material in both buttocks.

DR CHAPMAN There is no osteoporosis?

DR WYMAN Nothing significant.

DR CHAPMAN It seems to me that we are faced squarely with a differential diagnosis of a circumscribed, well outlined mass in the right-upper-lung field, not eroding bone, and not connected with the vascular system. In my simplicity, I would say that it boils down to a differential diagnosis between one of two diseases: gumma or malignant tumor of some type. From the clinical course and what happened to the patient I assume that the previous group of physicians in charge of him considered that the chance of a malignant tumor was greater than that of syphilis and advised operation. However, my reasoning, now that it is all over, is somewhat different. I think the weight of evidence rather favors syphilis of the lung and not a malignant lesion. Of course it could have been a malignant melanoma. We know that metastases occur years after the eye is originally enucleated. I think that we have to accept the other clinical signs and evidence of active syphilis. I would point out also that certain negative signs favor this as well. The absence of symptoms in this man, notably the lack of symptoms referable to the lungs, and the fact that cytologic smears failed to show cancer cells are against cancer. As you know syphilis of the lung is extraordinarily rare. We seldom see it here. In a large autopsy series, 2800 I believe, Osler\*

found only 12 cases of syphilis of the lung. It is not too uncommon in the congenital form in the infant, but in adults it is rare. Cases have been described that fall into three categories: syphilitic pneumonitis with a stenosing lesion of the bronchus, a fibrosing lesion within the lung that can simulate tuberculosis often to the point of cavity formation and the single gummatous form that may or may not have cavitation within it from necrosis. I cannot help feeling that this patient had syphilis, which was not thoroughly treated, that he had syphilitic heart disease, with aortic regurgitation and syphilitic aortitis, and that this lesion in the chest could perfectly well have been syphilis.

The physician obviously was looking for other sources. Hypernephroma is a possibility. I remember a patient who had a lymphoma removed four or five years before he came back with a single lesion in the lung. He did not have syphilis. I decided it was metastatic, the original lesion had been removed previously. He did nicely for a month but finally died with metastases in the brain.

I wonder why the clinicians did not try anti-syphilitic treatment. If it had been syphilis, it should have responded to iodides, arsphenamine or mercury. I do not know whether this was a recent case, but it seems that such a program of treatment should have been tried before operation.

A PHYSICIAN Do you think it could have been a tuberculoma, in which case the iodides would not be used?

DR CHAPMAN No, I do not. I thought of tuberculosis, but the patient had no fever, no elevated white-cell count, and no mention of the tuberculin test, and I cannot believe that it entered the minds of those taking care of him. I think they thought so strongly of its being a malignant tumor that they went ahead and removed it. But I think in view of the evidence of syphilis in the heart that it could have been a late manifestation of the disease. I do not know how I can arrive at a better diagnosis than one of those two. I cannot believe that it was pulmonary infarction. He had injection treatment for "calf pains." Did he have thromboembolic disease throwing off an embolus? I have never seen an infarct in a lung look like that, so I exclude embolic disease in the lung. Failure of progression of symptoms is against the diagnosis of cancer.

DR F DENNETTE ADAMS In my opinion, this lesion was too well defined in outline to be syphilitic. Syphilis of the lung is rare. This lesion was so typical of tumor in its appearance that I should definitely make a diagnosis of a metastatic lesion from the original disease of the eye even at this late date. The syphilis was probably purely incidental. Dr Wyman has just whispered in my ear that from the x-ray standpoint it could also have been a bronchiogenic carcinoma. I want to ask him a question. Does he believe that a bronchiogenic carcinoma of that size could have developed without any pulmonary symptoms or signs?

DR WYMAN We followed a patient with proved bronchiogenic carcinoma in the Thoracic Clinic for five years. The lesion was in the left lower lobe posteriorly, close to the chest wall, and sharply defined. It was thought to be inoperable metastatic carcinoma for a long time. This lesion was observed and filmed every few months, and during this entire time it grew very slowly and was symptomless.

From the x-ray point of view this lesion is consistent with metastatic disease or bronchiogenic carcinoma. I would not guess melanoma unless I knew about the eye. It is also quite typical of a hypernephroma.

DR CHAPMAN Would you think that it would occlude the bronchus and produce signs?

DR DAVID G FREIMAN Adenocarcinomas of the bronchus, usually seen in the peripheral portions of the lung, involve the smaller bronchial radicles and often give no clinical evidence of occlusion.

DR CHAPMAN I do not see how the clinician could make a diagnosis except after an adequate trial of antisyphilitic treatment.

DR ADAMS In the presence of aortic disease, however, one has to go slowly with antisyphilitic treatment. One might not want to wait so long to

find out. I believe operation was the correct procedure and that metastatic disease of the lung is the correct diagnosis.

#### CLINICAL DIAGNOSIS

Malignant tumor, metastatic?, primary?

#### DR CHAPMAN'S DIAGNOSES

Syphilis of the lung

Melanotic sarcoma, metastatic?

#### ANATOMICAL DIAGNOSIS

*Metastatic malignant melanoma of lung*

#### PATHOLOGICAL DISCUSSION

DR FREIMAN The operation performed was a lobectomy. We received the right upper and right middle lobes of the lung, and in the right upper lobe there was an apparently encapsulated tumor nodule, 5 cm in diameter. The outer portion was pale, and the central portion quite black. On section this proved to be a typical metastatic malignant melanoma. We were able to obtain a section of the eye previously removed, and this showed a tumor identical in appearance with that in the lung. As has been noted, the appearance of such metastases may be long delayed and intervals of ten to fifteen years have been described following enucleation of the involved eye.

A PHYSICIAN Is the metastasis usually single?

DR FREIMAN Metastases may be single or widely disseminated.

DR J GORDON SCANNELL Although a syphilitic lesion of the lung was considered preoperatively, we felt that the evidence for tumor that had increased during the past year was convincing. On seeing the patient one could not help thinking that this might have been a variation of the classic theme of a glass eye and a lump in the abdomen.

# The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established 1828

Official Organ of

THE MASSACHUSETTS MEDICAL SOCIETY

and

THE NEW HAMPSHIRE MEDICAL SOCIETY

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND

PUBLISHED WEEKLY UNDER THE JURISDICTION OF THE  
COMMITTEE ON PUBLICATIONS

James P. O'Hare, M.D.      Richard M. Smith, M.D., Chairman  
Oliver Cope, M.D.      Conrad Weiselhoeft, M.D.  
John Falloo, M.D.

Joseph Garland, M.D., Editor

ASSOCIATE EDITORS

Thomas H. Looman, M.D.

Donald Monro, M.D.

Henry Jackson, Jr., M.D.

Clara D. Davies, EXECUTIVE EDITOR

Robert O'Leary, ASSISTANT EDITOR

EDITORIAL BOARD

C. Gray Lane, M.D.  
Henry R. Viets, M.D.  
Robert M. Grieco, M.D.  
Dwight O'Hara, M.D.  
Fletcher H. Colby, M.D.  
Robert L. Goodale, M.D.  
Chester M. Joer, M.D.  
Harvey R. Morrison, M.D.

Maxwell Fioland, M.D.  
James M. Faulkner, M.D.  
Carroll B. Larson, M.D.  
Francis D. Moore, M.D.  
C. Stuart Welch, M.D.  
Vernon P. Williams, M.D.  
Benjamin Castleman, M.D.  
Hugh R. Leavell, M.D.

SUBSCRIPTION TERMS: \$7.00 per year in advance, postage paid for the United States (medical students, \$4.00 per year). Canada, \$8.00 per year (Boston funds). \$9.50 per year for all foreign countries belonging to the Postal Union.

MATERIAL should be received not later than noon on Thursday three weeks before date of publication.

THE JOURNAL does not hold itself responsible for statements made by any contributor.

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts. Telephone KE 6-2094.

NEW ENGLAND ADVERTISING REPRESENTATIVE: Edwin B. Tyler, 89 State Street, Boston, Massachusetts. Telephone LA 3-5516.

## ALLEGED PENICILLIN-RESISTANT GONORRHEA

AFTER a few years of the widespread and successful use of the sulfonamides in the treatment of acute gonorrhea, it was recognized by many observers that an increasing proportion of cases failed to respond to these drugs. Thus, during the year 1941, the late Oscar F. Cox<sup>1</sup> obtained unquestionable sulfonamide cures in 70 per cent of all male patients admitted to the Boston Dispensary with active gonococcal infections, whereas of similar cases admitted during 1944, clean-cut sulfonamide cures occurred in only 28 per cent, a complete reversal of the 1941 figure. Laboratory data in these cases indicated that the failures resulted from the resistance of the organisms and not from any change in the host. An increase in the prevalence of sulfonamide-resistant strains of *Neisseria gonor-*

*rhoeae* from 15 to 59 per cent in fifteen months was observed in Glynn County, Georgia, after the extensive use of the sulfonamides as a part of a special program for the control of gonorrhea.<sup>2</sup>

In Sweden, similar results were recorded in the same period. Seeberg,<sup>3</sup> in a report on 3428 cases of uncomplicated acute gonorrhea, mostly in males, observed that recurrences of infections after a single intensive course of sulfathiazole rose from 15 per cent early in 1941 to between 70 and 80 per cent at the end of 1943 and early in 1944. In women, the comparable failure rate was 30 per cent early in 1943 and 70 per cent at the end of the same year.

Several laboratory studies<sup>4-6</sup> have indicated that there is a fairly close correlation between the in vitro susceptibility of gonococci to sulfonamides and the clinical response of the patients to these drugs.

The gonococcus is one of the most susceptible organisms to the action of penicillin. The sensitivity of different strains of this organism—that is, the concentration of penicillin required to inhibit growth in the test tube—has varied somewhat depending on the methods used. The great majority of strains have been found by most workers to be completely inhibited by penicillin in concentrations well below 0.1 units per cubic centimeter and usually below 0.02 units per cubic centimeter.<sup>7-9</sup> Sulfonamide-susceptible and sulfonamide-resistant strains are equally sensitive to penicillin.<sup>7, 10</sup> In vitro, it is possible to enhance the resistance of the gonococcus to penicillin, but apparently this is not accomplished easily and the limit is soon reached at a moderate level even under optimum conditions. Thus, Miller and Bohnhoff<sup>11</sup> succeeded in raising the resistance of one strain so that it grew in 7.7 units per cubic centimeter by repeated transfers in penicillin-containing mediums and also caused the same organism to grow in 21 units per cubic centimeter by making alternate transfers in penicillin-free mediums. The maximum concentration of penicillin in which Bahn, Ackerman and Carpenter<sup>12</sup> got their strains of gonococci to grow in vitro was 2 units per cubic centimeter.

With the almost universal use of penicillin in the treatment of gonococcal infections, it was expected that penicillin-resistant gonococci would

sooner or later become disseminated. This has not yet been observed on any large scale, but cases of gonorrhea that are clinically resistant to treatment with even large doses of penicillin have been reported. Thus, Pulaski<sup>13</sup> reported 9 cases of penicillin-resistant gonorrhea successfully treated with streptomycin. The bacteriologic observations in these cases, however, were inadequate since they were mostly controlled by smears and the identity of the organisms was not checked by cultural methods.

Franks<sup>14</sup> reported 4 cases successfully treated with penicillin, sulfonamides and fever therapy after repeated large doses of penicillin had failed. The organisms in these 4 cases were tested by a method in which 2 drops of penicillin solution, each containing 400 units, were put into a glass cylinder within a chocolate-agar plate that was seeded with the organisms, and no zone of inhibition of growth was noted. However, no data concerning control cultures were given, and it is not known if any of the penicillin actually diffused into the agar. If the author's interpretation is correct, his findings indicate that these 4 strains were resistant to approximately 8000 units per cubic centimeter. This is extremely unlikely, and the findings can be interpreted as probably due to the result of an error either in the identity of the strains or in the determination of their sensitivity.

In another study by Duemling and Horton,<sup>15</sup> 24 cases of penicillin-resistant gonorrhea were presented in which the organisms were tested by a "gutter-strip" blood-agar plate or similar method. The gonococci were said to be resistant to 5 units of penicillin per cubic centimeter, and in 1 case to 20 units. Interestingly enough, in 4 out of 5 cases in which the organism was retested after a lapse of five to nine days, during which the patient was treated with sulfonamides, the organism had lost its penicillin resistance. Treatment with sulfathiazole or sulfadiazine and then with penicillin resulted in a complete bacteriologic cure in these 24 cases. In this instance also, the results of the sensitivity tests of control strains from cases responding to the usual course of penicillin treatment are not given nor are there complete details concerning the identity of the strains of gonococci. The findings in these and similar reports are there-

fore open to question, particularly because of the great discrepancy in the quantitative estimation of sensitivity in view of the comparative difficulty of experimentally inducing high degrees of resistance in authentic strains of gonococci.

Three recent reports shed further light on the validity of the bacteriologic findings and on the interpretations in the alleged cases of penicillin-resistant gonorrhea. Parkhurst, Harb and Cannefax,<sup>16</sup> in an attempt to study such cases, deliberately accepted cases of alleged penicillin-resistant gonorrhea for treatment at the Hot Springs Medical Center. In addition, they invited the Arkansas Board of Health to refer all cases of penicillin-resistant gonorrhea to them from the local health units. In a study of over 3000 cases in males and females, including those referred as penicillin-resistant cases, they did not encounter a single case in which adequate penicillin dosage did not render the patient culturally free of the gonococcus. They believed that they had good reason to question the reliability of the diagnosis of penicillin-resistant gonorrhea based only on the clinical response and on findings in bacteriologic smears. They also believed that adequate cultural methods, including tests of the biochemical reactions and penicillin sensitivity of the organism, should be carried out before a case was diagnosed as penicillin-resistant gonorrhea. They were firmly convinced that the urethral discharges that occurred after penicillin treatment were the result of nongonococcal or nonspecific infections.

Hughes and Carpenter<sup>17</sup> studied 216 soldiers referred to them from the Pacific Theater and from the Zone of the Interior as penicillin-resistant cases of gonorrhea. They found 86 of these cases to be completely asymptomatic, and only 117, or 56 per cent, had any urethral exudate. Bacteriologic studies of the latter cases revealed that only 19, or 9 per cent, were positive for a gonococcus, 16 by culture of the anterior urethral discharge and 3 only by smears. Cultures of the latter 3 and of the urinary sediments of all 19 were negative for gonococcus. The predominant organism in these cases was an alpha streptococcus in 41, a hemolytic or anhemolytic staphylococcus in 51 and miscellaneous organisms in some of the others. Only 6 of the gonococcus cultures could be main-

tained satisfactorily for sensitivity tests. These were all found to be sensitive to concentrations ranging from 0.01 to 0.08 units, a range similar to that usually reported by others as already noted. Treatment of the 19 cases with a single dose of 300,000 units of calcium penicillin in beeswax and peanut oil resulted in complete clearing of the exudate in twenty-four to seventy-two hours in 14 cases. The remaining 5 patients showed no improvement in twenty-four hours, but they were rendered completely asymptomatic in another forty-eight hours after a second dose of the same amount of penicillin. These authors concluded that penicillin-resistant gonorrheal urethritis is usually nongonococcal urethritis erroneously diagnosed because of unsatisfactory bacteriologic methods.

Finally, Hawks and Greer<sup>13</sup> tested 330 strains of gonococci—64 from the prepenicillin days and the rest from recent cases. The sensitivity of the strains in both groups was the same, all were inhibited by 0.06 units of penicillin, or less, per cubic centimeter.

Cases of acute gonorrhea may respond to streptomycin in moderate doses.<sup>13, 19</sup> It is very likely, however, that many of the cases that have been considered clinically to be penicillin-resistant gonorrhea, particularly the uncomplicated cases of urethritis that responded promptly to streptomycin, are actually cases of nongonococcal infection in which the organism is susceptible to streptomycin. It is of considerable theoretical interest as well as of practical importance to determine for certain whether or not there are any penicillin-resistant strains of gonococci prevalent in the community and whether or not their numbers are increasing. Physicians who encounter cases of infection in which the presence of such penicillin-resistant gonococci is suspected should make every effort to obtain proper cultures or see that such cultures are made in laboratories where there is sufficient interest and where facilities are available for the proper identification of the strains and the determination of their sensitivity to the antibiotic.

#### REFERENCES

1. Cox O F. Chemotherapy and venereal disease control. *Bull Geriatr Infectious Dis* 7:1 1944

2. Carpenter C, M. Ackerman H, Winchester M E, and Whittle J. Correlation of in vitro sulfonamide resistance of gonococcus with results of sulfonamide therapy. *Am J Pub Health* 34:250-254 1944
3. Seeberg G. Deteriorating therapeutic effect of sulfathiazole in gonorrhea. *Acta dermat-terreol* 25:361-379 1945
4. Godale W T, Gould R G, Schwab L, and Winter V G. Laboratory identification of sulfonamide resistant gonococcal infections. *J A M A* 123:547-549 1943
5. Cohn A, and Seijo I. Further observations on correlation between clinical and in vitro reactions of gonococcus strains to sulfathiazole. *Am J Syph. Goror & Fer Dis* 27:301-308 1943
6. Frisch A W, Edwards R B, Edwards M W, and Behr B. Sulfonamide resistant gonorrhea. *Am J Syph. Goror & Fer Dis* 28:397-405 1944
7. Lankford C E. In vitro tolerance of gonococcus for penicillin. *Am J Syph. Goror & Fer Dis* 29:56-63 1945
8. Meade M, Ory E M, Wilcox C, and Finland M. Penicillin sensitivity of strains of 6 common pathogens and of *Hemophilus hemolyticus*. *J Lab & Clin Med* 30:725-730 1945
9. R. Mansky M J, and Robin E V D. Comparison of in vitro susceptibility of gonococci to penicillin G and N. *Am J Syph., Goror & Fer Dis* 31:271-276 1947
10. Cohn A, and Seijo I H. In vitro effect of penicillin on sulfonamide resistant and sulfonamide susceptible strains of gonococci. *J A M A* 124:1125 1944
11. Miller C P, and Bobnoff M. Studies on action of penicillin development of penicillin resistance by gonococcus. *Proc Soc Exper Biol & Med* 60:354-356 1945
12. Babin J M, Ackerman H, and Carpenter C M. Development in vitro of penicillin-resistant strains of gonococci. *Proc Soc Exper Biol & Med* 58:21-24 1945
13. Polaski, E. J. Streptomycin therapy of penicillin resistant and sulfonamide resistant specific and nonspecific urethritis. *J Gen Dis Inform* 28:1-6 1947
14. Franks A G. Successful combined treatment of penicillin resistant gonorrhea. *Am J M Sc* 211:553-555 1946
15. Duemling W W, and Horton S H, Jr. Determination and treatment of penicillin resistant gonorrheal urethritis: report of twenty-four cases. *U S Nav M Bull* 47:605-616 1947
16. Parkhurst, G E, Harb F W, and Cunniff, G R. 'Penicillin-resistant gonorrhea' vs. 'nonspecific urethritis'. *J Fer Dis Inform* 28:211-214 1947
17. Hughes R. P, and Carpenter C M. Alleged penicillin resistant gonorrhea. *Am J Syph. Goror & Fer Dis* 32:263-271 1948
18. Hawks G H, and Greer P H. Penicillin sensitivity of gonococci (Abstr). *Canad J Pub Health* 39:74 1948
19. Putnam L E, Herwick, R. P, Taggart, S. R, and Chunn B D. Treatment of gonorrhea with streptomycin: preliminary report with cure of 4 cases. *M Ann District of Columbia* 16:14 1947

#### AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE

THE American Association for the Advancement of Science will hold its Centennial Meeting in Washington, D C, September 13 to 17, 1948. The morning programs will consist of technical symposiums on important scientific problems, the evening sessions, after the first evening, will be devoted to semipopular lectures that will be open to the general public. Two addresses will be given at the first evening meeting, by the President of the United States and by the retiring president of the Association, Dr Harlow Shapley.

A hundred years ago on September 20, 1848, the first meeting of this distinguished society was called to order in the library room of the Academy of Natural Sciences of Philadelphia by Professor William B Rogers, of Virginia. Professor Walter R Johnson, of Washington, served as secretary, and with the assistance of a special committee collected the proceedings of the sessions in a volume of 156 pages.

sooner or later become disseminated. This has not yet been observed on any large scale, but cases of gonorrhea that are clinically resistant to treatment with even large doses of penicillin have been reported. Thus, Pulaski<sup>13</sup> reported 9 cases of penicillin-resistant gonorrhea successfully treated with streptomycin. The bacteriologic observations in these cases, however, were inadequate since they were mostly controlled by smears and the identity of the organisms was not checked by cultural methods.

Franks<sup>14</sup> reported 4 cases successfully treated with penicillin, sulfonamides and fever therapy after repeated large doses of penicillin had failed. The organisms in these 4 cases were tested by a method in which 2 drops of penicillin solution, each containing 400 units, were put into a glass cylinder within a chocolate-agar plate that was seeded with the organisms, and no zone of inhibition of growth was noted. However, no data concerning control cultures were given, and it is not known if any of the penicillin actually diffused into the agar. If the author's interpretation is correct, his findings indicate that these 4 strains were resistant to approximately 8000 units per cubic centimeter. This is extremely unlikely, and the findings can be interpreted as probably due to the result of an error either in the identity of the strains or in the determination of their sensitivity.

In another study by Duemling and Horton,<sup>15</sup> 24 cases of penicillin-resistant gonorrhea were presented in which the organisms were tested by a "gutter-strip" blood-agar plate or similar method. The gonococci were said to be resistant to 5 units of penicillin per cubic centimeter, and in 1 case to 20 units. Interestingly enough, in 4 out of 5 cases in which the organism was retested after a lapse of five to nine days, during which the patient was treated with sulfonamides, the organism had lost its penicillin resistance. Treatment with sulfathiazole or sulfadiazine and then with penicillin resulted in a complete bacteriologic cure in these 24 cases. In this instance also, the results of the sensitivity tests of control strains from cases responding to the usual course of penicillin treatment are not given nor are there complete details concerning the identity of the strains of gonococci. The findings in these and similar reports are there-

fore open to question, particularly because of the great discrepancy in the quantitative estimation of sensitivity in view of the comparative difficulty of experimentally inducing high degrees of resistance in authentic strains of gonococci.

Three recent reports shed further light on the validity of the bacteriologic findings and on the interpretations in the alleged cases of penicillin-resistant gonorrhea. Parkhurst, Harb and Cannefax,<sup>16</sup> in an attempt to study such cases, deliberately accepted cases of alleged penicillin-resistant gonorrhea for treatment at the Hot Springs Medical Center. In addition, they invited the Arkansas Board of Health to refer all cases of penicillin-resistant gonorrhea to them from the local health units. In a study of over 3000 cases in males and females, including those referred as penicillin-resistant cases, they did not encounter a single case in which adequate penicillin dosage did not render the patient culturally free of the gonococcus. They believed that they had good reason to question the reliability of the diagnosis of penicillin-resistant gonorrhea based only on the clinical response and on findings in bacteriologic smears. They also believed that adequate cultural methods, including tests of the biochemical reactions and penicillin sensitivity of the organism, should be carried out before a case was diagnosed as penicillin-resistant gonorrhea. They were firmly convinced that the urethral discharges that occurred after penicillin treatment were the result of nongonococcal or nonspecific infections.

Hughes and Carpenter<sup>17</sup> studied 216 soldiers referred to them from the Pacific Theater and from the Zone of the Interior as penicillin-resistant cases of gonorrhea. They found 86 of these cases to be completely asymptomatic, and only 117, or 56 per cent, had any urethral exudate. Bacteriologic studies of the latter cases revealed that only 19, or 9 per cent, were positive for a gonococcus, 16 by culture of the anterior urethral discharge and 3 only by smears. Cultures of the latter 3 and of the urinary sediments of all 19 were negative for gonococcus. The predominant organism in these cases was an alpha streptococcus in 41, a hemolytic or anhemolytic staphylococcus in 51 and miscellaneous organisms in some of the others. Only 6 of the gonococcus cultures could be main-

and the consequent consumption of walrus meat, although there was reason for suspecting also the white whale

Bizarre phenomena still occur in nature, and one is repeatedly reminded that God moves in a mysterious way in the performance of His wonders. There is no evidence that the walruses of Greenland have ever been implicated in the fantastic social and gastronomic relations described by Carroll,<sup>3</sup> but one may wonder if the oysters on which they might have fed had had their prescribed veterinary inspection.<sup>4</sup>

### REFERENCES

- 1 Thorborg N, B. Tulinius S and Roth H. *Trichinose Paa Gronland*. *Lægek f læger* 110 595-602 1948
- 2 Annotation. *Trichiniasis from the walrus?* *Lancet* 1 997 1948
- 3 Carroll L. *Through the Looking Glass*. 198 pp. New York: Heritage Press 1941
- 4 Editorial. *Through the looking glass*. *New Eng J Med* 239 240 1948

## MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

### RHEUMATIC-FEVER FELLOWSHIPS

The United States Children's Bureau has made available through the Massachusetts Department of Public Health and Harvard Medical School two fellowships in rheumatic fever at the House of the Good Samaritan of the Children's Medical Center, Boston, for the year 1948, beginning immediately.

Trainees should be interested in working eventually in the field of rheumatic fever in public health or in teaching, rather than in private practice.

Work under these fellowships probably will be acceptable for credit by the Board of Internal Medicine or the Board of Pediatrics.

Application should be made to Dr. Benedict F. Massell at the House of the Good Samaritan, 25 Binney Street, Boston 15, or by telephone call to BEacon 2-3002.

### ADMISSION OF CRIPPLED CHILDREN TO LAKEVILLE STATE SANATORIUM

The Department of Public Health announces that under the provisions of Chapter 412 Acts of 1948, it has been authorized to admit to Lakeville State Sanatorium certain crippled children provided that they have been residents of the Commonwealth for at least twelve months preceding the date of application for admission. Prior to the passage of this act Lakeville Sanatorium had been authorized to admit only patients with extrapulmonary forms of tuberculosis and persons crippled with infantile paralysis.

Because of the steady decline in extrapulmonary forms of tuberculosis, beds are now available for

the treatment of other orthopedic conditions, and this act will make these facilities available for indigent children for whom the Commonwealth cannot provide necessary treatment in general hospitals.

Crippling conditions, including cerebropastic palsy, spina bifida, clubfoot, congenital dislocations and deformities, obstetric paralysis, osteomyelitis, osteochondritis, epiphysitis and scoliosis, are considered suitable for treatment at Lakeville.

Applications for admissions of crippled children may be filed by any registered physician with the Massachusetts Department of Public Health, Room 546, State House, Boston.

### COMMUNICABLE DISEASES IN MASSACHUSETTS FOR JULY, 1948

#### RÉSUMÉ

DISEASES	JULY 1948	JULY 1947	SEVEN-YEAR MEDIAN
Chancroid	4	2	2*
Chicken pox	619	664	516
Diphtheria	15	19	14
Dog bite	1517	1116	1229
Dysentery bacillary	9	11	11
German measles	61	52	116
Gonorrhea	284	352	56
Granuloma inguinale	0	0	1*
Lymphogranuloma venereum	0	0	2*
Malaria	4	1	15
Measles	2462	616	1159
Meningitis meningococcal	5	7	13
Meningitis Pfeiffer-bacillus	4	1	2
Meningitis pneumococcal	2	2	2†
Meningitis, staphylococcal	0	0	0†
Meningitis streptococcal	0	0	0†
Meningitis other forms	2	0	0†
Meningitis undetermined	6	3	4†
Mumps	787	347	434
Pneumonia lobar	124	107	100
Polio myelitis	9	21	11
Salmonellosis	2	15	11
Scarlet fever	269	120	241
Syphilis	225	216	263
Tuberculosis pulmonary	271	218	218
Tuberculosis other forms	19	12	17
Typhoid fever	1	1	4
Undulant fever	1	6	4
Whooping cough	10	551	562

\*Four year median

†Six-year median

#### COMMENT

Diseases with an incidence above the seven-year median were chicken pox, diphtheria, measles, mumps, lobar pneumonia, scarlet fever and undulant fever.

Diseases with an incidence below the seven-year median were bacillary dysentery, German measles, poliomyelitis and whooping cough.

The apparent increase in lobar pneumonia was due to delayed hospital reporting.

July had the highest incidence for mumps since 1915, whooping cough showed the lowest incidence since 1915.

#### GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Actinomycosis was reported from Brockton, 1, total, 1.

Diphtheria was reported from Athol, 1, Berkley, 2, Boston, 8, Braintree, 1, Cambridge, 1, Revere, 1, Weymouth, 1, total, 15.

Dysentery, bacillary, was reported from Dedham, 1, Waltham, 1, Worcester, 6, Wrentham, 1, total, 9.

Encephalitis, infectious, was reported from Hudson, 1, Milford, 1, Worcester, 1, total, 3.

Lymphocytic chorion meningitis was reported from Cambridge, 1, total, 1.

Malaria was reported from Greenfield, 1, Medford, 1, Revere, 1, Springfield, 1, total, 4.

Meningitis, meningococcal, was reported from Boston, 2, Brookline, 1, Cambridge, 1, Winchester, 1, total, 5.

Meningitis, Pfeiffer-bacillus was reported from East Bridgewater, 1, Marlboro, 1, Revere, 1, Salem, 1, total, 4.

Meningitis, pneumococcal, was reported from Boston, 1, Worcester 1, total, 2.

The origin and the organization of the Association were duly recorded " 'In conformity with a resolution of the Association of American Geologists and Naturalists,' adopted during its session at Boston in September, 1847, that body agreed to resolve itself into the American Association for the Advancement of Science "

The first president of the Association, William C Redfield, Esq., of New York, assumed office that afternoon. The first paper of the meeting was forthwith read by Peter A. Brown, L.L.D., on *Some Notice of the Fossil Cephalopodes Belemnosepia, Long Known by the Name of 'Belemnite,' and of the Diphosphate of Iron, called 'Mullicite,' Found Together at Mullica Hill*

The *Journal* wishes long life and continued prosperity to the American Association for the Advancement of Science. The next hundred years should be easier.

## BARUCH COMMITTEE REPORT

CONTINUED progress in the development of physical medicine and facilities for the rehabilitation of the sick and disabled is indicated in the annual report of the Baruch Committee on Physical Medicine, recently released. The Committee was founded by Mr. Bernard M. Baruch in 1944 in memory of his father, Dr. Simon Baruch, a pioneer in physical medicine.

According to this report, the committee has already achieved its major objectives of increasing the number of physicians trained to teach and use the methods of physical medicine, of providing facilities for more extensive research in physical medicine and for "insuring the proper use of physical medicine in relation to wartime rehabilitation and peacetime physical preparedness."

There are now, according to Dr. Frank H. Krusen, director of the Committee and director of physical medicine at the Mayo Foundation, approximately 150 communities in the country that have or are planning civilian rehabilitation programs. Already many of the rehabilitation services in Veterans Administration, Army and Navy hospitals are directed by physicians whose training the Baruch Committee sponsored.

As further evidence of an increased awareness of the need of opportunities for rehabilitation, the seventy residencies and fellowships now available at thirty-four medical centers may be compared with the five such appointments available five years ago. Today sixty medical schools instead of the thirty that existed before the Committee was organized offer instruction in physical medicine.

The need for an organized rehabilitation program has long existed. Four years of war increased the need and conditioned the public in its favor. The labors of the Baruch Committee and the generosity of its founder have provided much of the actual power for accomplishment.

## STRANGE HOST

AN interesting sidelight on the part that wild life may play in man's destiny has been exposed by Thorborg and his associates<sup>1</sup> and made the subject of an annotation in the *Lancet*.<sup>2</sup>

It appears that in May, 1947, the State Serum Institute in Copenhagen was made aware of a mysterious epidemic that had broken out in Greenland. During the previous five months about 300 cases of an acute and distressing malady had occurred, with a 10 per cent mortality. The disease usually began gradually although sometimes the onset was acute. Progressive lassitude became evident with headache, pains in limbs and trunk, and fever, slight at first, then rising to considerable heights. Gastrointestinal symptoms developed, and edema of the face, limbs or entire body was an almost constant feature. The cases of sudden death were apparently the result of myocardial failure.

Trichiniasis had never been known to occur in Greenland, but Thorborg, who was sent to investigate the epidemic, found eosinophilia, positive cutaneous reactions to trichina antigen, positive serologic tests on blood samples and encapsulated trichina larvae in the muscles of a patient who had died of the disease after a three months' illness.

Pork was not involved in this initial outbreak of trichiniasis, and only a few of the patients had eaten dog meat within a month of the onset of symptoms. The only common factor was the synchronization of the epidemic with the walrus-hunting season.

possible contributions to treatment and to constructive mental health that can be made by family physicians, social workers and psychologists and by the church, industry, community organizations and the Government. The final chapter presents a summary and prospect the individual and society. The objective of the book has been to show that mental and emotional ill health is a reaction of personality to the multiple stresses of the total environment, whether the stresses be in external environment, or in the patient's own complicated emotional imbalances. The authors state that mental health cannot be developed in a social vacuum and that to promote positive mental health will require the co-operation and help of many individuals and groups. The material is well organized, and the text is well written. A list of references is appended to each chapter. A good index concludes the volume. The publishing is excellent in every way. The printing is well done with a good large type on good nonglare paper. It is a pleasure to read the book. The book is recommended for all medical, social, public-health and general libraries and to all persons interested in the subject.

*Psychobiology and Psychiatry. A textbook of normal and abnormal human behavior.* By Wendell Muncie, M.D., practicing psychiatrist, chairman, Medical Advisory Board, Seton Institute, Baltimore, and associate professor of psychiatry, Johns Hopkins University, and consultant in psychiatry, U S V A. Second edition 8°, cloth, 620 pp., with 70 illustrations. St. Louis: The C V Mosby Company, 1948 \$9 00.

This second edition has been extensively edited by the author in the light of his experience gained in private practice since the publication of the first edition in 1939. The textbook is based on the teaching of psychiatry at Johns Hopkins University School of Medicine. The historical appendixes of the first edition have been omitted from this edition. A list of selected references is appended to each chapter. A good index concludes the volume. The publishing is well done. The work should be in all collections on psychiatry.

*Encyclopedia of Medical Sources.* By Emerson C Kelly, M.D., associate professor of surgery, Albany Medical College, and attending surgeon, Albany Hospital 8°, cloth, 476 pp. Baltimore: The Williams and Wilkins Company, 1948 \$7 50.

This book is essentially a medical biographic dictionary, in which the fundamental contributions of the persons listed are emphasized, and extensive biographic data omitted. Birth and death dates and domicile are given. Dr. Kelly contributed about 95 per cent of the original publications, a very large coverage, in the interest of accuracy. The names are listed alphabetically, and a comprehensive subject index concludes the volume. The index refers to names and not pages throughout the text. The book is recommended as an essential reference work for all medical and general libraries and to all medical historians.

*Clinical Diagnosis by Laboratory Methods. A working manual of clinical pathology.* By James C Todd, Ph.D., M.D., and Arthur H Sanford, A.M., M.D., professor of clinical pathology, Mayo Foundation, University of Minnesota, and senior consultant, Division of Clinical Laboratories, The Mayo Clinic. With the collaboration of George G Stilwell, M.D., Division of Clinical Laboratories, The Mayo Clinic. Eleventh edition 8°, cloth, 954 pp., with 397 illustrations. Philadelphia: W B Saunders Company, 1948 \$7 50.

This standard popular textbook was published first in 1908 and has gone through ten previous editions, the tenth being issued in 1943. The text of this eleventh edition has been completely revised, and some rearrangement has been made in the subjects. The former chapter on serodiagnostic methods has been divided into three short chapters, and the serodiagnostic tests for syphilis have been included in the second of these chapters. The material on medical mycology has been expanded into a new chapter. The illustrations have been carefully reviewed and rearranged, and new ones added, including new color plates on the blood. A list of references is appended to each chapter. A comprehensive index concludes the volume. The publishing is well done in the characteristic Saunders style. The book is recommended for all medical libraries and to the general practitioner.

*Introduction to Human Physiology.* By William D Zoethout, Ph.D. 8°, cloth, 424 pp., with 138 illustrations and 4 color plates. St. Louis: The C V Mosby Company, 1948 \$4 00.

This elementary manual is well written in a simple, lucid style, and the material is well organized. The type, printing and paper are excellent. The manual should prove of value to students and to all persons interested in the subject. It is recommended for public libraries, where it should prove useful in semipopular collections.

*Clinical Studies in Psychopathology. A contribution to the etiology of neurotic illness.* By Henry V Dicks, M.A., M.D. (Cantab.), F.R.C.P. (Lond.), Nuffield Professor of Psychiatry in the University of Leeds. Second edition 8°, cloth, 238 pp. Baltimore: The Williams and Wilkins Company, 1947 \$4 50.

The author has not made any major changes in this second edition of his small book on psychopathology, but has confined himself to making certain minor improvements. The case records remain the same as in the first edition. The author believes that psychopathology was not changed fundamentally by World War II and therefore has not felt compelled to change his point of view on the subject. Some of the subjects discussed include anxiety and obsessional states, hysteria, sexual perversions, abnormalities of sexual function and drug addictions. A good index concludes the volume. The composition and printing were done in Great Britain, accounting for the yellowish tinge in the paper. The sheets were bound in the United States. The book is essentially an English publication, reflecting the British viewpoint. The volume should be in all neurologic and psychiatric collections.

*Psychotherapy. Its use and limitations.* By D Rhodes Allison, M.D., M.R.C.P., and R G Gordon, M.D., D.Sc., and F.R.C.P. 12°, cloth, 160 pp. New York: Oxford University Press, 1948 \$3 00 (Oxford Medical Publications).

This semipopular manual has been written for the student, the physician and the intelligent layman. It does not describe the methods of psychotherapy but endeavors to present the subject in a broad way, pointing out to the physician and the family ways to help the patient by maintaining his morale and courage. The material is well organized and covers the field of the psychoneuroses, with chapters on the psychoses, mental deficiency and psychopathic personalities. There are chapters on the relation of rheumatism to mental illness, other psychomatic conditions and the patient's reaction to bodily disease. A good index concludes the volume. The book is well published and should prove useful to persons interested in the subject.

## NOTICES

### ANNOUNCEMENTS

Dr Harrison E Kennard announces the removal of his office to 1180 Beacon Street, Brookline, for the practice of general surgery.

Dr Aaron Thurman announces the removal of his office to the Lister Building, 475 Commonwealth Avenue, Boston.

### AMERICAN COLLEGE OF SURGEONS

As previously announced, the twenty-seventh annual Hospital Standardization Conference will be held at the Biltmore Hotel, Los Angeles, from October 18 to 22, in conjunction with the thirty-fourth annual Clinical Congress of the American College of Surgeons.

The opening session of the Clinical Congress is a joint meeting for surgeons and hospital representatives on Monday morning, October 18, at 10 o'clock, at which the president of the American College of Surgeons, Dr Arthur W Allen, of Boston, president-elect of the Massachusetts Medical Society, will preside and speak on "Looking Forward with Hospital Standardization."

Meningitis, other forms, was reported from Boston, 2, total, 2

Meningitis, undetermined, was reported from Arlington, 1, Cambridge, 1, Leominster, 2, Springfield, 1, Westfield, 1, total, 6

Polymyositis was reported from Boston, 2, Cambridge, 1, Dartmouth, 1, Great Barrington, 1, Natick, 1, Waltham, 1, Westford, 1, Worcester, 1, total, 9

Salmonellosis was reported from Medford, 1, Worcester, 1, total, 2

Septic sore throat was reported from Medford, 1, total, 1

Trichinosis was reported from Boston, 1, Cambridge, 1, Lexington, 1, total, 3

Typhoid fever was reported from Chelmsford, 1, Dartmouth, 1, Gloucester, 1, Melrose, 1, total, 4

Undulant fever was reported from Boston, 1, Cambridge, 1, Chesterfield, 1, Dudley, 1, Webster, 1, total, 5

## MISCELLANY

### NATIONAL HEART INSTITUTE

Establishment of the National Heart Institute as one of the National Institutes of Health in the United States Public Health Service has been announced by Oscar R. Ewing, federal security administrator.

Concurrently, Surgeon General Leonard A. Scheele, United States Public Health Service, has announced the appointment of Dr. Cassius J. Van Slyke as director of the National Heart Institute, under the general supervision of Assistant Surgeon R. E. Dyer, director of the National Institutes of Health. In addition, Dr. Van Slyke will be directly responsible to the Surgeon General for co-ordination of all heart-disease activities in the Public Health Service, representing the Service in maintaining relations with professional societies, voluntary agencies and other civic groups that are interested in the progress of the heart-disease program.

## BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

*Factors Regulating Blood Pressure. Transactions of the first conference, April 24-25, 1947, New York.* Edited by B. W. Zweifach and Ephraim Shorr, Department of Medicine, Cornell University Medical College, New York. New York: Josiah Macy, Jr., Foundation, 1947. \$1.90.

This new conference in the Josiah Macy, Jr., Foundation series of conferences was participated in by nineteen authorities from Boston, New York City and other parts of the country. The papers and discussions deal with the various aspects of the subject. The publication should be in all medical libraries.

*Treatment in General Practice.* By Harry Beckman, M.D., professor of pharmacology, Marquette University School of Medicine, Milwaukee. Sixth edition. 8°, cloth, 1129 pp. Philadelphia: W. B. Saunders Company, 1948. \$11.50.

Dr. Beckman has revised thoroughly this last edition of his standard work on treatment. Many subjects have been completely rewritten, and much material has been added, including balantidiasis, coccidiosis, Colorado tick fever, creeping eruption, geotrichosis, Listerellosis, Loeffler's syndrome, melioidosis, mite infestation, moniliasis, new anemias, non-meningococcal meningitides, North Queensland tick typhus, pulmonary aspergillosis, Reiter's syndrome, rickettsialpox, thrombosis and embolism and the management of penicillin reactions. A long bibliography of sixty-five pages is appended to the text, and a comprehensive index concludes the volume. The text is well printed with a good type, on good light paper. The work is recommended for all medical libraries and for the collections of practicing physicians.

*La penicillina in chirurgia per infiltrazione locale massi a Br. Sante Ciancarelli, chirurgo degli Ospedali di Roma—clin. mal. infettive (Dir. G. Caronia) 4°, paper, 47 pp. Roma: Luigi Pozzi, 1948.*

The author of this small monograph has used his method of local massive infiltration of penicillin in surgical conditions for three years with good results. He describes his method of administration and the dosage used. He has treated osteomyelitis, suppuration of the hand, empyema of the pleura, lung abscess, mastitis, tonsillitis, lymphadenitis, abscesses, peritonitis, cerebral abscess and Ludwig's angina. The text is in Italian. The pamphlet is well printed, with a good type on good paper.

*Conference on Liver Injury. Transactions of the fifth meeting, September 26-27, 1946, New York.* 8°, paper, 128 pp. \$2.25. *Liver Injury. Transactions of the sixth conference, May 1 and 2, 1947, New York.* 8°, paper, 74 pp. \$2.00. Edited by F. W. Hoffbauer, M.D., Mayo Foundation, Rochester, Minn. New York: Josiah Macy, Jr., Foundation, 1947.

The fifth conference on liver injury discussed the relation of dietary factors to chemical liver injury, hepatic functional impairment from vitamin deficiency, liver function, chronic hepatitis and therapy in liver diseases, the sixth considered cirrhosis, the hepatorenal syndrome, chromatography in the study of liver disease and massive hepatic necrosis. These two volumes and the set should be in all medical libraries.

*Diseases of the Skin.* By Oliver S. Ormsby, M.D., attending dermatologist to the Presbyterian Hospital of Chicago, and Hamilton Montgomery, M.D., M.S., associate professor of dermatology and syphilology, Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota, Rochester. Seventh edition, thoroughly revised. 8°, cloth, 1462 pp., with 683 figures and 11 plates. Philadelphia: Lea & Febiger, 1948. \$18.00.

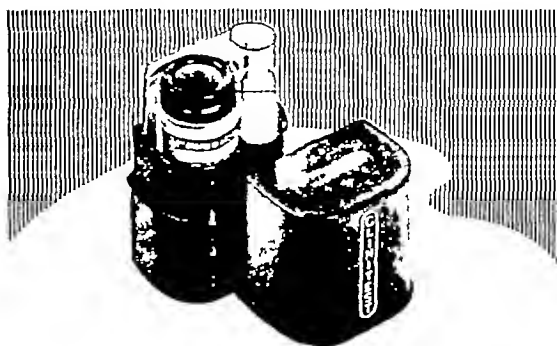
This standard authoritative text has been thoroughly revised by the incorporation of new material and the deletion of obsolete material. The additions include a number of new diseases not described in the previous edition and new methods of treatment of syphilis and other diseases with penicillin and other antibiotics. To keep the volume within bounds some chapters have been condensed and some of the text printed in small type. Ninety figures and eleven color illustrations have been added to the text. References have been limited and printed as footnotes on the appropriate pages. A good index concludes the volume. The book is well published and is recommended for all medical libraries and to dermatologists and physicians interested in diseases of the skin.

*Mental Health in Modern Society.* By Thomas A. C. Rennie, M.D., associate professor of psychiatry, Cornell University Medical College, and director, Division on Rehabilitation, National Committee for Mental Hygiene, and Luther E. Woodward, Ph.D., field consultant, Division on Rehabilitation, National Committee for Mental Hygiene. 8°, cloth, 424 pp. New York: The Commonwealth Fund, 1948. \$4.00.

The authors have based their book on actual work in the field of mental health, in psychiatry and psychiatric social work in the New York Hospital Rehabilitation Clinic for Psychiatrically Disabled Veterans and in field work in communities and states and in the sharing of experience with leaders in the various governmental and public services. The work is divided into three parts: lessons from the war period in four chapters, post-emergency problems in mental health, in one chapter, and sources of help in treatment and prevention, in eight chapters. The work is so comprehensive that an analytical review is excluded because of space limitations that will permit only an indication of the contents. The war period is discussed under the headings of mental-health services in the armed forces, emergency measures for aiding veteran-civilian adjustment, and psychiatric disabilities of war dynamics and motivation, principles, methods and results of treatment. The second part considers the continuing mental-health problems and needs, including problems of the wounded and veterans with psychiatric disabilities, the effect of war on the civilian population research and problems relating to more and better treatment of the mentally ill. The third part discusses the

# NOTICES (Concluded from page 418)

- SEPTEMBER 16-18 Vermont State Medical Society Annual Meeting Burlington
- SEPTEMBER 18 College of American Pathologists Page 418
- SEPTEMBER 20-22 American Hospital Association Page 310 issue of February 26
- SEPTEMBER 22 New England Conference of Industrial Physicians and Surgeons Page 244 issue of August 5
- SEPTEMBER 29 Mississippi Valley Medical Editors Association Page 170 issue of January 29
- OCTOBER 1 and 2 American Society of Anesthesiologists Inc Page 352 issue of September 2
- OCTOBER 1-MAY 20 Metropolitan State Hospital Page 418
- OCTOBER 6-9 American Board of Ophthalmology Page 170 issue of January 29
- OCTOBER 14 The Practical and Clinical Sides of the Management of the Rh Problem in Pregnancy Dr William C. Moloney Pentucket Association of Physicians 8 30 p.m. Haverhill
- OCTOBER 15 American Trudeau Society Page 418
- OCTOBER 18-22 American College of Surgeons Page 417
- OCTOBER 27 New England Obstetrical and Gynecological Society Annual Meeting Hotel Somerset, Boston
- NOVEMBER 1-3 American Clinical and Climatological Association Page 382 issue of April 15
- NOVEMBER 3 and 4 Annual Meeting of National Committee for Mental Hygiene, Inc. Page 282 issue of August 12
- NOVEMBER 4-6 American Society of Anesthesiologists Page 418
- NOVEMBER 6-12 American Public Health Association Page 420 issue of March 18
- NOVEMBER 10-13 Association of Military Surgeons of the United States Page 722 issue of May 13
- NOVEMBER 20-23 American Academy of Pediatrics Annual Meeting Chalfonte-Haddon Hall Hotel Atlantic City New Jersey
- DECEMBER 7-9 Southern Surgical Association Annual Meeting Page 343 issue of April 8
- DECEMBER 9 and 10 New York State Society of Anesthesiologists Page 34 issue of July 1
- FEBRUARY 4 1949 American Board of Obstetrics and Gynecology Inc. Page 244 issue of August 5
- MARCH 28-APRIL 1 1949 American College of Physicians Page 158, issue of July 22
- NOVEMBER 11-17 1949 Third Inter American Congress of Radiology Page 158 issue of July 22



"An excellent simple presumptive test for routine use in the diagnosis of diabetes"<sup>1</sup>

## CLINITEST

THE TABLET NO-HEATING METHOD FOR DETECTION OF URINE-SUGAR

**SIMPLE TECHNIC**—"My experience with Clinitest has convinced me beyond a shadow of a doubt that they are the *simplest* from the technical standpoint"<sup>2</sup>

**SELF-GENERATING HEAT**—"The reagent tablet, known as the Clinitest Urine Sugar Tablet generates heat when dissolved and the use of externally applied heat is not required"<sup>1</sup>

Clinitest—simple, speedy, compact, convenient—is distributed through regular drug and medical supply channels

1 Kasper J A and Jeffrey I A A Simplified Benedict Test for Glycosuria, Amer J Clin Pathology 14 117 21 (Nov ) 1944

2 Haid W H The Use of Screening Tests in the Clinical Laboratory, J Amer Med Tech. 8 606-14 (Sept.) 1947

## Washingtonian Hospital

41-43 WALTHAM STREET, BOSTON, MASS  
Incorporated 1859

Conditioned Reflex, Psychotherapy, Semi-Hospitalization For Rehabilitation of Male Alcoholics  
Treatment of Acute Intoxication and Alcoholic Psychoses Included

Outpatient Clinic and Social-Service Department for Male and Female Patients

JOSEPH THIMANK, M D, Medical Director

Visiting Psychiatric and Neurologic Staff  
Consultants in Medicine, Surgery and the Other Specialties  
Telephone HA 6-1750

## TWO-WAY PROTECTION

Tablets **FERROSATE** (Kenmore)  
(Ferrous Sulfate gr iv)

are coated twice to provide a doubly protected Ferrous Sulfate offering these therapeutic advantages

- 1 Inner coating prevents premature oxidation in vivo
- 2 Outer coating increases palatability and aids in preventing tooth discoloration

Write Dept. N9 for professional sample.  
**Kenmore Pharmacy, Inc.**  
500 Commonwealth Ave  
Boston Mass U S A

Identification cards for the protection of your diabetic patients now available free upon request

**AMES COMPANY, INC.**  
ELKHART, INDIANA

## COLLEGE OF AMERICAN PATHOLOGISTS

The Northeastern Regional Meeting of the College of American Pathologists will be held at the Massachusetts General Hospital, Boston, on September 18

## PROGRAM

- 8 30-9 30 a m Registration  
 9 30-10 00 a m Recent Advances in Laboratory Diagnosis of Pregnancy Stanley L Robbins, M D  
 10 00-10 30 a m Hormonal Alteration of Breast Carcinoma Ira T Nathanson, M D  
 10 30-11 00 a m Practical Problems in the Rh Investigation Louis K Diamond, M D  
 11 00-11 30 a m Neuropathology Its current methods and values Raymond D Adams, M D  
 11 30 a m-12 00 m The Use of Photoelectric Spectrophotometry in Clinical Problems Francis T Hunter, M D  
 12 00 m-12 30 p m The Role of the Laboratory in the Diagnosis of Tuberculosis William Steenken, Jr, M D  
 12 30-2 00 p m Luncheon in Cafeteria, Massachusetts General Hospital  
 2 00-2 30 p m Diagnostic Procedures in Virus Diseases of the Respiratory Tract Maxwell Finland, M D  
 2 30-3 00 p m Diagnostic Procedures in Certain Virus Diseases of the Central Nervous System John F Enders, M D  
 3 00-4 00 p m Pathology of the Newborn Sidney Farber, M D  
 4 00-5 00 p m Difficulties and Pitfalls in Interpretation of Vaginal and Pulmonary Smears by the Papanicolaou Method Ruth M Graham, S B  
 6 00 p m Fellowship  
 7 00 p m Dinner at Hampshire House, 84 Beacon Street, Boston (\$4.60 per person)  
 8 00 p m Human Sexuality John Roek, M D

## AMERICAN TRUDEAU SOCIETY

The Eastern Section of the American Trudeau Society will meet on October 15, 1948 at the Rutland State Sanatorium, Rutland, Massachusetts. This meeting will be among the events arranged to mark the fiftieth anniversary of the opening of the institution, the first of its kind in America.

## METROPOLITAN STATE HOSPITAL

The Fourteenth Postgraduate Seminar in Neurology and Psychiatry will begin on Friday, October 1. The program will be as follows: a review course in basic neurology and psychiatry, consisting of sixty-six lectures to be held every Friday from 2 to 10 p m from October 1 to December 3, 1948, and from March 4 to May 20, 1949, at the Metropolitan State Hospital, 475 Trapelo Road, Waltham, a course in social and special psychiatry consisting of thirty-six lectures, to be held every Wednesday from 5 30 to 10 p m from October 13 to December 8, 1948, and from March 16 to May 11, 1949, at the Boston Psychopathic Hospital, 74 Fenwood Road, Boston, and a course in pediatric neuropsychiatry (child psychiatry) consisting of twenty lectures, to be held every alternate Monday from 6 to 10 p m from October 11 to December 6, 1948, and from March 14 to May 9, 1949, at the Walter E Fernald State School, Waverley.

All interested graduate physicians should apply before October 1 in writing to Dr William C Gæbler, superintendent, Metropolitan State Hospital, Waltham.

The applicants should indicate which of the three courses of the Seminar they wish to attend. The registration is requested as a matter of courtesy to the institutions where courses are conducted and as a convenience for the registrants, who will thus be able to receive the schedules and who will be notified in time in case changes in the schedule should become necessary during the year.

## AMERICAN SOCIETY OF ANESTHESIOLOGISTS

The annual meeting of the American Society of Anesthesiologists will be held in St. Louis from November 4 to 6.

## THE FOUNDATION PRIZE

The South Atlantic Association of Obstetricians and Gynecologists announces the establishment of the Foundation Prize. Authors of papers on obstetric or gynecologic subjects desiring to compete for the prize may obtain information from Dr E D Colvin, secretary-treasurer, 1259 Clifton Road, N E, Atlanta, Georgia.

## COLORADO STATE MEDICAL SOCIETY

The annual meeting of the Colorado State Medical Society will be held in Glenwood Springs from September 22 to 25 (secretary, H T Sethman, Republic Building, Denver 2, Colorado).

## INDIANA STATE MEDICAL ASSOCIATION

The annual meeting of the Indiana State Medical Association will be held in Indianapolis from October 26 to 28 (secretary, Ray E Smith, 23 East Ohio Street, Indianapolis 4, Indiana).

## KENTUCKY STATE MEDICAL ASSOCIATION

The annual meeting of the Kentucky State Medical Association will be held in Covington from September 27 to 30 (secretary, P E Blackerby, M D, 620 South Third Street, Louisville 2, Kentucky).

## MICHIGAN STATE MEDICAL SOCIETY

The annual meeting of the Michigan State Medical Society will be held in Detroit, September 22 to 24 (secretary, L Fernald Foster, M D, 2020 Olds Tower, Lansing 8, Michigan).

## NEVADA STATE MEDICAL ASSOCIATION

The annual meeting of the Nevada State Medical Association will be held in Ely on September 24 and 25 (secretary, Roland W Stahr, M D, 118 California Avenue, Reno, Nevada).

## MEDICAL SOCIETY OF VIRGINIA

The annual meeting of the Medical Society of Virginia will be held in Richmond from October 18 to 20 (secretary, Miss A V Edwards, 1200 East Clay Street, Richmond 19, Virginia).

## WASHINGTON STATE MEDICAL ASSOCIATION

The annual meeting of the Washington State Medical Association will be held in Seattle from October 3 to 6 (secretary, John P McVay, M D, 327 Cobb Building, Seattle 1, Washington).

## STATE MEDICAL SOCIETY OF WISCONSIN

The annual meeting of the State Medical Society of Wisconsin will be held in Milwaukee from October 4 to 6 (secretary, C H Crownhart, 110 East Main Street, Madison 3, Wisconsin).

## SOCIETY MEETINGS AND CONFERENCES

## CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, SEPTEMBER 16

## FRIDAY, SEPTEMBER 17

\*9-00 a m-12 00 m Combined Medical and Surgical Staff Round  
 Peter Bent Brigham Hospital

## TUESDAY, SEPTEMBER 21

\*12 15-1 15 p m Clinicoroentgenological Conference Peter Bent Brigham Hospital

\*1 30-2 30 p m Pediatric Rounds Burreham Memorial Hospital for Children Massachusetts General Hospital

## WEDNESDAY, SEPTEMBER 22

\*12 00 m-1 00 p m Clinical Conference (Children's Hospital)  
 Amphitheater Peter Bent Brigham Hospital

\*Open to the medical profession

SEPTEMBER 13-15 American Academy of Pediatrics Olympic Hotel  
 Seattle Washington

SEPTEMBER 14 New England Society of Anesthesiologists Page 317  
 ISSUE OF AUGUST 19

(Notices concluded on page xv)

# The New England Journal of Medicine

Copyright, 1948 by the Massachusetts Medical Society

Volume 239

SEPTEMBER 16, 1948

Number 12

## EPIDEMIOLOGY IN COUNTRY PRACTICE\*

WILLIAM N. PICKLES, M.D.†

AISGARTH, YORKSHIRE, ENGLAND

AS I studied the long list of my illustrious predecessors who have presented the Cutter Lecture on Preventive Medicine I was truly grateful to the pious founder, that modest and yet forceful character, Dr. John Clarence Cutter, for the opportunity to visit this great country, to receive so many kindnesses from so many people and to find a truly New World opened to us on this side of the Atlantic. But what had I to offer in comparison with such eminent men? For I come to speak about very simple things, everyday happenings and elementary deductions drawn from them such as are within the scope of but a meager intellectual equipment. Yet I feel, as William Budd felt a hundred years ago, that country districts have certain advantages for the study of epidemiologic problems and that the ability of the observer is of secondary importance to his opportunities, which indeed are great. It is always my delight to quote this pioneer, whose conclusions were assailed with fierce criticism in his lifetime and who was completely forgotten until a very few years ago. I shall let him speak for himself.

It is obvious that the formation of just opinions on the question how diseases spread may depend less on personal ability than on the opportunities for its determination which may fall to the lot of the observer.

It is equally obvious that where the question at issue is that of the propagation of diseases by human intercourse, rural districts, where the population is thin and the lines of intercourse are few and easily traced, offer opportunities for its settlement which are not met with in the crowded haunts of large towns.

William Budd began his career with a term of country practice in his native village in Devonshire, where he made his memorable observations on typhoid fever.

The other pioneer whom I should like to quote is Peter Ludwig Panum, the Dane who was sent as a youngster to the Faroe Islands to investigate an epidemic of measles. Although this is also a hundred years ago there is little to add to the knowledge of the epidemiology of measles that he acquired. He wrote similarly to Budd the

isolated situation of the villages and their limited intercourse with each other made it possible in most cases to ascertain where and when the person who fell ill had been exposed to infection and to prove that the contagion could not have affected him either before or after the date stated.

Reminiscences are the privilege of the garrulous old, and I hope I shall be forgiven at this point if I am autobiographical. I recall most vividly the following incident: a gypsy woman driving a caravan into a village in the summer twilight, a sick husband in the caravan, a faulty pump at which she proceeded to wash her dirty linen, and shortly afterward my first and only serious epidemic of typhoid fever, which left me with a lasting impression of the unique advantages of the country doctor for the investigation of infectious disease. This incident showed me the ease with which an epidemic can be traced in the country and the ease with which it can be brought to an end. The handle of the Broad Street pump was removed at the urgent request of John Snow, because he believed that its clear and sparkling water contained the deadly poison of cholera. In this instance of mine, the handle was chained to the pump, where indeed it remains to this day, and there were no more primary sufferers. This was in 1910. I was twenty-five years of age and a very inexperienced assistant in a country practice, very near the one in which I have spent my life. Shortly afterward I had another memorable experience.

Now I have a friend, a very young friend—he is not yet five years of age. He is accomplished. He can play quite pleasingly on the piano. He can read and even write a little. I said to him one day, "John, you'll soon be going to school, you will enjoy that." He replied, "I'm not going to school, I know it all." That is the attitude of many young doctors entering general practice, especially if they have done a number of house jobs, and that, in those far-off days, was my attitude. I knew it all, and I got some shocks. And one of the shocks was the presence of an entirely new infectious disease—jaundice in epidemic form.

\*The Cutter Lecture on Preventive Medicine delivered at the Harvard School of Public Health, Boston, April 12, 1945.

†Medical officer of health, Aysgarth Rural District, Yorkshire, England.

This baby's mother learned  
about Mead's Oleum Percomor-  
phum from her physician, not from  
public advertising or displays

*"Servamus Fidem"*

## HOW much sun does the infant really get?

*Not very much* (1) When the baby is bun-  
dled to protect against weather or (2) when  
shaded to protect against glare or (3) when  
the sun does not shine for days at a time  
Mead's Oleum Percomorphum is a pro-  
phylactic against rickets available 365½  
days in the year, in measurable potency and  
in controllable dosage *Use the sun, too*

Mead Johnson & Co , Evansville, Ind., U S A

SEP 13 1948  
LIBRARY

# The New England Journal of Medicine

Copyright, 1948 by the Massachusetts Medical Society

Volume 239

SEPTEMBER 16, 1948

Number 12

## EPIDEMIOLOGY IN COUNTRY PRACTICE\*

WILLIAM N. PICKLES, M.D.†

ALSGARTH, YORKSHIRE, ENGLAND

AS I studied the long list of my illustrious predecessors who have presented the Cutter Lecture on Preventive Medicine I was truly grateful to the pious founder, that modest and yet forceful character, Dr. John Clarence Cutter, for the opportunity to visit this great country, to receive so many kindnesses from so many people and to find a truly New World opened to us on this side of the Atlantic. But what had I to offer in comparison with such eminent men? For I come to speak about very simple things, everyday happenings and elementary deductions drawn from them such as are within the scope of but a meager intellectual equipment. Yet I feel, as William Budd felt a hundred years ago, that country districts have certain advantages for the study of epidemiologic problems and that the ability of the observer is of secondary importance to his opportunities, which indeed are great. It is always my delight to quote this pioneer, whose conclusions were assailed with fierce criticism in his lifetime and who was completely forgotten until a very few years ago. I shall let him speak for himself.

It is obvious that the formation of just opinions on the question how diseases spread may depend less on personal ability than on the opportunities for its determination which may fall to the lot of the observer.

It is equally obvious that where the question at issue is that of the propagation of diseases by human intercourse, rural districts, where the population is thin and the lines of intercourse are few and easily traced, offer opportunities for its settlement which are not met with in the crowded haunts of large towns.

William Budd began his career with a term of country practice in his native village in Devonshire, where he made his memorable observations on typhoid fever.

The other pioneer whom I should like to quote is Peter Ludwig Panum, the Dane who was sent as a youngster to the Faroe Islands to investigate an epidemic of measles. Although this is also a hundred years ago there is little to add to the knowledge of the epidemiology of measles that he acquired. He wrote similarly to Budd the

isolated situation of the villages and their limited intercourse with each other made it possible in most cases to ascertain where and when the person who fell ill had been exposed to infection and to prove that the contagion could not have affected him either before or after the date stated.

Reminiscences are the privilege of the garrulous old, and I hope I shall be forgiven at this point if I am autobiographical. I recall most vividly the following incident: a gypsy woman driving a caravan into a village in the summer twilight, a sick husband in the caravan, a faulty pump at which she proceeded to wash her dirty linen, and shortly afterward my first and only serious epidemic of typhoid fever, which left me with a lasting impression of the unique advantages of the country doctor for the investigation of infectious disease. This incident showed me the ease with which an epidemic can be traced in the country and the ease with which it can be brought to an end. The handle of the Broad Street pump was removed at the urgent request of John Snow, because he believed that its clear and sparkling water contained the deadly poison of cholera. In this instance of mine, the handle was chained to the pump, where indeed it remains to this day, and there were no more primary sufferers. This was in 1910. I was twenty-five years of age and a very inexperienced assistant in a country practice, very near the one in which I have spent my life. Shortly afterward I had another memorable experience.

Now I have a friend, a very young friend—he is not yet five years of age. He is accomplished. He can play quite pleasingly on the piano. He can read and even write a little. I said to him one day, "John, you'll soon be going to school, you will enjoy that." He replied, "I'm not going to school, I know it all." That is the attitude of many young doctors entering general practice, especially if they have done a number of house jobs, and that, in those far-off days, was my attitude. I knew it all, and I got some shocks. And one of the shocks was the presence of an entirely new infectious disease—jaundice in epidemic form.

\*The Cutter Lecture on Preventive Medicine delivered at the Harvard School of Public Health, Boston, April 12, 1948.

†Medical officer of health, Aysgarth Rural District, Yorkshire, England.

## EPIDEMIC HEPATITIS

My elderly principal, having been born, brought up and having practiced in the neighborhood, had seen several similar epidemics of jaundice. They were familiar experiences to him, and he laughed at my perplexity. However, reference to my textbooks somewhat restored my self-esteem for the writers seemed to be, and actually were, in precisely the same state of abysmal ignorance as I was myself, and only touched on a very serious form of infectious jaundice, which they called "Weil's

form of jaundice upon which a quack doctor could thrive, I suppose even he would be baffled by sufferers from stone in the common duct or cancer of the head of the pancreas. He was only doing what so many of us do — keeping his patient in a state of tranquillity while nature effected the cure. That there actually was a man who acquired this title presupposes a large number of sufferers and that most certainly of epidemic hepatitis. His remedy, by the way, was a decoction of barberry bark or the bark of the common berberis, which grows wild in the district, most likely an escape

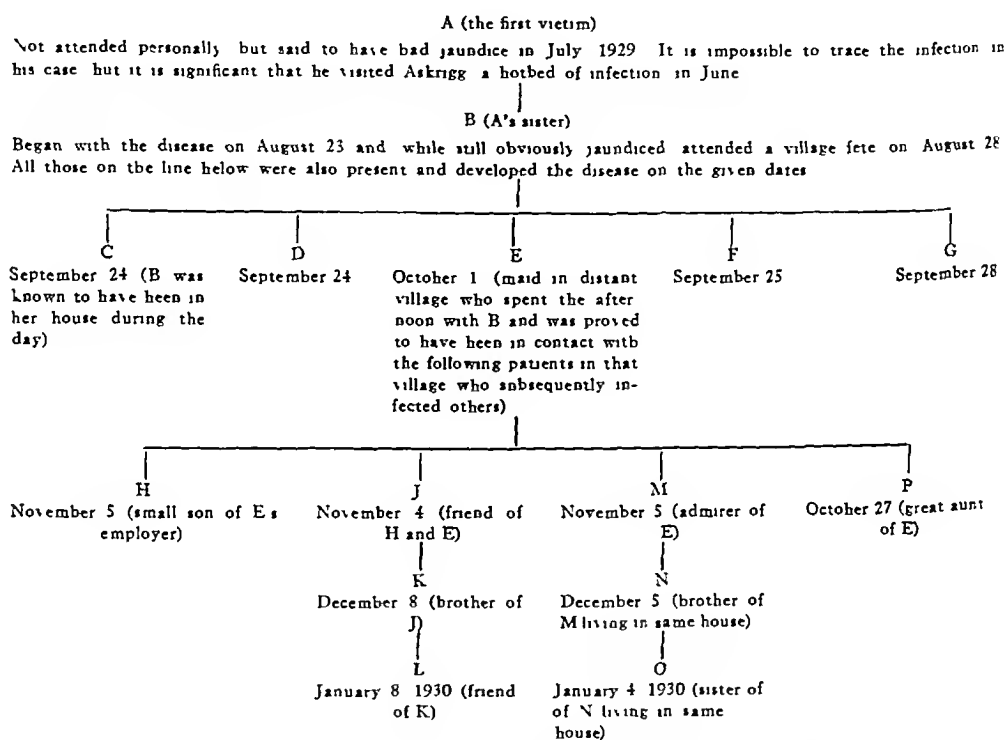


FIGURE 1 Course of Epidemic Hepatitis among Villagers Who Attended a Fete

disease", I pondered long and often whether this could be the same disease as that I was faced with. Others have pondered in the same way. It is a strange thought that the same agent that produced these epidemics so prevalent in country districts, and more interesting than serious, should in the late war have assumed such importance. That these epidemics have been for long prevalent in country districts is to my mind clear. So far as my own district is concerned, I have the evidence of my old principal, — no mean practitioner of his art, — the tradition of the countryside and the knowledge that seventy years ago there lived in Wensleydale a jaundice doctor who combined this useful occupation with that of a castrator.

Epidemic hepatitis as I have seen it — generally speaking requiring no treatment — is just the

from some ancient herb garden. After 1910 I never saw epidemic jaundice until 1929, and then I saw it to some tune. In a population of 5700 there were at least 250 sufferers, and of these I myself attended 115. I do not intend to enter the clinical field beyond stating that the disease ran a mild course in the great majority of my patients. It is on the epidemiology that I wish to concentrate.

Now, those busybodies the pathologists — or that branch of them which deals with and, of course, knows all about the virus — have gravely prejudiced the issue by discovering the virus of hepatitis in the stools of sufferers from this disease and have to such an extent captured the imagination of observers that it is almost assumed that infection must be by this means and no other. He would be a bold man who now asserted that the infection

could not be by the feces, but I do not want to stress that, in this and all succeeding epidemics that I have encountered, I felt justified in attributing the spread to personal contact, most likely by droplet infection. Contact sufficient to reproduce the disease was often casual, and there were no explosive outbreaks such as would have occurred from the contamination of food and water. Just the same thing has happened in poliomyelitis, and although I have not seen any reference to the discovery of virus A or B of influenza in feces — except in those of inoculated mice — I think that their presence is highly probable in this disease, and yet we shall most of us still go on believing that influenza is spread from person to person by droplet infection.

I am afraid I have repeated very often the story of a village fete depicted in Figure 1, but it gives evidence of the incubation period of about a month suggested by Booth and Okell and it is definitely my best example. Looking half way down the story one sees that five people began with the disease within a week, and I discovered that they had one experience in common: they had all been present at a fete in one of our villages on August 28. Some sufferers from the disease had therefore probably been present at the fete. After prolonged search I found that a young girl who had begun with the disease on August 23 had been at the entertainment. I had actually seen her in bed in the morning and never dreamt she could have left it. She must have eluded me with great skill throughout the afternoon, since I was there myself and never set eyes on her. She spent the afternoon with E, another young girl, and was in the house of Mrs. C, so that I think it is a fair presumption that she infected them and the other three. This young girl E, a maid in another village, infected four others. One was her employer's small son, another his friend, and another her own great-aunt. All this was reasonably clear. Of the fourth — M — there was some doubt. He was a rather pathetic little fellow of forty (since dead of a tuberculous kidney) and denied all acquaintance with this young girl. However, his sister gave him away shamelessly. "Robert not know Margaret?" said she, "Why he's very fond of her — he generally goes in at the back door in the evenings and helps her to wash up." Robert might well have said with Samson, "If ye had not plowed with my heifer, ye had not found out my riddle." A brother of Robert succumbed a month later, and in January, with poetic justice, the tell-tale sister. Thus, to my knowledge, one young girl determined to have what she considered her legitimate amusement, jaundice or no jaundice, and was responsible for 13 sufferers.

Figure 2 thus shows an epidemic in a family of young adults and among their friends. It shows rather clearly the monthly incubation period and suggests a short period of infectivity. I do not

think one could explain this serial incidence without this assumption. I have acted on this assumption and allowed children, if they were well enough, to resume school after the fourteenth day, — well on the safe side, — with no evidence of spread of the disease. I came to the conclusion in 1930 that the incubation was about a month, the infectivity period about a week and the disease was spread by personal contact, probably by droplet infection, and I have nothing to add to these conclusions,

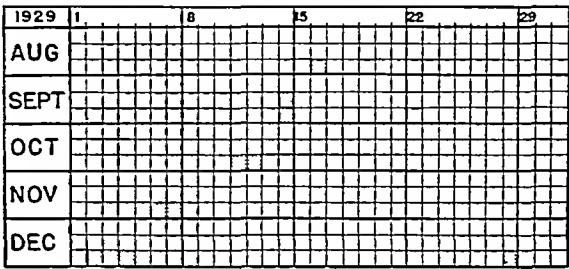


FIGURE 2 Epidemic Hepatitis

since I have been fortunate enough to observe seven further — if smaller — epidemics, which have all faithfully reproduced these features.

EPIDEMIOLOGIC METHOD

Let us return for a few moments to the peculiar opportunities of the country doctor. I recall a particularly lovely evening in early summer when I climbed alone to the top of one of our noble hills. The setting sun lit up the grim pile of an ancient castle, once the prison of that unhappy queen, Mary of Scotland. Our attractive little lake seemed to lie at my feet, and one by one I made out most of our gray villages with their pall of smoke. And as I watched the evening train creeping up the valley, with its pauses at our three stations, I had this strange thought, that there was hardly a man, woman or child in all those villages of whom I did not know even the Christian name and with whom I was not on terms of friendship. My wife and I say we know nearly all the dogs and indeed many of the cats. Now, does not this intimate knowledge of his flock put the country doctor in a superior strategic position for the study of such a subject as epidemic disease? I could say much of my patients, the Yorkshire dalesfolk, of their shrewdness and ability, of their remarkable memories, of their startling intelligence, which tempts me to deplore that in some ways education blunts the edge of intelligence, of that seemingly impenetrable crust, which is only a crust, concealing great friendliness and goodness of heart. These are just the people to help a doctor in his investigations. Matters so delicate as heredity and consanguinity have to be

approached with care, but on the whole I have found my patients co-operative and slow to take offense. Also, I cannot help knowing much about the details of their relatively simple existence. I have known the grandparents of many of my present-day patients and have been able to trace characteristics, medical and otherwise, through the generations to the present day. Today I know what markets the farmers frequent, the schools their children attend, the young people's love affairs, the festivities that take place at intervals in every

retire with reluctance, knowing that our real life is then over and fearing to experience that utter loneliness which comes from a separation from our work and from our friends. Not everyone has the temperament of a Diocletian — content to throw aside the purple and grow cabbages, and, as good students of Gibbon will remember, even he lived to regret it.

You have, of course, in the United States the very best example of continuity in a practice. In 1872 George Huntington described examples of

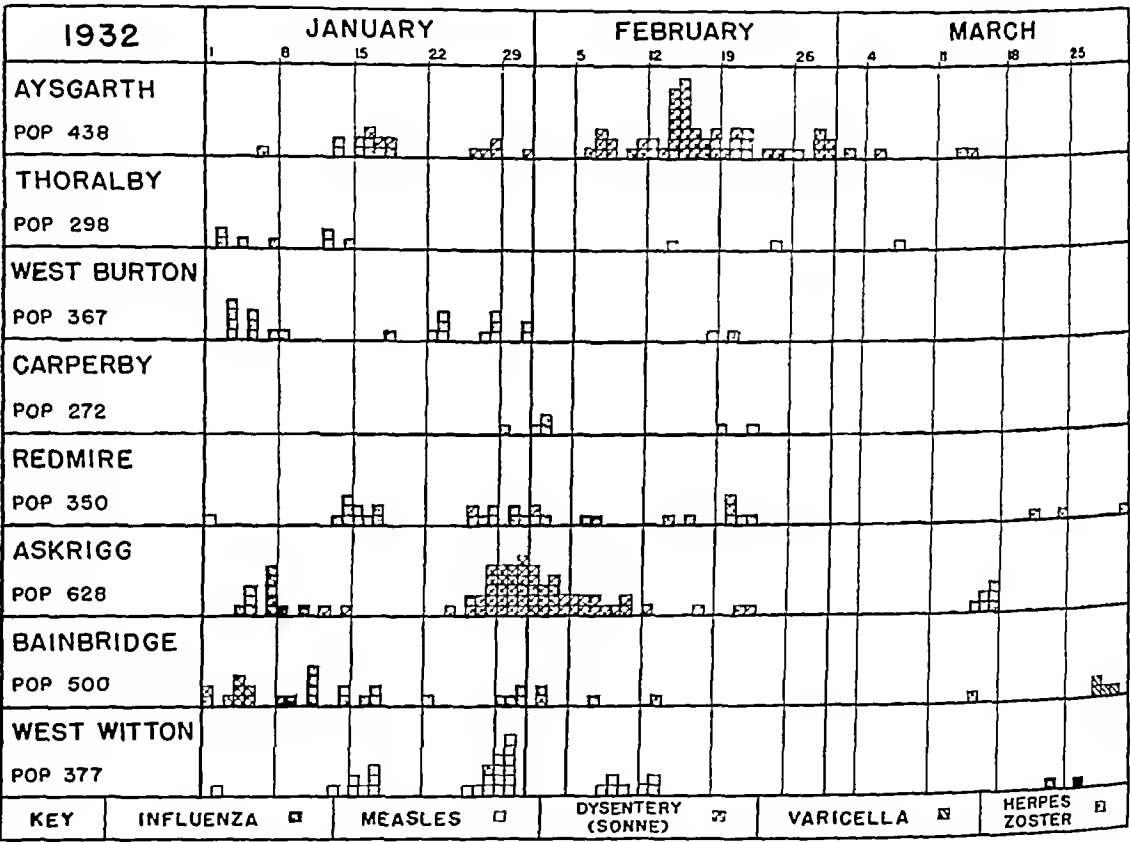


FIGURE 3 Example of Village Epidemiologic Records (in the Actual Charts the Key Squares Are in Various Colors)

village of the dale, the visits to the large towns for shopping or the yearly expedition to the Pantomime and the summer trip to the seaside. On many of these expeditions, infectious disease has been introduced into our midst, and one is rarely in doubt about the origin of any epidemic. A little help and encouragement turns the schoolmaster into an enthusiastic epidemiologist, and I have been fortunate all these years in having an ally, the headmaster of the grammar school, which serves a large area and is often responsible for the spread of epidemics. There is, moreover, stability and continuity of country practice. Most of us show but little inclination to change our habitat and

the chorea that bears his name, and it was a fact that his father, grandfather and great-grandfather had traced these sufferers through the generations and found among other things that the disease did not skip a generation.

Now a few words on technic. If one sets about to study epidemics in country practice one must have some simple technic. I carry a pocket diary, and at the bedside each sufferer is entered in the diary under the date on which the disease began — for example, March 10, 1947, Jonathan Metcalfe, aged ten, village of Aysgarth, measles and so forth. At suitable intervals these are entered on the charts (Fig 3).

A chart is kept of every quarter as it comes along. The names of the villages are arranged in what I consider their natural groups, the whole on graph paper. A colored square is decided on for each infectious disease, and each patient is allotted a square placed opposite the appropriate group of villages and beneath the date on which the disease began. These charts are bound in book form. The names and ages of the sufferers are written on the opposite side of the page under the particular symbol of the disease, with short notes, clinical and epidemiologic, as necessary. It is the short and only possible exposure that one is always on the lookout for, the following examples occurred during an epidemic of measles.

A man in a village remote from the prevailing epidemic exhibited the disease. Twelve days previously a friend of his had called at my surgery and, finding no one at home, had repaired to the inn conveniently situated on the other side of the road, and sat cheek by jowl with this man over their drinks. Returning to the surgery he was found to be suffering from measles. During the short visit to the inn he appeared without a reasonable doubt to have infected his companion, and the incubation period was most accurately twelve days.

A boy employed on a farm arrived at the surgery on his bicycle and announced he had "gotten mazzles" (contracted measles). This certainly was the case, and he was told to go to his mother's house and shout to her the same tidings outside the door, that she might have the living room cleared of his young brothers and sisters. He then remained in his bedroom for a fortnight. On the twelfth day after his arrival, his aunt, and only his aunt, became a victim of the disease although she had never seen the boy and had left the house the morning after his arrival. It was found that the boy's bedroom and the living room directly below, by a usual and capricious arrangement of the builder, were lighted by one long window, giving direct aerial access from one room to another. The meal table was directly below this gap and the aunt, who sat directly underneath at meals, was apparently thus infected.

Mumps pays only occasional visits and in the last large epidemic, in 1935, traversed the district with measured stride, owing to its long incubation period, and lasted a whole year. It was a long time before I had a case of the short and only possible exposure, but it arrived. Betty was a bridesmaid at a wedding outside the district on June 11. She was a rather sick little bridesmaid and was later found to have this disease. On the evening of June 26 her mother first had symptoms and a few days later showed a letter from her sister, the bride of the eleventh, stating that her symptoms had also begun on the same evening. The incubation period in the bride was definitely fifteen days. Later, I had several similar cases and the period was never less

than fifteen days and never longer than seventeen or eighteen.

### INFLUENZA

At this point I think we should enter on the subject of influenza, the most important of our epidemic visitants. Influenza, more than any other disease, transforms the busy but orderly existence of the country doctor into a nightmare. To visit fifty houses as I have done in a country district and see three times that number of patients is no small feat in the space of a working day, however long. Some of these have to be visited a second time late at night and there are always visits to our *malades imaginaires*, who dread that they will be neglected in such a strenuous period. In the 1937 influenza epidemic the ferocity lasted under a month as it spread quickly from village to village, owing, I believe, to the improved methods of transport.

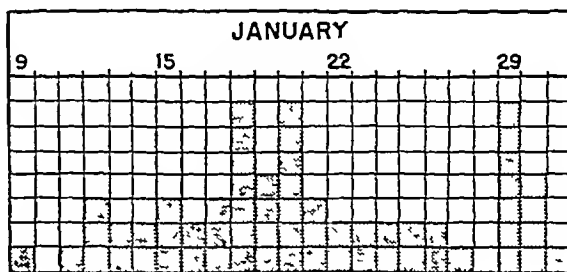


FIGURE 4 Influenza.

Lately, it has been the policy of the education authorities to close the small schools and concentrate on those in the larger villages. This may be good in the cause of education, but it adds substantially to the spread of infection. It gives us visits to isolated farms that might otherwise have escaped and many walks in the midst of strenuous days over sodden fields, not at all acceptable.

Figure 4 shows part of an epidemic in 1935. A schoolmistress returning from a Christmas visit to her parents in Scarborough, feeling far from well, attended her school on the first day of opening. She attended a brief morning session and then was quite unable to continue. In this session she was responsible for 78 victims among her charges and their families. I was not aware of this until I studied my charts later, and the worthy lady is probably not aware of it to this day. It is quite definite that this village, which was the only one to suffer severely in 1935, almost escaped in 1937, suggesting some measure of immunity in a village population. In 1946 I had the privilege and pleasure of a visit from that great Australian scientist, Professor Frank Burnet. He agreed with me on this point, and later we were able to prove from my charts that in a

village community there was a considerable degree of immunity to influenza for four years but that this declined and faded altogether in seven I think the help I got from Burnet on this occasion illustrates what I have often said that it is the role of the country doctor to collect facts from which others more skilled can draw conclusions

Influenza appeared in Wensleydale in 1943, imported by a schoolmistress who had spent the half-

the only occasion in which I have attended the same patient with this disease twice

On May 6, 1937, a young married woman developed shingles, and on the following day, a young farmer in a village four miles distant. They had an experience in common, having attended a sale in the latter's village a fortnight before and having tea at the farmer's house, his wife being a great friend of the young married woman. Infection for both appears to have been acquired at one or other of these entertainments, although in this case I was unable to trace the culprit. The male sufferer was present on the day of national rejoicing, May 12, the Coronation of King George VI, at the local junketings, which took the form of the usual tea and sport, and his victims are shown in Figure 6. The grandfather of one of these later developed shingles. I take it that the close connection between the two diseases is now firmly established, but it has been interesting on many occasions to find cases of this association, if only to show the advantages of country practice.

In the months June to October, 1940, we also had the two diseases and during the same period five sufferers from Bell's palsy. Bell's palsy has been a very rare disease to me. Actually, in thirty years of practice I had never seen a single case, and naturally 5 sufferers in a short period set me thinking. The presence of shingles and chicken pox was significant, although there appeared to be no direct connection between them and the sufferers from facial paralysis. Professor J. F.

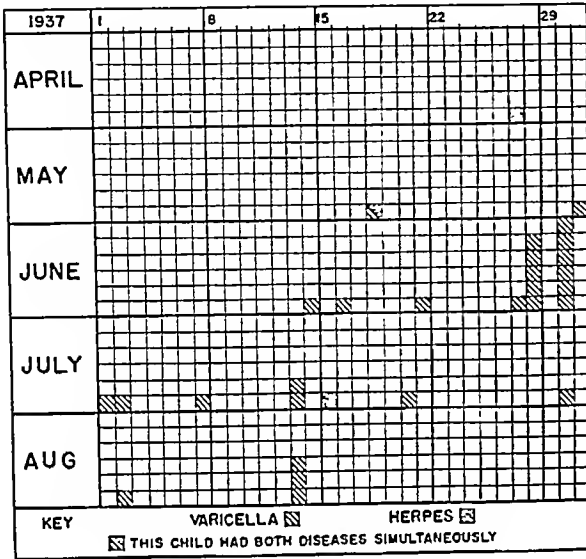


FIGURE 5 Chicken Pox and Shingles I

term holiday in Manchester. I saw several girls in this school suddenly stricken with what was undoubtedly clinical influenza in the first week of November when there was no sign of the presence of an epidemic in the country at large according to the weekly records of influenza deaths. By the end of the year these had risen to 1300 per week.

#### CHICKEN POX AND SHINGLES

On April 27, 1937, a young married woman exhibited the initial symptoms of supraorbital herpes. On May 18 her baby daughter developed herpes zoster in the lumbar region and widespread chicken pox, a fairly rare combination (Fig 5). On May 31, a little girl much attached to the baby next developed the disease, but returning to school one week after falling ill, I believe, also infected this one, explaining why the entry comes out of its turn. The epidemic spread to the sister village and claimed another victim from herpes zoster. This patient lived at a farm really in the wilds, and the only possible infector was a small girl who was taken there by her mother three days before she developed a rash, suggesting that she was infectious at the time. This child also added to one's knowledge later, in that she again developed chicken pox in 1945,

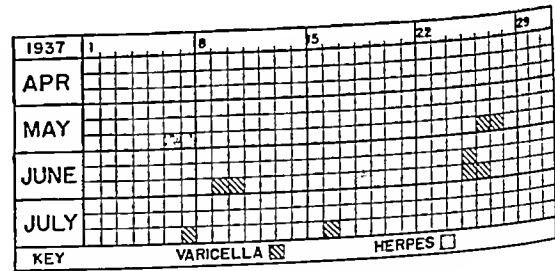


FIGURE 6 Chicken Pox and Shingles II

Bedson, of the London Hospital, most kindly undertook complement-fixation tests on the serum of three of these, but only one was positive for the virus of herpes and varicella. Thinking about this afterward, I do not consider that one would have got valuable information from these tests, except for negative reactions, for most people have had one or other disease and would presumably give positive serum results. One of the negative reactors gave us far more information by developing a most severe attack of chicken pox within the year showing I believe, conclusively that the facial paralysis was not due to the virus. I am inclined to

believe that these sufferers were infected by some virus allied to poliomyelitis of which they were the only efflorescent examples. Later I did have a patient suffering from facial paralysis who had unmistakable herpes vesicles in his auditory meatus. In the autumn of 1947, when we also had our first experience of a poliomyelitis epidemic, one little boy developed facial paralysis with no further extension. All these patients completely recovered.

#### FREQUENCY OF INFECTIOUS DISEASE

That the charting of epidemic disease in country practice is a formidable task may be gathered from the fact that in fifteen years and three months, 4855 cases of infectious disease have been recorded (Table 1). Influenza tops the list, followed by the diarrheal diseases—often Sonne dysentery. At the bottom, thank God, comes diphtheria.

It was recently pointed out by a colleague to whom I was showing this list that perhaps teaching bodies did not realize how few of these diseases, which loom large in a general practitioner's work, are even seen by the student in his ordinary course. This seems to suggest that facilities should be given him to visit patients in their own homes so that he does not see sufferers from these diseases for the first time when he takes up practice on his own account. Furthermore, I believe from the human point of view it would be a corrective to hospital outpatients—that varied collection of interesting cases—for a student to go alone into a patient's house and find out that his life is to be spent attending to men, women and children—not cases—and also to see at first hand under what conditions they live.

#### ERYTHEMA NODOSUM

Erythema nodosum is not a common disease in any experience and many years ago I began charting sufferers, thinking the complaint had many points in common with the exanthemas. Now the record is there so that I can follow up the connection with tuberculosis. To my sorrow in 1 case in the spring of 1946, the connection was only too obvious. A little girl of eight—the idol of her family—having just recovered from this disease died within two days from tuberculous meningitis.

#### PREVENTION OF DIPHTHERIA

I think I should say a little about diphtheria prophylaxis. In my time in Wensleydale diphtheria has rarely appeared, but when it comes it kills, and consequently protective inoculation has now for many years been an especial care. Bearing in mind that in inoculated children added protection is acquired by subsequent actual experience of the organism, I had a little doubt whether it was possible to produce permanent immunity in a child population in which this experience was largely lacking. Dudley showed in his inoculated boys at

Greenwich Hospital School that there was a temporary rise in the carrier rate, but in Hamilton, Ontario, after many years of a high percentage of inoculations, carriers virtually disappeared suggesting that the germ had been banished from the city. That is all to the good if one remains in Hamilton, but if one becomes a Canadian soldier and is drafted to a camp in England, it is possible that one's immunity may be low and if exposed to diphtheria,

TABLE 1 *Cases of Epidemic Disease*

DISEASE	NO OF CASES
Influenza	1112
Diarrhea and vomiting	1018
Measles	510
Febrile catarrh	407
Chicken pox	318
Whooping cough	295
Tonsillitis	289
Mumps	235
German measles	175
Herpes zoster	140
Hepatitis	122
Scarlet fever	117
Lobar pneumonia	41
Glandular fever	41
Bornholm disease	25
Diphtheria	12
Total	4855
Erythema nodosum	12

one may develop diphtheria, and that is precisely what did happen.

Bearing all this in mind, it was with some trepidation that I undertook a Schick-testing campaign some years ago. The numbers, I realize, are small, but this would be the experience of anyone undertaking such a campaign in a country practice. I tested in all 306 inoculated children, some two years and some five years after the inoculation. I found 36 reactors—that is, 11.76 per cent. Omitting the control and using only the toxin, reading at the end of the week even slight redness as positive, it is very probable that some pseudo-reactions were included. Therefore, the total of only 36 reactors in these children was not discouraging.

#### BORNHOLM DISEASE

Let me give you a personal experience of a somewhat rare infectious disease. When I have touched so lightly on the common infectious diseases I feel I must quote

Who goes gleaming  
Hedge-side chance blades, while full sheaved  
Stand cornfields by him

To meet with one illness to which formal diagnosis cannot be given is no rare experience, but to be faced with a series of 7 cases of what was apparently an undescribed infectious disease was the lot of my partner, the late Dr. Dean Dunbar, and myself in the summer of 1933. I should like to emphasize the atmosphere of utter helplessness that

prevailed before a diagnosis was forthcoming, believing that a like experience might be the fate of other general practitioners

In the early morning of a bright July day I was roused from my bed by a young farmer, thoroughly alarmed, who asked if I would come to one of his small boys who had been taken seriously ill. This boy, aged two and a half years, had been quite well and lively while being dressed but then was suddenly attacked with pain in the upper part of the abdomen, sweated profusely and was thought by his mother to have had a fit. When I saw him the pain was not so acute, but he was deadly pale, looked limp and ill, and was taking short shallow breaths, which were obviously causing him discomfort. At this stage his temperature was 98°F. Later in the morning my partner saw him with a return of the acute pain and suggested that there was a painful spasm of the respiratory muscles, probably of the diaphragm — a very acute clinical observation. We saw him together at 3 o'clock, and again the picture was changed. His face was flushed, his temperature was 101°F, and his respirations were definitely 60 to the minute. At this point we felt on firmer ground and believed that we were justified in suggesting to the parents that the child was beginning with acute pneumonia although physical signs of this disease were entirely absent. I still think, and believe you will agree, that this was a reasonable suggestion. In the evening the patient seemed better, to add to our difficulties if at the same time to bring us peace of mind. His temperature now was only 100°F, he seemed to have little respiratory distress, and he had no pain. The next morning — really, we were dealing with a strange disorder — the little rascal, standing on the window sill and thumping on the pane, greeted me smilingly, but I thought derisively, as I walked up the garden path. I examined him carefully and could find nothing to account for the happenings of the previous day, I told his mother that I had no idea what had been the matter with her boy but that his troubles were now over and that she should worry no more. This was an extremely rash remark, as I was to learn later, for on the next day I found the boy very much as he was on the first day of his illness, and he had several hours of distressing symptoms with the addition of pain in his back, which prevented him from raising himself from the bed. On the next day his evening temperature was 99.8°F, but thereafter he completely recovered. The family consisted of father, mother and three little boys in addition to the first victim, and the boon companions of the boys were three little girls who lived on the other side of the main road. Two of these were bending over the little sufferer's couch with interest and solicitude on the very first morning of the illness. I told the mother that these

young women were better off in their own home until we decided what was the matter with her own child and packed them off, little thinking that the damage was already done. To cut a long story short, two of the brothers were attacked on the second and third days respectively of the first boy's illness, and the two little girls on the fourth day. Four days after his boy's complete recovery the father contracted the disease.

We were therefore dealing with an infectious disease quite unknown to us, in which our textbooks gave us no assistance and two problems presented themselves for solution. Where did this strange disease come from, and could we give it a name? The first was partially answered immediately. Four days before the appearance of the illness in the first child, 2 children were brought from the York neighborhood and spent a day on the farm. I was told that one, a little girl, spent it sobbing with pain doubled up on the sofa, and although I did not see her I have no doubt that she was the infecting party. The second problem was more difficult but was eventually solved completely. I had the good fortune the previous year to be in correspondence with Dr. Ejnar Sylvest, a general practitioner of Copenhagen, on the subject of epidemic jaundice, and he very naturally sent me articles on a condition he called "myositis epidemica" or "Bornholm disease." I was unable to read his article in Danish, but his references to epidemic pleurodynia, epidemic pleurisy and above all epidemic diaphragmatic spasm made me suspect that I was on the right track. Finally a copy of his paper submitted to the International Office of Hygiene settled the matter without a shadow of a doubt. I have had further experience with this disease and have seen in all 28 patients. Three points in diagnosis I should like to stress are the greatly increased respiratory rate, whether the pain is thoracic or abdominal, the almost invariable absence of vomiting, and the rarity and lack of prominence of cough.

This, then, is Bornholm disease, epidemic myalgia or as it is called in America, "the devil's grip," a disease of alarming symptoms but with no death rate whose only danger is that it may and has indeed come under the care of the surgeon through lack of diagnosis.

#### COUNTRY BELIEFS

I wonder if a few words on the usefulness of the beliefs of the countryside would interest you in the way they interest me. I recall the story of a saucy little milkmaid who declared to her companion, in the pride of her youthful beauty, "I shall never get smallpox, I shall never have an ugly pock

marked face, I've had cow pox and girls who have had cow pox never catch smallpox" Jenner overheard this conversation and consulted his old chief, the great John Hunter, whose advice not to accept theories or jump to conclusions led to one of the basic discoveries in medicine. William Withering's old country woman selling her dropsy cure—country minds work on simple lines—had no doubt that it was a dropsy cure, and it is still a dropsy cure after the lapse of two centuries. My own district two or three generations ago cherished a dropsy cure—"pellitory of the wall." I have seen it growing in the neighborhood of an ancient castle, at Fountains Abbey, our best preserved Cistercian Monastery, and in New College Lane at Oxford, and I believe that in both it is an escape from a medieval herb garden. It is said to have been brought from the East at the time of the Crusades. In 1 case, an elderly colleague tells me, the diuresis it produced was so alarming he was called in to stop it. I must record that the link between chicken pox and shingles was accepted

quite naturally by our country folk long before it became a commonplace in the textbooks of medicine

\* \* \*

I do hope I have been able to pass on to you a little of the atmosphere of a busy country practice in England, and as I speak from thirty-seven years' personal experience, it is a full and happy life. It may, of course, be a mere repetition of irksome tasks, but this is probably the fault of the practitioner who, like Bunyan's man with the muck rake "rakes to himself the straws and sticks and dust of the floor and can look no way but downward regardless of the crown which is being held above his head." I finish with a quotation from a letter of T. H. Huxley, the advice in which is so hard to follow—

Sit down before fact as a little child, be prepared to give up every preconceived notion, follow humbly and blindly wherever nature leads, or you shall learn nothing.

## RADIOACTIVITY AND URINARY-TRACT CALCULI

DAVID S. CRISTOL, M.D.,\* ALBERT E. BOTHE, M.D.,† AND PAUL W. GROTZINGER, M.D.‡

PHILADELPHIA

**A**n interesting observation promises to open other avenues of approach in the methods for investigating the formation of urinary-tract calculi.

A patient who proved to have a vesical calculus as well as multiple prostatic calculi recently came under our care. In the course of the physical examination he was also found to be suffering from polycythemia vera. In an effort to bring the blood hematocrit within normal limits prior to surgery, it was decided to subject the patient to radioactive phosphorus therapy and thereafter to observe any changes in the size and configuration of the calculi. In preparation for surgery, two doses of radioactive phosphorus were given orally. The first dose contained 6 millicuries, and the second, administered five months later, 10 millicuries. Periodically during the seven-month period before operation, the calculus was observed radiographically and cystoscopically and appeared to grow larger. The bacterial and chemical constituents of the urine were also repeatedly examined both before and during the course of therapy. Blood counts were made at regular intervals, and when the hematocrit appeared optimal, one of us (D. S. C.) performed a suprapubic removal of the vesical calculus, together with

a revision of the vesical neck. At the time of surgery, as many of the prostatic calculi as could be



FIGURE 1 *Autoradiograph of Intact Vesical Calculus (Twenty-Four-Hour Exposure)*

dislodged from their position adjacent to the prostatic capsule were also removed.

These calculi were removed on the sixty-first day after the second oral dose of radioactive phosphorus. Immediately afterward they were bathed in water

\*Associate in urology, Jeanes Hospital.

†Associate professor of urology, Graduate School of Medicine, University of Pennsylvania.

‡President in surgery and oncology, Jeanes Hospital.

prevailed before a diagnosis was forthcoming, believing that a like experience might be the fate of other general practitioners

In the early morning of a bright July day I was roused from my bed by a young farmer, thoroughly alarmed, who asked if I would come to one of his small boys who had been taken seriously ill. This boy, aged two and a half years, had been quite well and lively while being dressed but then was suddenly attacked with pain in the upper part of the abdomen, sweated profusely and was thought by his mother to have had a fit. When I saw him the pain was not so acute, but he was deadly pale, looked limp and ill, and was taking short shallow breaths, which were obviously causing him discomfort. At this stage his temperature was 98°F. Later in the morning my partner saw him with a return of the acute pain and suggested that there was a painful spasm of the respiratory muscles, probably of the diaphragm—a very acute clinical observation. We saw him together at 3 o'clock, and again the picture was changed. His face was flushed, his temperature was 101°F, and his respirations were definitely 60 to the minute. At this point we felt on firmer ground and believed that we were justified in suggesting to the parents that the child was beginning with acute pneumonia although physical signs of this disease were entirely absent. I still think, and believe you will agree, that this was a reasonable suggestion. In the evening the patient seemed better, to add to our difficulties if at the same time to bring us peace of mind. His temperature now was only 100°F, he seemed to have little respiratory distress, and he had no pain. The next morning—really, we were dealing with a strange disorder—the little rascal, standing on the window sill and thumping on the pane, greeted me smilingly, but I thought derisively, as I walked up the garden path. I examined him carefully and could find nothing to account for the happenings of the previous day, I told his mother that I had no idea what had been the matter with her boy but that his troubles were now over and that she should worry no more. This was an extremely rash remark, as I was to learn later, for on the next day I found the boy very much as he was on the first day of his illness, and he had several hours of distressing symptoms with the addition of pain in his back, which prevented him from raising himself from the bed. On the next day his evening temperature was 99.8°F, but thereafter he completely recovered. The family consisted of father, mother and three little boys in addition to the first victim, and the boon companions of the boys were three little girls who lived on the other side of the main road. Two of these were bending over the little sufferer's couch with interest and solicitude on the very first morning of the illness. I told the mother that these

young women were better off in their own home until we decided what was the matter with her own child and packed them off, little thinking that the damage was already done. To cut a long story short, two of the brothers were attacked on the second and third days respectively of the first boy's illness, and the two little girls on the fourth day. Four days after his boy's complete recovery the father contracted the disease.

We were therefore dealing with an infectious disease quite unknown to us, in which our textbooks gave us no assistance and two problems presented themselves for solution. Where did this strange disease come from, and could we give it a name? The first was partially answered immediately. Four days before the appearance of the illness in the first child, 2 children were brought from the York neighborhood and spent a day on the farm. I was told that one, a little girl, spent it sobbing with pain doubled up on the sofa, and although I did not see her I have no doubt that she was the infecting party. The second problem was more difficult but was eventually solved completely. I had the good fortune the previous year to be in correspondence with Dr. Ejnar Sylvest, a general practitioner of Copenhagen, on the subject of epidemic jaundice, and he very naturally sent me articles on a condition he called "myositis epidemica" or "Bornholm disease." I was unable to read his article in Danish, but his references to epidemic pleurodynia, epidemic pleurisy and above all epidemic diaphragmatic spasm made me suspect that I was on the right track. Finally a copy of his paper submitted to the International Office of Hygiene settled the matter without a shadow of a doubt. I have had further experience with this disease and have seen in all 28 patients. Three points in diagnosis I should like to stress are the greatly increased respiratory rate, whether the pain is thoracic or abdominal, the almost invariable absence of vomiting, and the rarity and lack of prominence of cough.

This, then, is Bornholm disease, epidemic myalgia or as it is called in America, "the devil's grip," a disease of alarming symptoms but with no death rate whose only danger is that it may and has indeed come under the care of the surgeon through lack of diagnosis.

#### COUNTRY BELIEFS

I wonder if a few words on the usefulness of the beliefs of the countryside would interest you in the way they interest me. I recall the story of a saucy little milkmaid who declared to her companion, in the pride of her youthful beauty, "I shall never get smallpox, I shall never have an ugly pock

lished a diagnosis of polycythemia vera within the previous 3 months. The patient had been bled on several occasions, with temporary relief from the symptoms.

Physical examination gave negative results except for dusky complexion, coronal hypospadias and a moderately firm and enlarged prostate with numerous crepitant areas.

The blood pressure in both arms was 160/100. Examination of the urine revealed a moderate trace of albumin, and the sediment was loaded with erythrocytes and leukocytes. A gram stain disclosed numerous gram-positive cocci and diplococci.

An excretory urogram demonstrated a vesical calculus, numerous prostatic calculi and an essentially normal-appearing upper urinary tract.

Cystoscopy revealed 100 cc. of residual urine, minimal trabeculation, a yellow, smooth, egg-shaped calculus measuring approximately 4 cm in length and 3 cm in its widest diameter, a moderate degree of trilobar intraurethral prostatic hyperplasia, numerous dilated prostatic ducts and subacute cystitis over the trigone.

After a blood count had been made, the patient was given 6 millicuries of radioactive phosphorus orally on January 9, 1947. The urine, as well as the blood, was repeatedly examined. The vesical calculus was also repeatedly observed both radiographically and cystoscopically. On May 10 radioactive phosphorus in a dose of 10 millicuries was given orally.

The hematocrit became normal, and the patient was hospitalized on July 8. A roentgenogram of the chest was normal. The urea, sugar, calcium, phosphorus, proteins and alkaline and acid phosphates were all within normal limits. The blood serologic findings were negative. On July 11, under spinal anesthesia and through a suprapubic incision the bladder was opened and the vesical calculus as well as some pros-

tatic tissue containing calculi was removed. The pathologist reported that the removed prostatic tissue represented benign prostatic hyperplasia. The patient made an uneventful recovery and left the hospital free from urinary symptoms 5 weeks after operation.

A follow-up re-examination 3 months later revealed the urinary tract to be entirely within normal limits except for the presence of some residual prostatic calculi.

## DISCUSSION

In addition to the dramatic and graphic representation of stone formation, the employment of the radioactive element may prove to have many worthwhile uses in the study of urinary-tract-calculus formation. This method might serve as a check on various proposed methods of preventing additional stone formation. It gives an opportunity for one to observe, for example, the effect of an acid ash diet on the formation of alkaline stone. It also suggests the study of the effect of radioactive materials on associated urinary-tract infections. The possible effects of residual radioactivity in calculi on the containing tissues are also under investigation.

This is apparently the first recorded case of removal of a radioactive calculus.

Medical Tower Building

## PREMEDICATION AND ANESTHESIA IN OBSTETRICS\*

### Current Practices at the Boston Lying-in Hospital

BERT B. HERSHENSON, M.D.†

BOSTON

THE first recorded obstetric operation under anesthesia in the Americas was performed by Dr. Walter Channing on May 5, 1847, at the Boston Lying-in Hospital. He wrote of his book, which was published in 1848<sup>1</sup> and which has become a classic, that "it treats of a noble subject, the remedy of pain" in childbirth. Today, a century later, this subject is still well deserving of consideration.

At the Boston Lying-in Hospital, there has been an evolution through various developmental phases of the subject. The keynote has always been the practice of safe relief of pain, permitting the obstetrician to carry on a conservative policy in the conduct of labor. All the known regional and inhalational anesthetic agents and technics have been employed, and all routes of the body have been utilized for the introduction of amnesic and analgesic drugs. At one time or another, Simpson's and Channing's methods of ether inhalation, John Snow's chloroform *à la reine*, intermittent nitrous oxide through long hours of vigil, twilight sleep and most of the pharmacologic agents known

for their effects on the central nervous system have been administered.

Out of this experience certain facts appear significant. First and most important is the obstetric team and the environment under which it functions.<sup>2</sup> The greatest emphasis should be placed on the knowledge, experience, skill, judgment, attention and mutual professional confidence of the members of the obstetric team rather than on the agent or technic employed. Secondly, the complete individualization of selection of agents, dosage and routes of administration in the able hands of a well trained team of obstetrician and anesthesiologist is the only true path to safety. Thirdly, the ideal agent or combination of agents is not available to meet all the requirements necessary for safe, controllable and effective obstetric amnesia, analgesia and anesthesia. Finally, we have been impressed with the fact that our most successful methods have included the use of scopolamine.<sup>3</sup> Its advantages and disadvantages for the obstetric patient have been dealt with elsewhere.<sup>2</sup>

We are of the opinion that misuse of analgesic drugs in obstetrics is more productive of ill effects

\*Presented at a meeting of the Merrimack County Medical Society, Concord, New Hampshire, April 7, 1948.

†Director of anesthesia, Boston Lying-in Hospital.

for forty-eight hours to remove the residual dried radioactive urine. Then they were placed before a Geiger counter,\* and the degree of radioactivity

window of the Geiger tube was recorded from the vesical calculus. The cosmic background count was 30 per minute. Autoradiographs were then made using four-hour and twenty-four-hour exposures of the intact vesical calculus and of the divided vesical calculus. A blackening of the film of the intact stone (Fig 1) was obtained, with a rather hazy border that was due to the fact that the stone was somewhat semicircular in shape and that there was some scattering of the beta rays at the margin. The stone was then cut in half in its long dimension, and the flat surface placed on a film first for four hours and then for twenty-four hours as before. A ring-like area of blackening was obtained, with a



FIGURE 2 *Autoradiograph of Divided Radioactive Vesical Calculus (Twenty-Four-Hour Exposure)*  
Intense area of blackening at the periphery represents deposited radioactive phosphorus

recorded. The vesical calculus proved to be markedly radioactive. The prostatic calculi, which were not in contact with the urine and also were



FIGURE 3 *The Divided Vesical Calculus, with a Portion of the Radioactive Lamina Removed*

presumably not enlarging during the period of phosphorus therapy, were not radioactive. A count of 2000 per minute at a distance of 10 cm from the

\*Dr. John H. Freed of the University of Pennsylvania Radiology Department, performed the radioactivity measurements.



FIGURE 4 *Roentgenogram before Operation*

somewhat hazy border. An intense area of blackening, which represented deposited radioactive phosphorus, could be seen (Fig 2) at the outermost periphery. No radioactive phosphorus was deposited in the central portion. Thus, one has a true picture of the radioactive phosphorus in the stone and an estimate of the increase in the size of the stone during the time when the patient was receiving the drug. Figure 3 shows the divided stone, with a corresponding radioactive lamina chipped off from the lower half. Figure 4 reveals the flat plate, including the renal, ureteral and vesical areas before surgery. Further details are presented below.

#### CASE REPORT

A S., a 56-year-old man, was first seen in December, 1946, complaining of marked diurnal and nocturnal urinary frequency, dysuria and intermittency of urination that had progressed over a period of approximately 2 years. During the previous 4 months, he had also suffered numerous hot flushes, frontal headaches and periodic episodes of vertigo.

The past history was none contributory except for the fact that a physician had treated him for 6 months as a suspected case of pulmonary tuberculosis 30 years before and had estab-

If more advanced renal-function impairment exists the drugs for premedication are omitted, or reduced to one fourth the usual dosages. The delivery is completed under a regional analgesic procedure, and the patient is provided with oxygen-enriched atmospheres.

#### *Gastrointestinal Complications*

If a patient has had food or fluid within six hours of hospital admission, she is considered as presenting the complication of a "full stomach." It must always be remembered that fluid or food in the stomach is compatible with life, but in the lungs means death. If delivery is imminent the patient's stomach is washed out, and to make certain that the procedure is successful she receives but half the usual dosage of barbiturates and the first dose of apomorphine is 1.2 mg instead of the usual 0.6 mg. When the foregoing procedures have been effective in emptying the stomach, the patient receives the usual premedication and anesthesia. In the event that the preanesthetic preparatory procedures have been ineffective in emptying the stomach, the plan is to retain consciousness and protective reflexes by employing a regional analgesic block for the termination of labor and the completion of the delivery.

In cases requiring operative abdominal or other surgery during the course of pregnancy, the plan of premedication and anesthesia is decided upon an individual basis and after consultation between the surgical consultant and the anesthesiologist.

Hospitalized patients are not permitted food or fluid by mouth during labor. Fluids are administered parenterally, as indicated, to meet the patient's physiologic requirements.

#### *Central-Nervous-System Complications*

In premedication the drugs, dosages and routes are employed as for the uncomplicated case. Individualization is the basis in actual practice.

Regional analgesia and the use of solid anesthetic agents are contraindicated in this group of cases. An inhalational anesthetic procedure is planned for the following problem cases: patients with a previous history of headache or backache, patients with a suspected, or known, lesion of any part of the nervous system, and patients presenting a history of previous difficulty with regional anesthesia.

#### *Metabolic Disturbances*

**Diabetes.** The plan of premedication is essentially the same regarding selection of amnesic and analgesic drugs, but the dose is reduced so as to avoid loss of consciousness. The purpose is to utilize the aid of the patient during administration of a regional block for the termination of labor and delivery.

**Hyperthyroidism.** The agents employed for premedication are the same, but the dose is increased by one eighth to one fourth the amount, the interval and routes of administration remaining the same. The anesthetic procedure of choice is inhalation, employing oxygen-enriched atmospheres.

#### *Specific Obstetric Complications*

For patients who are to have cesarean section or "double set-up" examination to determine the cause of late antepartum hemorrhage, premedication consists of the administration of 0.2 gm of sodium amytal by mouth, or rectum, two hours preoperatively, scopolamine and apomorphine 0.6 mg of each, are injected intramuscularly one hour later. The anesthetic procedure of choice is inhalation—otherwise, there is a consultation by the attending obstetrician and the anesthesiologist.

For patients presenting the problem of prematurity or suspected immaturity of the fetus, premedication consists of a minimal dose of a barbiturate, usually 0.1 gm of seconal one hour before delivery, followed by a regional analgesic procedure.

For patients who are to have a test of labor the plan of premedication is essentially the same as that for the uncomplicated case, but the dose of drugs is reduced by half. If the delivery is completed vaginally, the choice of anesthesia is an inhalational procedure. Otherwise the case is treated on an individual basis.

In patients with pre-eclampsia or eclampsia, if the case is one of mild or Grade I pre-eclampsia premedication and anesthesia are planned as for the uncomplicated case to be delivered vaginally, in the absence of other complications. The severer cases presenting this obstetric complication are individualized. If premedication is employed demerol in doses of 50 to 100 mg every three or four hours intramuscularly is administered and light inhalation anesthesia with highly enriched oxygen atmosphere is used for the delivery. When possible the delivery is completed under the premedication alone, any further depression or interference with vital functions being avoided. It is important to remember that a "whiff" of gas alone is a dangerous procedure. Intravenous anesthesia and nitrous oxide (or either procedure alone) are contraindicated for this group of cases. If regional anesthesia is to be employed, the decision rests on consultation between the attending obstetrician and the anesthesiologist. In any case the guiding principle is that safety must never be sacrificed for comfort or convenience.

#### SPINAL ANALGESIA

When we employ one of the methods of regional anesthesia we are governed by the presence of a definite indication. This policy is best illustrated

upon both mother and baby than properly administered inhalational anesthetic agents. Judicious selection and skillful administration of inhalation anesthetic agents are most successful for the termination of labor. Among some of the advantages of inhalation anesthesia are the rapidity of exchange of agent via the lungs, short induction and recovery periods, predictable and controllable depth and duration of anesthesia, retrievableness of the agent without residual injury, wide margin of safety, lack of extra load on the detoxifying mechanisms of the body and permissibility of employment of highly oxygenated atmospheres.

We employ regional and inhalational anesthetic procedures. The selection of agent and technic is based on many factors, some of the more important of which are physical status of the patient, the gestational age and condition of the fetus, the degree of muscle relaxation necessary to complete a given obstetric procedure, the duration and depth of narcosis required, the action of the agents selected and their influence on the conduct of labor and the skill and experience of the obstetrician and anesthetist.

For the purposes of guiding the resident and house staff in the selection of premedication and anesthetic procedures the outline presented below has been devised.

#### UNCOMPLICATED VAGINAL DELIVERY

Early in labor following the admission enema, the patient receives 0.1 gm of scopolamine, usually by mouth, for the purposes of determining sensitivity to barbiturates and to provide some psychic sedation. If no untoward reaction exists she receives 0.1 gm of scopolamine along with 0.1 gm of sodium amytal at the end of an hour by mouth or rectum. If the latter route is used the ends of the capsules are perforated before administration. At that time 0.6 mg of scopolamine hydrobromide is administered intramuscularly. The total dosage of barbiturates during labor is limited to 0.4 gm.

As labor progresses and becomes more active so that the patient complains of painful contractions of the uterus, intramuscular injections of scopolamine and apomorphine of 0.6 mg each are given, followed in an hour by an intramuscular injection of 0.4 mg of scopolamine and 1.2 mg of apomorphine. The latter dosage combination of scopolamine-apomorphine is administered intramuscularly every two hours until the patient is ready for delivery. In the event that the patient shows muscular overactivity or agitation (scopolamine reaction), additional doses of 0.6 to 1.2 mg of apomorphine are administered intramuscularly and may be repeated at intervals of fifteen minutes until the desired therapeutic response is reached. This is rarely more than two doses.

The delivery is completed under an inhalational procedure. A clear, unobstructed airway must

be maintained constantly. Any cause inhibiting normal thoracic excursions must be eliminated. Employment of highly oxygenated atmospheres is encouraged, until the delivery of the fetus is completed and the cord is clamped. At the completion of anesthesia and delivery, the nurse is instructed to turn the patient on her side to drain any secretions, at the same time the patient's head is slightly extended. An unconscious patient constantly demands careful and intelligent supervision and protection.

#### SPECIAL PROBLEMS

##### *Respiratory Complications*

For patients with active respiratory infections, such as upper-respiratory-tract infections with temperature or cough, premedication consists of the measures outlined above for the uncomplicated case, but the barbiturates are reduced to half the dosage outlined, or less. Delivery is completed under the plan of premedication or supplemented with a regional block, usually low spinal analgesia. The spinal analgesia is administered by a member of the resident staff or under the supervision of the anesthesiologist.

For patients with asthma the barbiturates are reduced to a minimal dosage range, not exceeding 0.03 to 0.2 gm of scopolamine and apomorphine are administered as outlined above. The delivery is completed under inhalation anesthesia, ether being employed as the agent of choice. A skin test with the drugs and anesthetic agents before administration is given to any patient suspected of having asthma or of being allergic.

Patients with previous thoracic operative procedures or with active tuberculosis are treated as for active respiratory infections.

##### *Cardiovascular (Circulatory) Complications*

Both premedication and anesthesia are individualized for patients with Class IA cardiac disease (unfavorable cardiac cases).

For those with Class I cardiac disease (favorable cardiac cases), medication consists of administration, intramuscularly, of 100 mg of demerol when the patient is in active labor and thereafter of 50 to 100 mg of demerol every three or four hours. Inhalation anesthesia is employed for termination of the labor. After delivery the patient receives oxygen-enriched atmospheres as indicated.

Patients with Class II and III cardiac disease (functional) are treated like those with uncomplicated vaginal delivery, untoward manifestations being watched for.

##### *Genitourinary Complications*

If moderate to mild impairment of renal function exists the dosages of the drugs used for premedication are reduced to one half. The delivery is completed under inhalation anesthesia.

is withdrawn, and the needle and syringe examined. A sterile dressing is applied to the puncture site. The patient is turned on her back, with one or two pillows under her upper back, neck and head. The level of analgesia is frequently tested, and the patient cautiously positioned, as indicated. The patient is leveled when the desired height is reached, that is the tenth dorsal dermatome for pelvic deliveries and the sixth to the fourth dorsal dermatome for abdominal delivery.

#### *Therapeutic and Prophylactic Measures*

The clinical course of the patient is checked, and at intervals of at least five minutes the blood pressure, pulse rate, respiratory rate and volume are recorded. Intercostal breathing, the development of pallor and other skin changes, disorientation or other changes in behavior, nausea or emesis, thirst, air hunger, palpitation, precordial distress and other psychosomatic changes are watched for.

The patient is supplied early and immediately with air that is highly oxygen enriched. Carbon dioxide is avoided, for it only increases the vascular dilatation and augments spinal shock. An adequate airway is watched for and maintained, the thorax is inflated manually via the rebreathing bag with oxygen, should intercostal paralysis exist.

The use of the Trendelenburg position is avoided until the anesthetic agent is fixed — that is for 25 to 30 minutes after induction.

Measures are instituted to support depressed respiration and circulation at once. Venoclysis or transfusion is employed promptly as indicated. During acute hemorrhage there is no substitute for compatible whole-blood transfusion.

Supplementary anesthetic agents and technics are employed when indicated. Adequate assistance, suction, oxygen, fluids, drugs (ephedrine sulfate, prepared) and indicated agents must be available constantly. The patient must be watched by the anesthetist responsible for the case, and knowledge must be had of all the patient's psychic, psychosomatic, somatic and reflex responses constantly.

#### DISCUSSION

It should be emphasized that about 80 per cent of our deliveries are completed by the use of in-

halational anesthesia. Under inhalational technics are included open-drop ether and semiclosed and closed carbon dioxide absorption methods, both circle-filter and Waters to-and-fro procedures. We stress the use of oxygen-enriched atmospheres, especially during the terminal portion of the second stage of labor. The delivery is actually accomplished in the topmost portion of the first plane of the third stage in accordance with Guedel's classification of the stages of anesthesia. The accumulation of carbon dioxide, even in the presence of oxygen-enriched atmospheres, is neither encouraged nor desired.

In another paper<sup>2</sup> several case histories of vaginal deliveries are presented as typical of our current practices of premedication and anesthesia. The drugs are essentially the same in all cases. The method of delivery with reference to the terminal anesthetic procedure is different in each case. The problems presented by each patient during her period of hospitalization are discussed in some detail.

#### SUMMARY

The current practices of premedication and anesthesia at the Boston Lying-in Hospital are presented and discussed. Emphasis is placed upon the knowledge, experience, skill, judgment, attention and mutual professional confidence of the team, composed of the obstetrician and the anesthesiologist and their co-workers. The keynote is the practice of safe relief of pain permitting application of a conservative policy in the conduct of labor. Over 80 per cent of our deliveries are completed under inhalation anesthesia. The advantages of inhalation anesthesia are discussed. An outline of the conduct of premedication and anesthesia with reference to the obstetric problem is presented.

The policy regarding regional analgesia is considered. An outline of indications, contraindications, technic, agents, therapeutic and prophylactic measures for spinal analgesia in obstetrics is included.

#### REFERENCES

- 1 Channing W. *A Treatise on Etherization in Childbirth*. 400 pp. Boston: W. D. Ticknor & Co. 1848.
- 2 Hershenon B. B. Premedication and anesthesia in obstetrics: practical aspects. *Anesthesiology* 9:73-85, 1948.
- 3 Hershenon B. B. and Brubaker E. R. Scopolamine and apomorphine in labor. *Am. J. Obst. & Gynec.* 53:980-995, 1947.

by a brief consideration of spinal analgesia as currently used at the Boston Lying-in Hospital

### *Indications*

When the patient presents one or more of the following complications spinal analgesia constitutes the usual practice in the termination of delivery, respiratory complications, including fever or cough, a recent meal, when delivery is imminent and unconsciousness may be a threat to life, fetal distress, when further depression is best avoided, prematurity or immaturity of the fetus, diabetes mellitus, particularly if severe or uncontrolled, and other complications, such as a surgical procedure other than obstetric. The final decision rests between the attending obstetrician or consulting surgeon and the anesthesiologist.

### *Contraindications*

We consider that the majority of obstetric cases fall in this group, and may be listed as follows: known or suspected disease of the central nervous system, such as tumors, hemorrhage or lesions of the brain or spinal cord, syphilis of the central nervous system, pernicious anemia involving the nervous system and other pathologic processes involving the parenchyma or coverings of the central nervous system, infection of the skin at or close to the point of spinal puncture, known history of headaches or backaches, mental aberrations such as psychoses and psychoneuroses or marked fears or anxieties, congenital anomalies—for example, pilonidal cysts and spina bifida—or other malformations of the structures about the spinal column, hemoglobin of 50 per cent or less, cardiovascular disease, labile vasomotor system or unstable autonomic nervous system, marked malnutrition, septicemia, hemorrhage or shock, known allergic responses to solid anesthetic agents, or previous history of undesirable experience with a regional anesthetic, marked obesity, serious uterine complications, such as uterine apoplexy, rupture and hemorrhage, necessary intrauterine manipulation—for example, internal podalic version or breech delivery, abnormal spinal fluid—turbid, cloudy or bloody spinal tap (also, patients with increased spinal-fluid pressure, for this may mean a block in the spinal canal), fear of post-spinal sequelae, and other patients so considered by the attending obstetrician in consultation with the anesthesiologist.

### *Technic and Agents*

Evaluation of the patient, her disease, state of maturity of the fetus, and previous anesthetic experiences should be made. Premedication consists of the administration of 0.1 to 0.2 gm of sodium amytal two hours prior to delivery and 50 to 100 mg of demerol one hour later injected intramuscularly. The patient's blood pressure, pulse rate

and respiratory rate and character are noted and recorded on the obstetric anesthesia study sheet. The patient is then placed in the lateral or sitting position and supported by an assistant. The skin over the lumbar portion of the back is prepared with ether, followed by tincture of zephiran, and sterile towels or sheets are applied. With sterile gloved hands the site of puncture is located, the third or fourth lumbar interspace being used. Ampoules are examined for cracks, only ampoules that are clear and colorless being used. A wheal is raised with a 0.5 per cent procaine containing not over 50 mg of ephedrine sulfate. If an allergic response is elicited the spinal analgesic procedure is discontinued. Otherwise, the path to and including the interspinous ligaments is anesthetized. Flexible needles with short bevel and properly fitting stylets are employed for the spinal tap, the needle being tested before use. The bevel is inserted caudad. A spinal needle of 20 to 22 gauge is selected, if the needle is made of gold or platinum, the gauge should be 22 to 24. In the latter instance a groove director is previously inserted into the spinous ligaments. The needle is slowly introduced with the stylet into the dural sac and thence into the subarachnoid space. The stylet is carefully withdrawn, and clear fluid should appear. The procedure is discontinued if the spinal fluid is bloody, turbid or cloudy, or if under abnormal pressure. Otherwise, with the needle held fixed in place, the anesthetic solution is slowly injected at an approximate rate of 0.25 cc per second. The anesthetist should always be on the alert for any untoward reactions. Our selection of agents is limited to the following:

For pelvic delivery procaine hydrochloride, 50 to 100 mg in a concentration of not over 5 per cent is used, with spinal fluid as the diluent. The expected duration is approximately from one to one and a half hours and not infrequently longer. The height of sensory analgesia is governed by the rate of injection, dilution, amount of drug, interspace employed and positioning of the patient as the more controllable variables. We avoid barbotage. If saddle block is desired, injection is performed slowly, and the sitting position is maintained about 3 to 5 minutes, the level being frequently tested. For abdominal delivery the agent of choice is procaine hydrochloride, 100 to 150 mg in 5 per cent dilution. The duration of effect may be expected for one to one and a half hours. If a longer duration is required, this being a teaching service, pontocaine hydrochloride (5 to 8 mg) with procaine hydrochloride (50 to 100 mg) is resorted to. In that case we prefer to limit the dose of pontocaine to 5 mg, and in any case the concentration of drugs injected is not over 5 per cent. At the end of the procedure the needle

The patient was last seen on July 17, 1947, when the hemoglobin was 34 per cent and the red-cell count 3,120,000. She had experienced several slight episodes of bleeding since leaving the hospital. Rutin therapy is now faithfully followed.

### DISCUSSION

This patient presented the typical findings associated with familial hereditary hemorrhagic telangiectasia. The life-long history of nosebleeds, increasing in severity with advancing years, together with the presence of multiple telangiectatic areas on the skin and mucous membranes established the diagnosis without question. It is unfortunate that a definite familial incidence could not be traced. The history of the deceased brother who had nosebleeds is suggestive, but vague, and impossible to substantiate. The possibility that the patient had some admixture of white blood cannot be ruled out, of course, even though she had no knowledge of Caucasian consanguinity.

Whether the profound anemia was the result of the epistaxes alone, or the result of additional bleeding from lesions in the gastrointestinal tract is a matter for speculation, for such lesions do occur frequently. It was believed that the potential danger involved in gastroscopy of such a patient was too great to warrant the procedure.

Although no treatment is entirely satisfactory in these cases, the administration of rutin appears to have been of some benefit, the use of snake venom was apparently without avail.

### SUMMARY

A case of hereditary hemorrhagic telangiectasia occurring in a forty-eight-year-old Negress is presented, no previous report in a Negro being available.

The administration of rutin appears to have been of some value in this case.

## MEDICAL PROGRESS

### PLASTIC SURGERY

#### Skin Transplantation

BRADFORD CANNON, M.D.\*

BOSTON

THE essence of plastic surgery is the transplantation of tissue. Skin is the one most commonly transplanted. It is therefore proposed to review the development of the methods of skin transplantation that have led to some of the modern principles on which the present management of plastic surgical problems is based. In any young surgical specialty much emphasis is placed on methods and techniques, which, as they improve and are standardized, pave the way for the formulation of basic principles that apply in the broadest sense. Many of these principles bear directly on all phases of reconstructive surgery, but particularly on the surgery of trauma. Their elaboration has been stimulated by the concentrated experience of plastic surgeons in caring for war casualties, as well as by varied and extensive experiences in civilian reconstructive surgery.<sup>1-4</sup>

Skin transplantation is carried out in two basic ways: free transplantation or skin grafting, which means that the skin is completely detached from the body in its transfer, and transplantation as a flap, which means that at all times the skin and subcutaneous tissue remain attached to the body and receive blood supply through this attachment

or pedicle. The free skin graft must be thin, without any subcutaneous tissue, to survive and grow after transfer, whereas the flap must retain the subcutaneous tissue in which the nutrient vessels of the skin lie.

In the primary or secondary closure of traumatic or surgical wounds and in the resurfacing of scarred areas, the simplest, most effective approach is desirable. Four principal methods are generally used, the indications for which are frequently emphasized in the papers reviewed for this report on skin transplantation. The first and simplest closure is by direct suture, which implies an adequate amount of healthy skin to allow approximation of the edges without tension. The second method is by a free skin graft. The split skin graft is readily available, and since the donor area heals within two weeks,<sup>5</sup> no additional deformity results. The graft will take on a well prepared granulating wound, such as that resulting from a burn, but may not survive on an avascular surface of scar tissue such as that underlying a thin layer of excised scar epithelium or that in an area with deep radiation damage. It will usually grow on cancellous bone but seldom on cortical bone.

The free skin graft has widespread usefulness as a primary skin dressing of large and small un-

\*Associate in surgery, Harvard Medical School; chief, Plastic Clinics, Massachusetts General and Mt. Auburn hospitals.

## FAMILIAL HEREDITARY HEMORRHAGIC TELANGIECTASIA IN THE NEGRO\*

## Report of a Case

STEVEN O. SCHWARTZ, M.D.,† AND BERTHE E. ARMSTRONG, M.D.‡

CHICAGO

**B**ECAUSE familial hereditary hemorrhagic telangiectasia in the Negro has not been previously described in the literature, it was believed that the following case deserved mention.

A 48-year-old Negress first entered the Cook County Hospital on October 31, 1945, because of a nosebleed lasting 8 hours. She had had frequent epistaxes all her life, and 2 weeks before admission had noted vertigo, syncope and edema of the face and feet. The nosebleeds had occurred at intervals "as long as she could remember" but had been inconsequential until the menopause, at the age of 42. During the next 4 years they increased both in frequency and severity until at the time of admission she was averaging three episodes a week, each one lasting from 3 to 9 hours. There was also a history of bleeding from the tip of the small finger of the right hand on two different occasions about 1½ years previously. There was no recurrence of this bleeding after she learned to guard this spot from trauma. The menstrual periods were regular with a moderately heavy flow until the menopause. There had been no post-menopausal bleeding. She had been pregnant twice, one pregnancy terminating in a destructive operation because of a dystocia, and the other in the normal delivery of a healthy child.

The past history was eventful but had no relation to the present episode.

No familial history of bleeding could be elicited, with one exception, that of a brother, recently dead of "heart trouble," who had had moderately severe nosebleeds once or twice a year. Efforts to communicate with members of the family were unsuccessful. Inquiry into the racial background failed to reveal any known admixture of white blood, but the maternal grandmother was said to have been an American Indian.

Physical examination showed the patient to be well developed and well nourished, she appeared much younger than her chronologic age. She was intelligent and co-operative and did not appear acutely ill. There was continuous bleeding from the nose. The mucous membranes were extremely pale. Multiple small, bright-red areas varying in size, the largest approximately 3 mm in diameter, were present on the tongue, buccal mucosa, gums, soft palate, face and chest. A similar spot was present under the tip of the nail of the small finger of the right hand. The lungs were normal. The heart was enlarged, the apical beat being visible 9 cm to the left of the midclavicular line in the sixth interspace. A loud, harsh systolic murmur was heard over the entire precordium, but was loudest in the third interspace. The liver was palpable 7 cm below the costal margin and was firm and smooth. A firm, slightly tender mass, about 3 or 4 cm in diameter, was palpated in the right lower quadrant of the abdomen. On pelvic examination this was found to be connected with the right adnexa. Examination of the nose revealed bleeding from the right Kiesselbach's area. This was treated with silver nitrate, and the nose was packed.

The temperature was 98.6°F, the pulse 88, and the respirations 20, the blood pressure was 120/75.

Examination of the blood revealed a red-cell count of 1,560,000, with a hemoglobin of 13 per cent (20 gm.), and a white-cell count of 5050, with a normal differential. The

red cells were microcytic and markedly hypochromic, with moderate anisocytosis and poikilocytosis. The bleeding time was 1 minute, 35 seconds, and the coagulation time 8 minutes (by the multiple tube method), prothrombin activity was 90 per cent, and the platelet count was 217,500. Urinalysis, blood Kahn and Wassermann tests and x-ray examination of the colon were negative. The nonprotein nitrogen, total serum protein and cevitamic acid determinations from time to time revealed no significant information.

Moderately severe epistaxes occurred at intervals during the following 10 days but were controlled by packing. The patient received 2000 cc of whole blood during this period. She left the hospital on iron therapy on November 19, feeling well but still moderately anemic (on November 19 the red-cell count was 4,280,000, and the hemoglobin 72 per cent).

She was readmitted to the hospital on January 23, 1946, with a history of massive hemorrhages from the nose for several days. Physical examination was essentially the same as previously.

Examination of the blood disclosed a red-cell count of 1,080,000, with a hemoglobin of 11 per cent (17 gm.), and a white-cell count of 12,400.

The bleeding was again treated locally with silver nitrate, and she received 500 cc of whole blood. As no further bleeding occurred during the next 10 days, she was transferred to the dermatology ward for treatment with moccasin venom intradermally. This she received twice weekly in doses ranging from an initial dose of 0.1 cc. up to 1.0 cc. In spite of this treatment the epistaxes recurred, became both frequent and severe, and required packing. Two 500-cc blood transfusions were given during that time. On March 24 a new telangiectatic area was noted on the ball of the right thumb. On April 3 the patient was discharged to the dermatology outpatient clinic for further treatment.

The patient was readmitted to the hospital on September 3. There had been three severe nosebleeds since discharge, and she had experienced progressively increasing weakness, which had necessitated confinement to bed for the preceding 2 months. Nausea and vomiting had been present for 4 hours during the night before admission. Examination of the blood disclosed a red-cell count of 1,090,000, with a hemoglobin of 9 per cent (14 gm.), and a white-cell count of 7950. She was given 1000 cc of whole blood immediately and placed on iron therapy. Further treatment was hampered, as in the past, by the difficulty of obtaining blood donors. Moccasin venom was continued in doses from 0.4 to 0.8 cc. Three weeks after admission she left the hospital against advice, although her condition was very little improved and she was still experiencing frequent and severe epistaxes.

She was again admitted on March 31, 1947, with complaints of edema of the face and legs for 2 weeks and epistaxis for 12 hours. The red-cell count was 1,600,000, and the hemoglobin 21 per cent (33 gm.). She was given a transfusion of 500 cc of whole blood and rutin<sup>§</sup> was administered in a dosage of 20 mg four times daily. Only a few minor hemorrhages occurred during this hospital stay, and at the time of discharge from the hospital at the end of April the red-cell count was 3,210,000, and the hemoglobin 53 per cent.

On June 16 the patient re-entered the hospital after two severe nosebleeds during the previous 3 weeks. She had not been taking rutin during the interval because her supply was exhausted. The hemoglobin was again down to 23 per cent. Since no blood was available the patient was treated with iron and rutin only.

<sup>§</sup>The rutin was furnished by the Abbott Laboratories through the courtesy of Dr. Richard K. Richards.

\*From the Hematology Laboratory and the Hektoen Institute for Medical Research of the Cook County Hospital.

This study was aided by a grant from the Wilson Laboratories, Chicago, Illinois.

†Attending hematologist, Cook County Hospital, assistant clinical professor of medicine, University of Illinois, Chicago.

‡Formerly research fellow, Hematology Laboratory, Cook County Hospital, Chicago.

Cleanly care of the wound itself is also important.<sup>24</sup> Frequent change of dressing, scrupulous removal of crusts, exudate and debris, and application of moderate pressure will change the appearance of a wound completely. Saline tub baths have been used frequently by Brown,<sup>15</sup> and by Allen and Koch<sup>25</sup> to aid in the preparation of large raw surfaces for closure with skin grafts. Brown<sup>15</sup> has emphasized the importance of the use of fine mesh gauze against a granulating surface. This prevents the growth of granulations into the meshes of the gauze and thus reduces the likelihood of bleeding at the time dressings are changed. He has also introduced the use of the short fiber mechanic's waste, a universally available material and one that is just as effective as the more expensive sea sponges or fluffed gauze. Mechanic's waste can be made to mold itself against an uneven surface better than other materials and furnishes the resiliency needed for immobilization and support of the granulations and the later skin graft. Antibiotics and chemotherapy are, of course, very valuable aids but cannot supplant meticulous care of the wound.

The following is a brief summary of the management of skin grafts based on the reports of those who have had the widest experience in their use. The grafting of a raw surface is undertaken only when the patient's general condition is stabilized and when the granulating surface is firm and free from active infection. This condition can be judged best by clinical evaluation of the wound.<sup>25</sup> If the granulation tissue is thin and firm, it may be unnecessary to disturb it, but usually in long-standing ulcerations or old burns it is thick and irregular and should be carefully and smoothly shaved off.

The split thickness graft obtained either with a knife or by a mechanical device is the most satisfactory graft for healing granulating wounds or for large repairs. If adequate fixation of the graft is possible with the dressing alone, the grafts can be "snubbed" in place. Otherwise, suturing may be desirable. Sometimes the Reverdin or "pinch graft" may be used but this leaves a mottling of both the donor and the recipient site. Sheets of skin cut up into small pieces of postage-stamp size and held against the raw surface by the dressing are also useful.

Either grease gauze or wet fine mesh gauze is used immediately over the graft. Support of the graft and immobilization of the part is obtained by a bulky dressing of mechanic's waste and, if indicated, a splint.

A change of dressing is usually done by the fifth day if the grafted surface was granulating. This permits inspection of the operated area, removal of any marginal necrotic skin and mechanical cleaning of the surface. If the operated area was healed, the first dressing need not be done so early, the exact time is a matter of individual preference. All sub-

sequent dressings are planned according to the condition of the grafts.

In the late care of skin grafts, supportive bandages are necessary. This is particularly true of the lower extremity until normal vasomotor tone is re-established. In large grafts this may take six to eight months. For the upper arm, where the column of blood is not long, only a short period of support is necessary. In grafts for contractures of the neck, MacCollum<sup>26</sup> has recommended the wearing of a Thomas collar to stretch the graft.

Marginal scars, in elective skin grafting following the release of contractures or following surgical excision, must be so placed that a contracture will not develop or recur. This may be done by incisions or "darts" extending out from the margin, which are grafted with the central defect. Or should there be such a contracture, it can often be released by a local shifting of flaps or Z-plastic.

Skin grafts have proved useful in extremity wounds with chronic osteomyelitis and large bone cavities. Among others, two valuable reports concerning this complex problem have appeared. Knight and Wood<sup>27</sup> have followed a three-stage procedure in obliteration of bone cavities: a thorough sequestrectomy and excision of all adjacent scar tissue, early split skin grafting of the cavity, and excision of the graft, filling the cavity with bone chips, and immediate closure with a flap either direct or prepared earlier. Kelly et al.<sup>28</sup> using the same procedure in the first two stages have found that a third stage is often not required. Their results with bone grafting of the cavity have been disappointing and they prefer using a thick abdominal flap with abundant fat to fill it. They emphasize the importance of the vascularity of the final skin covering and the limited usefulness of chemotherapy and biotherapy.

Brown and McDowell<sup>29</sup> have reported follow-up studies on a large group of skin grafts in children. They find that the grafts grow, and function persists throughout the child's development.

A recent study of sensory regeneration in transplanted skin by McCarroll<sup>30</sup> confirms the clinical impression that the rate of return is inversely proportional to the thickness of the transplanted skin. Pain sensation returns sooner than touch, and the temporal dissociation is greater with a thicker graft.

Conway<sup>31</sup> reports a qualitative study of sweating function in transplanted skin. There is sweating only when the full thickness of the skin is transplanted. In thinner grafts, the functioning portions of the glands are apparently destroyed.

Space does not permit a more detailed presentation of the many recent publications about skin grafting. Methods and principles in using skin grafts, perfected largely by American plastic surgeons, have been so simplified that they are now generally available. The successful use of these

healed surfaces,<sup>6, 7</sup> in replacing damaged or lost skin,<sup>8</sup> in the closure of burn wounds after surgical excision,<sup>9</sup> in the resurfacing of superficial scars and release of deforming scar contractures<sup>10</sup> and in many other conditions. A free skin graft may have to be replaced with a flap, or a flap used primarily, when deeper structures such as bone, tendon or nerve are damaged, or when operation on these structures is contemplated. If the condition of the deep tissues will not support a graft—for example, in a deeply penetrating wound, or when the full thickness of a part, such as the nose or cheek, is missing—a flap must be used.

The third and fourth methods available for wound closure, resurfacing of a scar, or restoration of a part are the use of a local and a remote flap.<sup>11</sup> A local flap is desirable if sufficient skin is obtainable in the vicinity without interfering with function or creating additional deformity, and a remote flap is desirable if these conditions cannot be fulfilled or if larger amounts of skin are necessary. Flaps find their greatest usefulness in reparative surgery following compound traumatic wounds, either civilian or military. Usually there is damage and scarring of the deep structures, which delays their healing and disrupts their function. The restoration of surface covering<sup>12, 13</sup> and improvement in general nutrition of the part<sup>14</sup> are the first steps in the preparation for orthopedic or other surgical repair. The deep repair can be only as successful as the surface healing. In the absence of a part, not only skin but also subcutaneous tissue is necessary for bulk. Thus the destroyed nose, cheek, finger or ear is restored with one or more flaps.

#### FREE SKIN GRAFTING

The free transplantation of skin has been practiced only during the last seventy or eighty years. Reverdin, in 1869, first demonstrated that small bits of epidermis could be transplanted to unhealed surfaces in other parts of the body. According to Koch,<sup>15</sup> Lawson was the first to transfer a sheet of skin successfully, but Ollier, Thiersch, Wolfe and Krause are more often thought of in connection with the early development of methods in transplanting skin of intermediate and full thickness.

Little except a description of "small deep grafts" by Davis<sup>16</sup> was added to the technics and understanding of free skin grafting until after World War I. The challenge of the war and the increasing interest in the initial and late care of burns led to the development and perfection of methods for obtaining large sheets of skin and to a better appreciation of the conditions necessary for successful transplantation.

The modern concept of the use of free skin grafts had its beginning in 1929, when Blair and Brown<sup>17</sup> published the first of a long series of papers. These important publications were summarized in

1943 by Brown and McDowell<sup>18</sup> in a monograph. Their basic contribution was the description of a simple, efficient method for obtaining large sheets of skin. With the use of a long thin knife and a suction box to hold the skin taut, grafts as large as 90 by 10 cm. have been cut.<sup>19</sup> This method is still standard practice with many surgeons. A moderate amount of skill and experience is necessary for the effective use of this technic. Variations in the procedure, devised to minimize the human factor, have been suggested by Marcks<sup>20</sup> and Caltagironi. The introduction of the dermatome by the late Earl Padgett<sup>21</sup> in 1939 makes it possible for surgeons with minimal experience to have adequate amounts of skin available for grafting. The dermatome is an accurately machined half-drum with a knife blade attached by radial arms to the axis of the drum. The thickness of the skin graft, which is stuck to the drum by rubber cement, is determined by the distance between the edge of the knife blade and the drum. The method immediately received widespread acceptance. Donor areas not easily adaptable to the use of a knife are available as sources of skin with the dermatome. The value is obvious in extensively burned patients. Padgett<sup>22</sup> summarized his experience in a monograph published in 1942. Several improvements in the dermatome have been suggested, all following the same principle. Webster<sup>23</sup> uses phlofilm to back the skin graft on the drum, which simplifies separation from the drum and prevents shrinking and wrinkling of the graft. May<sup>24</sup> employs nylon cloth for the same purpose. Reese<sup>25</sup> has constructed a precision dermatome and uses a rubber sheet, called "dermatape" for backing of the graft. In my experience, this is the most accurate and effective machine for cutting skin grafts yet introduced. Douglas,<sup>26</sup> by attaching a windshield wiper to the dermatome, mechanically supplied reciprocating motion to the knife.

As mentioned above, the most important and most frequent use of the skin graft is in the covering of unhealed wounds. Although many of these are the result of burns, it is not the purpose of this paper to discuss the early care of burns. Success in the skin grafting of raw surfaces depends to a large extent on management before and after operation. Seldom is a raw surface sterilized before grafting. The aim of the surgeon is to have firm flat granulations without cellulitis and with minimal drainage and minimal bacterial growth on culture. To achieve this goal, particularly in extensive areas, requires more than merely local therapy. The importance of maintaining normal protein, vitamin and electrolyte levels in the blood and a normal red-cell count and hemoglobin has been repeatedly stressed.<sup>27-30</sup> This necessitates frequent transfusions and other supportive measures to replace cells, protein and vitamins deficient in the all too often seriously debilitated patient.<sup>31-33</sup>

the nose The composite graft has been used by Armstrong and Garcia<sup>57</sup> in repairs of the eyelid margin

### HOMOTRANSPLANTATION

Ever since the first free skin graft was used the possibility of transplantation from one person to another has been the cause of much speculation and investigation At the turn of the century there were isolated reports of successful isografting or homotransplantation of skin Davis,<sup>55</sup> in his monograph on plastic surgery in 1919, reported a review of hospital records and concluded that such homotransplantation was possible Later, he was convinced that the observations were faulty One of the most enlightening reports on this whole problem is that of Loeb,<sup>59</sup> a pioneer in tissue culture Loeb considered individual biologic differences to be very specific The more closely related the species, the less marked the individuality differential which he characterized as chemical differences in the cells In isografting these differentials come into play, and the evidence indicates that a primary substance or toxin is produced by the graft that causes a reaction in the host, making the graft disappear That this is not a true immune reaction is indicated by Loeb's observation of the absence of an accelerated reaction on secondary transplantation Studies by Medawar<sup>60</sup> shed further but somewhat different light on the subject He presents contradictory evidence that the reaction to a homograft is a true immune phenomenon, with acceleration in proportion to dosage of the reaction to a second graft Medawar also reports no evidence that red cells and skin share similar antigens, although leukocytes and skin do share them Such an observation disproves the value of blood typing in homotransplantation Barker<sup>61</sup> doubts that failure of homotransplantation is on the basis of sensitization to homologous skin proteins

Stone,<sup>62</sup> in 1934, stimulated interest in homotransplantation by his studies of tissue culture of the parathyroid glands He investigated the possibility of adapting the graft by first growing it as a tissue culture in a medium containing the body fluids of the future host "This we have done in all cases in which we have secured successful grafts," he writes

Both Padgett<sup>63</sup> and Brown<sup>64</sup> have reported successful homotransplantation of human skin in identical twins An elective interchange of full thickness grafts on the upper arm was carried out by Brown One of the most recent reports was that by Converse<sup>65</sup> in which one of twins was severely burned in the leg, and skin from the twin brother was used with the patient's own skin for covering The behavior of the homografts, he reports did not differ from that of the autografts, and a two year follow-up confirms the stability of

the homografts These observations of successful transplantation between identical twins suggests a very fundamental individual cell specificity However, the fact that practically inert lymph-nourished tissues like cartilage and cornea can be permanently transplanted indicates that it pertains only to the more highly involved tissues of the human body

Recent studies by Longmire<sup>66</sup> confirm the temporary survival of homotransplants and the insignificance of blood group of donor and recipient in skin homografting He also presents evidence that, unlike blood types, skin types do not exist

Barker<sup>67</sup> reports studies of pigment changes in iso skin transplants between black and white rabbits Black skin is transplanted to white animals, and white skin to black White skin on the black animal is completely pigmented in sixty to one hundred and twenty-nine days Hair color remains unchanged up to five months despite a change in the color of the skin Pigmentation of the white skin surrounding a black graft likewise occurs

The chief clinical interest in homotransplantation is as a life-saving measure in badly debilitated patients with extensive burns The homografts are used as a temporary skin dressing until the patient's condition warrants the use of autografts<sup>19</sup> This method of homotransplantation has been successfully used for large granulating wounds in a badly debilitated burned patient Skin was removed from a cadaver six hours after death and applied to the recipient seven hours later The cadaver had been refrigerated and was cold when the grafts were taken The grafts were wrapped in a moist sponge and left refrigerated until used<sup>68</sup> The three-month survival period of these grafts is one of the longest on record Unfortunate false publicity has led to the useless taking of skin from donors, who are led to believe that their skin will survive permanently Skin banks have even been proposed The occasions when homotransplants are indicated are very rare

### TRANSPLANTATION OF FLAPS

The transplantation of flaps is one of the oldest of all surgical technics Plastic surgery can thus claim its origin centuries before the Christian Era War injuries, accidents and punishments and the ever-present congenital deformities have always provided a stimulus for the development of reparative surgery Both Davis<sup>69</sup> and Koch<sup>15</sup> have reviewed the early history of skin transplantation and paid tribute to those who paved the way to modern plastic surgery According to Davis, the Hindus (750 to 800 B C) were the earliest recorded practitioners of real plastic surgery They understood the local shifting of skin flaps or sliding flaps that later somehow became known as the French method Other technics, such as the repair of a nose with a forehead flap, were developed by members of the lower castes in India who in-

technics in skin grafting should make possible the prompt healing of burns, the immediate closure of most traumatic or surgical wounds and the early repair of deforming scars and chronic ulcerations.

In 1943 Sano<sup>42</sup> described a method of adhesive fixation of skin grafts to a raw surface. By mixture of a specially prepared plasma solution with leukocyte extract a fibrinous adhesive coagulum is formed that eliminates the need for a dressing or suturing the graft. The leukocyte extract is "painted" on the graft, and the plasma solution on the recipient surface before the graft is applied.

Several other methods of fixation of skin grafts and for "gluing" severed nerves were suggested, and there are still occasional reports of the value of these methods.<sup>43, 44</sup>

Young<sup>45</sup> reports fibrin fixation of skin grafts by the addition of thrombin to the recipient area and plasma to the graft. A clot forms when the two are brought in contact. He concludes that the method has value in applying grafts to fresh surgical wounds, for holding grafts while compression dressings are being applied, and as a means of holding small grafts that are not to be held with a dressing. He does not recommend the use of fibrin fixation for granulating wounds.

Brown<sup>46</sup> cites his use of coagulum fixation of skin grafts to a granulating surface. In each case a graft without adhesive substance was applied as a control. None of these grafts were sutured in place, and there was a complete take of all the grafts, including the controls. Brown reports the observation of many surgeons performing skin grafts to granulating surfaces that spontaneous adhesion occurs if the graft is pressed against the raw surface for a few minutes.

An interesting suggestion explaining the value of adhesive methods in skin grafting has come from Medawar.<sup>47</sup> He points out that the lower the temperature the less enzymic autolysis occurs and the less the risk of loss of the dormant graft from infection. Fixation with bulky pressure dressings tends to keep the graft at a higher temperature and increases this danger. The adhesive method, without a dressing, allows the graft to remain at a lower temperature and favors its survival. This technic of open grafting was used successfully for many years by Porter and Greenough at the Massachusetts General Hospital, without, however, adhesive fixation of the grafts.

#### FULL THICKNESS GRAFTS

Wolfe-Krause or full thickness grafts, consisting, as the name implies, of the epidermis and full thickness of the dermis, have several advantages over grafts of intermediate thickness. One of the clearest and most complete expositions of the value of and indications for the full thickness skin graft has been presented by Byars.<sup>48</sup> Two important advantages of these grafts are emphasized the

minimal tendency to contract and wrinkle, and better color and texture of the surface. Full thickness grafts are harder to prepare and tedious to apply. They are more liable to failure, and the amount that can be transplanted is limited. The donor site must often be closed with a split skin graft. The advantages of these grafts are the reasons for their use.

Flexion is the functional motion of the hand so that little active stretching of the palmar skin occurs. Skin resurfacing of the palm is thus often best done with a full thickness graft that shrinks little. The same principle may apply in the definitive release of contracting scars of the neck. On the face there are delicate motions of expression, and the skin is exposed, so that both functionally and cosmetically the full thickness graft is preferred.

Full thickness grafts are usually taken from the groin, inner surface of the upper arm or abdominal wall. Skin from the fold behind the ear is available in small amounts and usually matches the skin of the face. Skin from the upper eyelid has been used by Wheeler<sup>49</sup> for repairs of the lids. A recent suggestion by Brown and Cannon<sup>50</sup> of full thickness grafts from the base of the neck has proved valuable because the grafted skin matches that of the face well, it is available in large amounts, and its function in kinetic areas of the face cannot be distinguished from the normal. An explanation for this observation is that only in the neck is there skin whose normal environment overlying the platysma muscle is similar functionally to the skin of the face, beneath which lie the delicate muscles of expression. In resurfacing the dorsum of the fingers to prepare for definitive tendon surgery, this graft has been used because of the loose areolar tissue beneath it in which the tendon will glide.

If a graft on the face fails to match the color of the adjacent skin, the color can be changed by permanent pigment injection, the same method used in tattooing. This technic of skin pigmentation was first described by Hance<sup>51</sup> and Byars.<sup>52</sup> It is not only of value in tinting grafts but also in masking the redness of capillary hemangioma or port-wine stain.<sup>53, 54</sup> The mixed pigments in the form of a thin paste are imbedded in the dermis by multiple puncture using fine cambric needles. The puncture is done either by hand or by a vibrating device.

Brown and Cannon<sup>55</sup> have described the composite graft from the ear for alar and columellar repairs. The graft, which comprises two layers of skin with the cartilage between, makes possible tissue replacement about the nostrils in a single operation. Minimal deformity of the ear, which can be repaired with local tissue, results. Dupertuis<sup>56</sup> has independently used segments of the ear lobe for similar repairs, particularly on the tip of

narrow pedicle containing only the coronary artery and vein that encircle the lip. Rotation of the flap through 180° is possible. Its greatest usefulness is in direct closure after excision of the lip for cancer and in secondary repairs for harelip or trauma.<sup>95-97</sup>

Brown and his associates<sup>12, 13</sup> have emphasized the value of more direct methods in the transfer of flaps in preference to the slower delaying and tubing technics. By providing an adequately broad base with a short pedicle the viability of the flap is assured. The flap can be accurately prepared to fit the defect resultant from trauma or surgical excision of scars and attached at the same time. This direct transfer may save many weeks or even months of hospitalization and disability. This method has proved of value not only for the upper extremity but also, surprisingly enough, for the lower extremity. Either the thigh or the calf can be the source of these flaps for the opposite leg if local flaps are inadequate.

For more extensive resurfacing of the lower extremity or other parts, open jump flaps from the abdominal wall carried on the forearm have been described.<sup>98, 99</sup> Edwards<sup>100</sup> has compared the experience in 26 cases of open jump flap with a similar series using tubed flaps also carried on the forearm. The 26 jump flaps took an average of one hundred and six days and six operations to complete, and none were lost. Thirty-five tubed flaps were started, and 9 failed, so that only 26 were completed. An average of three hundred and thirty-three days and ten operations were necessary for the repair.

The application of the principles of plastic surgery to problems of general surgery is well demonstrated in the recent articles on decubitus ulcers in paraplegia and in repairs of the chest wall following very radical surgery.

Barker<sup>101</sup> reports that excision and suture or the advancing of flaps has proved satisfactory in the closure of decubitus ulcers. Grafts are reserved for patients whose condition does not warrant the use of flaps. Gibbon and Freeman<sup>102</sup> report experience with 65 patients with decubitus ulcers treated by excision and closure by advancing local skin flaps. White and Hamm<sup>103</sup> describe 14 cases of decubitus ulcers in patients with spinal paraplegia in which repair was accomplished by the rotation of local flaps. A trend toward the use of rotated flaps rather than advancing of flaps through stellate incisions is noted in the more recent writings. This is emphasized by Conway,<sup>104</sup> who says "large ulcers are closed successfully in the highest percentage of cases when a flap of skin and subcutaneous tissue is rotated from an adjacent area and the defect at the site of procurement of the flap surfaced by a free graft of skin." The important additional factor in success of removing all bony prominence is stressed by Kostrubala.<sup>105</sup> I have found this to be true in my experience with decubitus

ulcers and in several cases have excised the outer table of the sacrum, removing with the bone all avascular and necrotic ligamentous and fascial tissue and leaving a base of healthy cancellous bone.

Both Maier<sup>106</sup> and Pickrell<sup>107, 108</sup> have reported the use of rotated flaps from the thoracic or abdominal wall and the skin of the breast and, in Pickrell's report, the use of free skin graft on the pericardium, for repairs of large defects of the chest wall following radical resection of tumors, resection of areas of radiation necrosis and in repairs following trauma.

## SUMMARY

An attempt is made to review early and recent developments that have led to present understanding of skin transplantation. Some of the principles of repair that have evolved with the perfection of methods and technics are presented. In the future, the development of direct methods and a more widespread understanding of basic principles throughout the surgical profession can be expected. Studies in wound healing and homotransplantation may cast further light on these puzzling problems.

## REFERENCES

1. Blair V. P. Editorial. *Plast. & Reconstruct Surg.* 1:1 1946.
2. Brown J. B. Military plastic surgery. *Plast. & Reconstruct Surg.* 1:58-59 1946.
3. Brown J. B. General plastic surgery. *Surg. Gynec. & Obst.* 86:627-629 1948.
4. Conway H. and Coldwater K. V. Principles in reparative plastic surgery: experiences in general hospital in tropics. *Surgery* 19:437-459 1946.
5. Cannon B. and Cope O. Rate of epithelial regeneration: clinical method of measurement and effect of various agents recommended in treatment of burns. *Ann Surg.* 117:85-92 1943.
6. Brown J. B. Covering of raw surfaces. *Internat. Abstr. Surg.* 67:105-116 1938.
7. Cannon B. Procedures in rehabilitation of severely burned. *Ann Surg.* 117:903-910 1943.
8. Brown J. B. Restoration of entire skin of penis. *Surg., Gynec. & Obst.* 65:362-365 1937.
9. Cope O., Langohr J. L., Moore F. D. and Webster R. C., Jr. Expedient care of full thickness burn wounds by surgical excision and grafting. *Ann Surg.* 125:1-22 1947.
10. Brown J. P., Blair V. P. and Hamm W. G. Release of axillary and brachial scar fixation. *Surg. Gynec. & Obst.* 56:750-795 1933.
11. Cannon B. and Graham W. C. Plastic and reconstructive surgery of hand. *Wil. Surgeon* 97:137-139 1945.
12. Brown J. B. et al. Direct flap repair of defects of arm and hand: preparation of gunshot wounds for repair of nerves, bones and tendons. *Ann Surg.* 122:705-715 1945.
13. Brown J. B. and Cannon B. Repair of surface defects of foot. *Ann Surg.* 120:417-430 1944.
14. Bunnell S. *Surgery of the Hand*. 734 pp. Philadelphia: J. P. Lippincott Co. 1944.
15. Koch S. L. Transplantation of skin and subcutaneous tissue to hand. *Surg. Gynec. & Obst.* 72:1-14 1941.
16. Davis J. S. Use of small deep skin grafts. *J. A. M. A.* 63:985-989 1914.
17. Blair V. P. and Brown J. B. Use and uses of large split skin grafts of intermediate thickness. *Surg. Gynec. & Obst.* 49:82-97 1929.
18. Brown J. B. and McDowell F. *Skin Grafting of Burns: Primary care treatment repair*. 204 pp. Philadelphia: J. P. Lippincott Co. 1943.
19. *Idem*. Massive repairs of burns with thick split skin grafts: emergency dressings with homografts. *Ann Surg.* 115:658-674 1942.
20. Marcks A. M. Modified calibrated skin grafting knife. *Wil. Surgeon* 92:653 1943.
21. Padgett, E. C. Calibrated intermediate skin grafts. *Surg. Gynec. & Obst.* 69:779-793 1939.
22. Padgett, E. C. *Skin Grafting from a Personal and Experimental standpoint*. 149 pp. Springfield: Ill. Charles C. Thomas, 1942.
23. Webster J. P. Film-cemented skin grafts. *S. Clin. North America* 24:251-260 1944.
24. May H. *Reconstructive and Reparative Surgery*. 964 pp. Philadelphia: F. A. Davis Co. 1947.

herited surgical practice when it came to be thought unclean. Today the use of a flap of forehead skin for nasal reconstruction is spoken of as the Indian method. This method was brought to the United States by Warren<sup>70</sup> after a sojourn in Europe and described by him in 1837. Another important method of nasal reconstruction, using a flap from the upper arm, has come to use from the writings of Taliacotius<sup>71</sup> of Bologna, whose face is engraved on the certificate of the American Board of Plastic Surgery. In 1840 Warren<sup>72</sup> again wrote about nasal reconstruction. He pointed out the value of this flap in avoiding a deforming scar of the forehead. Today, this type of nasal reconstruction is known as the Italian method.

The tubing of a flap as a preliminary to its transfer was reported independently by Gillies<sup>73</sup> and Filatoff,<sup>74</sup> but Gillies was its greatest proponent. Through his writings and his disciples, who carried his teachings to many parts of the world, the method gained widespread recognition and popularity. For the first time multiple-stage migration of flaps to remote parts of the body was possible. The skin surface remained closed at all times, and the hazard of infection and thrombosis was reduced.

Webster,<sup>75</sup> in 1937, described the thoracoepigastric tubed pedicle flap, which utilized for blood supply the long thoracic, the superficial thoracic and the superficial epigastric arteries and thoracoepigastric veins. These vessels lie subcutaneously on the abdominal and chest walls and are thus included within the substance of the flap. Large flaps of this type have proved useful for many types of surgical repair on many parts of the body.

That the use of tubed pedicle flaps is not without hazards, however, is indicated by Macomber and Rubin,<sup>76</sup> who list the precautions in the preparation of tubed flaps and the complications that may arise in their preparation, delay and transfer. These include necrosis from tension or from excessive length, hemorrhage within the tube, infection, improper timing of delays, kinking or angulation of the tube, use of an inadequate flap and improper closure following delays and several others. This report is based on a series of over 300 cases of tubed flaps prepared for repairing complicated war wounds of the extremities.

To reduce the possible complications in the preparation of tubed flaps, Shaw and Payne<sup>77</sup> have found it advantageous in applying small flaps to the hand to tube the pedicle at the same time. This method combines the speed of the abdominal flap with the cleanliness of the tube. Macomber and his associates<sup>78, 79</sup> have re-emphasized the value of a skin graft in the bed from which a tubed flap is prepared as a means of primary wound closure. The free skin graft is also useful in closing the donor area and undersurface of large direct abdominal flaps.

The forehead flap, or Indian method, has found increasing usefulness today in the repair of surgical and traumatic cases not only of the nose<sup>80</sup> but also of other parts of the face (eyelid, lip, mouth, orbit, cheek and chin). Blair et al.<sup>81</sup> report from a wide experience with this type of flap in repairs of the face following radical surgery for cancer. The authors describe the methods used, and the principles underlying their use are illustrated in detail. Various descriptions of flaps for facial repairs have been presented by other authors.<sup>82-85</sup> The major disadvantage of the forehead flap is the deformity that results. Since a normal feature is destroyed, this flap should be avoided in young people. In a large Army plastic center, the arm flap, or Italian method, was used almost exclusively in nose reconstruction for this reason.<sup>86</sup>

New<sup>87</sup> has described the "sickle flap" as a method that minimized the deformity. The skin for the repair is taken high in the temple along the hairline. The flap is carried on a sickle-shaped pedicle extending upward along the temporal artery and lying completely within the hairline. Very large repairs are possible by this method, including the nose, lip, eyelid or cheek.

Kazanjan<sup>88</sup> has described the "median forehead flap," which is elevated from the midline of the forehead and carried on a pedicle between the brows. The vertical scar in the forehead is not deforming. A surprising amount of skin can be mobilized by this method, which can be used in repairs of the eyelid, nose or upper lip.

The "island flap," devised by Gursnay in 1887 and later presented by Monks<sup>89</sup> in 1898, also leaves no deforming scars. Only two vessels, branches of the temporal artery and vein, form the pedicle of the flap, which can be either hairless forehead skin or hair-bearing scalp. The vessels are identified by palpation and dissected free through an overlying linear incision. The mobilized flap and vessels are passed through a tunnel to the recipient area. This flap is most useful for the eyelids and brow.

Large flaps from the anterior portion of the neck and chest wall are also used in facial repairs to avoid any additional deforming scars of the face. These methods have been described and utilized by many authors.<sup>90-92</sup> Flaps from the neck have the additional advantage of matching facial skin in color and texture. Brown and Cannon<sup>93</sup> describe a large flap with the base above the clavicle that lies vertically down the chest or crosses to the opposite side above the nipple level. This flap provides a method of obtaining large amounts of skin for the face without the need of migration in multiple stages.

A very useful direct method for repairs about the mouth is the vermilion-bordered lip flap, originally described by Estlander<sup>94</sup> in 1872. This flap, comprising the full thickness of the lip, is carried on a

## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

EDITH E. PARRIS, *Assistant Editor*

### CASE 34381

#### PRESENTATION OF CASE

A seven-year-old girl was admitted to the hospital because of pain and swelling of the left ankle.

The mother dated the illness back four months at which time the girl struck her left ankle and subsequently developed a slight limp. Four months before admission swelling was noted for the first time, and the ankle became painful. The pain gradually became more severe. Three months before admission the patient was said to have been feverish, although the temperature was not taken. X-ray films were taken by a physician, who made a diagnosis of Brodie's abscess.

On examination there was marked dental caries. There were bilateral palpable shotty inguinal nodes which were not tender. There was a 5-cm by 7-cm, firm, slightly tender swelling of the anterior medial aspect of the left ankle that seemed contiguous with the lower end of the tibia and did not appear to cross the ankle joint. The foot was held in valgus position, although flexion and extension were normal as compared to the opposite side. The left medial malleolus was lower than the right. Measurements from the midpatella to the medial malleolus were, on the right,  $9\frac{3}{8}$  and, on the left,  $9\frac{7}{8}$  inches. The circumference of the leg, measured 1 inch above the medial malleolus, was right,  $6\frac{1}{2}$  and left, 7 inches. There was no remarkable redness or increased heat. There was no bruit. The temperature was normal.

Laboratory examination revealed a normal urine, a hemoglobin of 11.8 gm, a white-cell count of 8200 and a normal differential. The blood calcium was 8.8 mg per 100 cc, the phosphorus 5.3 mg per 100 cc, and the alkaline phosphatase 5.5 units per 100 cc. The total protein was 6.7 gm per 100 cc. The sedimentation rate was 16 mm in 1 hour. The blood Hinton and tuberculin tests were negative.

An x-ray film showed a rarefied area within the cancellous portion of the distal end of the tibial epiphysis, more toward the medial side (Fig 1). The rarefaction extended to the metaphysis and also seemed to involve the cortex of the bone in one

area. There was some suggestion of local decalcification within the adjoining epiphysis. Soft-tissue swelling was present, and there was some periosteal new-bone formation along the medial aspect of the distal tibia. There were no lesions in the spine,



FIGURE 1

pelvis, skull or lungs. Measurement of teleroentgenograms showed  $\frac{1}{4}$ -inch lengthening of the left tibia.

On the seventh hospital day an operation was performed.

#### DIFFERENTIAL DIAGNOSIS

DR. CHANNING C. SIMMONS: According to the x-ray films this patient has an area of bone destruction with slight periosteal proliferation in the lower end of the left tibia. It can be noticed that this tibia is slightly larger than the other. It is a question whether the lesion extends across the epiphysis or whether the appearance in the film is due to rarefaction of disuse. The lymph node in the groin, I think, is of very little significance.

Diagnosis of these bone tumors, as I have said many times, lies between a diffuse skeletal disease, an inflammatory condition, and some form of tumor. From the data at hand, I think we can fairly well rule out a general skeletal disease. Inflammatory conditions such as syphilis, tuberculosis and osteomyelitis are all possibilities. The blood Hinton

- 25 Reese J D Dermatop new method for management of split skin grafts *Plast & Reconstruct Surg* 198 10> 1946
- 26 Douglas B Unpublished data presented before the Society of University Surgeons Nashville Tennessee 1944
- 27 Cope O and Moore F D Redistribution of body water and fluid therapy of burned patient *Ann Surg* 126 10 0 1045 1947
- 28 Moore F D Peacock W C Blakely E and Cope O Anemia of thermal burns *Ann Surg* 124 811 839 1946
- 29 Lund C C Green R W, Taylor F H L and Levenson S M Burns collective review *Internat Abstr Surg* 82 443-478, 1946
- 30 Harkins H N *The Treatment of Burns* 457 pp Springfield Ill Charles C Thomas 1942
- 31 Mascoe M L Wound healing *Internat Abstr Surg* 69 303 315 1939
- 32 Allen H S and Koch S L Treatment of patients with severe burns *Surg Gynec & Obst* 74 914 924 1942
- 33 Owens N Surgical treatment of burns use of pressure dressings *Plast & Reconstruct Surg* 2 226-233 1947
- 34 Brown J B and Blair V P Repair of defects resulting from full thickness loss of skin from burns *Surg Gynec & Obst* 60 379 389 1935
- 35 Churchill E D Surgical management of wounded in Mediterranean Theater at time of fall of Rome *Ann Surg* 120 268 283, 1944
- 36 MacCallum D Early and late treatment of burns in children *Am J Surg* 39 275 311 1938
- 37 Knight M P and Wood G O Surgical obliteration of bone cavities following traumatic osteomyelitis *J Bone & Joint Surg* 27 547-556 1945
- 38 Kelly R P Rosario L M and Murray R A Traumatic osteomyelitis use of skin grafts Technique and results *Ann Surg* 122 1-11 1945 II Subsequent treatment *Ibid* 123 688-697 1946
- 39 Brown J B and McDowell F Persistence of function of skin grafts through long periods of growth *Surg Gynec & Obst* 72 848-853 1941
- 40 McCarroll H R Regeneration of sensation in transplanted skin *Ann Surg* 108 307-320 1938
- 41 Conway H Sweating function of transplanted skin *Surg Gynec & Obst* 69 756-761 1939
- 42 Sano M E Coagulum contact method of skin grafting as applied to human grafts *Surg Gynec & Obst* 77 510 513 1943
- 43 Tarlov I M and Benjamin B Plasma clot and silk suture of nerves I Experimental study of comparative tissue reaction *Surg Gynec & Obst* 76 366-374 1943
- 44 Young J Z and Medawar P B Fibrin suture of peripheral nerves measurement of rate of regeneration *Lancet* 2 126-128 1940
- 45 Young F Skin graft fixation by plasma-thrombin adhesion *Ann Surg* 120 450-462 1944
- 46 Brown J B Discussion of Young<sup>44</sup>
- 47 Medawar P B Experimental study of skin grafts *Brit. M Bull* 3 79 81 1945
- 48 Byars L T Free full thickness skin grafts principles involved and technique of application *Surg Gynec & Obst* 75 8-20 1942
- 49 Wheeler J M *Collected Papers of John M Wheeler* 431 pp New York Columbia University Press 1939
- 50 Brown J B and Cannon B Full thickness skin grafts from neck for function and color in eyelid and face repairs *Ann Surg* 121 639-643 1945
- 51 Hance G Brown J B Byars L T, and McDowell F Color matching of skin grafts and flaps with permanent pigment injection *Surg Gynec & Obst* 79 624-628 1944
- 52 Byars L T Tattooing of free skin grafts and pedicle flaps *Ann Surg* 121 644-648 1945
- 53 Brown J B Cannon B and McDowell A Permanent pigment injection of capillary hemangiomas *Plast & Reconstruct Surg* 1 106 1946
- 54 Conway H and Dockert J P Neutralization of color in capillary hemangiomas of face by intradermal injection (tattooing) of permanent pigments *Surg Gynec & Obst* 84 866-869 1947
- 55 Brown J B and Cannon B Composite free grafts of skin and cartilage from ear *Surg Gynec & Obst* 82 253 255 1946
- 56 Dupertuis S M Free ear lobe grafts of skin and fat their value in reconstruction about nostrils *Plast & Reconstruct Surg* 1 135 144 1946
- 57 Armstrong C J and Garcia F A Use of composite graft in reconstructive surgery of lower eyelid *Plast & Reconstruct Surg* 3 79-83 1948
- 58 Davis J S *Plastic Surgery Its principles and practice* 770 pp Philadelphia Blakiston's Sons Co 1919
- 59 Loeh L Transplantation and individuality *Physiol Rev* 10 547-616 1930
- 60 Medawar P B Second study of behaviour and fate of skin homografts in rabbits *J Anat* 79 157-176 1945
- 61 Barker D E Anaphylaxis and homotransplantation of skin *Plast & Reconstruct Surg* 3 34 36 1948
- 62 Stone H B, Owens J C, and Gey G O Transplantation of living grafts of thyroid and parathyroid glands *Ann Surg* 100 613-628 1934
- 63 Padgett E C Is iso-skin grafting practicable? *South M J* 25 895 900 1932
- 64 Brown J B Homografting of skin with report of success in identical twins *Surgery* 1558-563 1937
- 65 Converse J M and Dinet G Successful homologous skin grafting in war burn using identical twin as donor *Plast & Reconstruct Surg* 2 342 344 1947
- 66 Longmire W P Jr Stone H B, Daniel A S and Goon C D Report of clinical experiences with homografts. *Plast & Reconstruct Surg* 2 419-426 1947
- 67 Barker D E Pigment changes in experimental whole thickness skin grafts *Arch Path* 44 163 165 1947
- 68 Webster J P Refingerated skin grafts. *Ann Surg* 120 431-449 1944
- 69 Davis J S Story of plastic surgery *Ann Surg* 113-641-656, 1941
- 70 Warren J M Rhinoplastic operation *Boston M & S J* 16 69 79 1837
- 71 Taliacotus, G *De curtorum chirurgica per institutionem.* 436 pp Venice G Bindoom 1597
- 72 Warren J M Taliacotian operation *Boston M & S J* 22 261 1840
- 73 Gillies H D *Plastic Surgery of the Face Based on Selected Cases of War Injuries of the Face including Burns with Original Illustrations* London Oxford University Press 1920
- 74 Filatoff W P Cited by Gillies.<sup>73</sup>
- 75 Webster J P Thoraco-epigastric tubed pedicles. *S Clin. North America* 17 145 184 1937
- 76 Macomber W B and Ruhin L R Tubed pedicle complications in repair of massive tissue defects *Plast & Reconstruct Surg* 2 10-20 1947
- 77 Shaw, D T and Payne R L Jr One stage tubed abdominal flaps single pedicle tubes *Surg Gynec & Obst* 83 20> 207 1946
- 78 Macomber W B and Patton H S Split thickness graft—useful adjunct in tube pedicle preparation *Surg Gynec & Obst* 84 97-100 1947
- 79 Macomber W B, and Briele H A Modern experience with tubed pedicle flaps of thigh *Plast & Reconstruct Surg* 2 163-170 1947
- 80 Blair V P, and Byars L T "Hits strikes and outs in use of pedicle flaps for nasal restoration or correction *Surg Gynec & Obst* 82 367-385 1946
- 81 Blair V P Moore S and Byars L T *Cancer of the Face and Mouth Diagnosis treatment surgical repair* 599 pp St. Louis C V Mosby Co 1941
- 82 Cannon B Care of military and civilian injuries use of remote flaps in repairing defects of face and mouth *Am J Otolaryngology* 29 77 85 1943
- 83 Daland E M Repair of large defects after removal of cancer of lips *Surg Gynec & Obst* 69 347-357 1939
- 84 Gillies H D Experiences with tubed pedicle flaps. *Surg Gynec & Obst* 60 291 303 1935
- 85 Webster J P Plastic surgery In *A Textbook of Surgery by American Authors* Edited by F Christopher Third edition, Second edition 1764 pp Philadelphia W B Saunders 1942 Pp 1576 1597
- 86 Brown J B Personal communication
- 87 New G B Sickle flap for nasal reconstruction *Surg Gynec & Obst* 80 497-499 1945
- 88 Kazanjian V H Repair of nasal defects with median forehead flap primary closure of forehead wound *Surg Gynec & Obst* 83 37-49 1946
- 89 Monks G H Reconstruction of lower eyelid by new method *Boston M & S J* 139 385-387 1898
- 90 Ivy R H Repair of facial defects by low neck pedicle flaps *Plast & Reconstruct Surg* 1 119 123, 1946
- 91 Brown J B Closure of surface defects with free skin grafts and with pedicle flaps *Surg Gynec & Obst* 84 862-865 1947
- 92 Macomber W B and Berkeley W T Use of neck tubed pedicles in reconstruction of defects of face *Plast & Reconstruct Surg* 2 585 596 1947
- 93 Brown J B and Cannon B Repair of major facial injuries *Ann Surg* 126 624-632 1947
- 94 Eutander J A Cited by Cannon B<sup>93</sup>
- 95 Brown J B Switching of vermilion-bordered lip flaps. *Surg Gynec & Obst* 46 701-701 1928
- 96 Cannon B Use of vermilion bordered flaps in surgery about mouth *Surg Gynec & Obst* 74 458-462 1942
- 97 Webster J P Operation for epithelioma of lip *Am J Roentgenol* 30 82-91 1933
- 98 Cannon B Lischer C E, and Brown J B Open jump flap repairs of lower extremity *Surgery* 22 335 340 1947
- 99 Cannon B et al Use of open jump flaps in lower extremity repairs *Plast & Reconstruct Surg* 2 336-341 1947
- 100 Edwards W S Personal communication
- 101 Barker D E, Elkins C W and Poer D H Methods of closure of decubitus ulcers in paralyzed patient. *Ann. Surg* 132 523 530 1946
- 102 Gibbon J H Jr and Freeman L W Primary closure of decubitus ulcers *Ann Surg* 124 1148 1164 1946
- 103 White J C and Hamm W G Primary closure of bedsores by plastic surgery *Ann Surg* 124 1136-1147 1946
- 104 Conway H et al Plastic surgical closure of decubitus ulcers in patients with paraplegia *Surg Gynec & Obst* 85 321 332 1947
- 105 Kostrohala J C, and Greeley P W Problem of decubitus ulcers in paraplegics. *Plast & Reconstruct Surg* 2 403-412 1947
- 106 Maier H C Surgical management of large defects of thoracic wall *Surgery* 22 169 178 1947
- 107 Pickrell K L Baker H M and Collins J P Reconstructive surgery of chest wall *Surg Gynec & Obst* 84 465-476 1947
- 108 Pickrell K L Kelly J W and Marzoni F A Surgical treatment of recurrent carcinoma of breast and chest wall *Plast & Reconstruct Surg* 3 156-172 1948

The temperature and pulse were normal

Laboratory examination revealed a normal urinalysis. The clotting time varied between 20 seconds and 2 minutes and 5 seconds. A bilateral lumbar sympathectomy was done, and communicating leg veins were ligated.

*Second admission* (three months later) Following the operation the patient did well until she developed an acute maxillary sinusitis. She noticed some painless swelling of both lower extremities at this time. Three days after the onset of the sinusitis she noted left-sided back pain on breathing. She developed a cough, fever and bloody sputum. On readmission to the hospital the chest findings, including x-ray examinations, were consistent with pulmonary infarction. The clotting time was 5 minutes, and the prothrombin time 27 seconds (normal, 22 seconds). Venograms showed no filling of the deep veins in either leg. A ligation of the inferior vena cava in continuity was done.

*Third admission* (two years and five months later) Following the vena-cava ligation the patient had bilateral varicose ulcers, which kept breaking down. A bilateral femoral-vein ligation was done at this time, and a dilatation and curettage were performed. x-ray treatment (1000r) was given to stop menstrual bleeding.

*Fourth admission* (fourteen months later) In the interval the patient's condition was unchanged, and the leg ulcers continued to break down if the patient walked excessively. Three months before admission the patient developed shingles around the buttocks. This subsided but six weeks before admission an abscess the size of a billiard ball developed over the lower spine. This broke spontaneously and subsided.

On examination there were moderate external hemorrhoids, but there was no pilonidal dimple. A hemorrhoidectomy was done.

*Fifth admission* (one and a half years later) Ten days before admission the patient noticed a steady gnawing pain under the tip of the xiphoid. This persisted and became more severe and shifted to below the original site. The pain was aggravated by movement and only partially alleviated by rest and medication. The pain radiated to the upper lumbar region and back. There was no nausea, vomiting or anorexia. The bowel movements were regular, and there was no melena. There were no chills, no fever and no bouts of crampy pain. There was no weakness or weight loss.

On examination there was some vague, not localized, slight abdominal tenderness.

The blood pressure was 116 systolic, 70 diastolic. Examination of the blood disclosed a white-cell count of 14 200, with 81 per cent neutrophils. The platelets were somewhat decreased. The serum amylase was 13 units, and the prothrombin time was 18 seconds (normal, 16 seconds). The specific gravity of the urine was 1.012. There was a + test for albumin and the sediment contained an occasional red cell and 25 white cells per high-power field. The stool was guaiac negative.

The pain was much relieved by the third hospital day, and the patient was taking fluids comfortably. A gastrointestinal series, Graham test and barium enema were negative.

During the evening of the fourth day there was an exacerbation of pain with vomiting of recently ingested water. Abdominal tenderness was not well localized to either side of the abdomen. There was no spasm or distention. The vomiting continued, and the maximum pain and tenderness shifted to the right, chiefly in the upper quadrant. There was a sense of resistance to palpation on the right. The temperature was normal. The abdomen was quiet on auscultation, and an occasional normal peristaltic sound was heard. There was no change in the sound with exacerbations of pain. On the fifth hospital day severe pain, nausea and vomiting recurred and persisted, and the tenderness was constantly referred to the right lower quadrant.

An operation was performed.

#### DIFFERENTIAL DIAGNOSIS

DR ARTHUR W ALLEN Have you some films of the abdomen? May we see them now?

DR JAMES J MCCORT Do you want to see the early films of the infarct?

DR ALLEN I do not know that we need to. I am more interested in the films of the present illness. You probably have a plain film of the abdomen taken shortly after admission.

DR MCCORT No, we do not have that. These films you see are of the gall bladder on the last admission, and the gall bladder is seen to concentrate the dye well. No calculi are present. This is the barium enema. There is no definite abnormality demonstrated in the large bowel. There is only slight filling of the terminal ileum on this examination. There are no defects, and no evidence of

test was negative, which pretty well rules out syphilis, although bone syphilis might give a negative Hinton test. An inflammatory condition has to be considered — a Brodie's abscess, so-called, or localized osteomyelitis. We have to consider osteogenic sarcoma, Ewing's sarcoma, plasma-cell myeloma, eosinophilic granuloma and giant-cell tumor.

An inflammatory condition in a child usually is found in the epiphyseal region, which is stimulated, causing the bone to grow longer as in this case. Whether tumor in the same situation will do this, I do not know. However, the normal temperature militates against an inflammatory condition. Of the tumors, osteogenic sarcoma may be present. It is rarely found in this position or gives this picture, although osteogenic sarcoma can simulate any condition. Giant-cell tumor gives a picture of bone destruction without new-bone formation, but there was new-bone formation associated with this lesion. Eosinophilic granuloma I should not consider. Plasma-cell myeloma is usually a multiple disease, although single bones are occasionally involved. Ewing's sarcoma may perfectly well give this picture of destruction but usually with much more tumor clinically than is suggested by the x-ray film. In other words, the whole leg is enlarged. Ewing's sarcoma may give a little fever or a slightly elevated white-cell count.

I think, frankly, that it is impossible to make a diagnosis. It would lie between an early giant-cell tumor and an inflammatory condition, such as Brodie's abscess. The only way to make a diagnosis definitely in this case would be to do a biopsy and let the treatment be governed by what was found. Whether or not it would be possible to do a suction aspiration biopsy, I do not know.

DR STANLEY M. WYMAN: From the radiologist's point of view, everything Dr. Simmons has said is entirely correct. My own feeling about it is that the chief thing to decide is whether the lesion is inflammatory or neoplastic, and if neoplastic, whether it is benign or malignant. In favor of infection are the soft-tissue swelling, the elongation of the bone, the periosteal reaction and the circumscription of the lesion without any perceptible or gross reaction about the lesion. I think I should place inflammation of low grade as my first bet.

DR BENJAMIN CASTLEMAN: Are there any other suggestions?

A PHYSICIAN: How often does a giant-cell tumor occur in this age group?

DR CASTLEMAN: According to Jaffe\* one does not see it before twenty.

DR LAURYNCE L. ROBBINS: Oh, yes you do, I have seen it in patients around fourteen.

DR CASTLEMAN: I do not believe I have seen one in a child of seven.

\*Jaffe H. L., Lichtenstein L. and Porus R. B. Giant cell tumor of bone: its pathologic appearance, grading, supposed variants and treatment. *Arch. Path.* 30:993-1031, 1940.

DR ROBBINS: We do not see them until the epiphysis is closed because they are usually in the epiphysis.

#### CLINICAL DIAGNOSIS

Bone sarcoma?  
Brodie's abscess?

#### DR SIMMONS'S DIAGNOSIS

Benign giant-cell tumor?  
Brodie's abscess?

#### ANATOMICAL DIAGNOSIS

*Brodie's abscess of tibia*

#### PATHOLOGICAL DISCUSSION

DR CASTLEMAN: At operation the surgeon exposed a trap door in the cortex and curetted some material that appeared grossly to be chronic inflammatory tissue. On microscopical examination we found an exudate of polymorphonuclears, lymphocytes, monocytes and plasma cells that would fit in with a Brodie's abscess. Culture showed *Staphylococcus albus*. The patient is doing well.

DR SIMMONS: What was the preoperative diagnosis in the ward?

DR CASTLEMAN: It varied. Everyone who examined her had a different diagnosis. On the anesthesia sheet the preoperative diagnosis was given as sarcoma of the lower tibia, but several members of the orthopedic staff said it was a Brodie's abscess. Neurofibroma was also suggested because the leg was longer on one side.

#### CASE 34382

##### PRESENTATION OF CASE

*First admission.* A forty-year-old woman was admitted to the hospital because of persistent phlebitis and ulcers on the lower legs. The phlebitis had commenced twenty-five years previously following an appendectomy, had recurred following childbirth eleven years later, and a bilateral high saphenous ligation was done after another five years. Seven years before entry, again following childbirth, there was an attack of phlebitis of the right arm. The legs were not involved. Since then there were recurring ulcers on the lower legs. One year before entry because of swelling around the hips, thrombosis of the pelvic vein was diagnosed.

The patient was well developed and well nourished. Examination of the heart, lungs and abdomen was negative. There was no edema of the legs although they appeared swollen and the skin was tense. There was no palpable arterial pulsation below the femoral veins. There were ulcers on the medial aspect of both legs, around and above the malleoli.

thrombin level at the time of the second admission was 27 seconds, with a normal of 22 seconds, and on the last admission it was still a little higher than normal, 18 seconds. It is a fairly well understood fact throughout the country that we do not often have thrombophlebitis or thrombosis of blood vessels occur in persons who have a higher than normal prothrombin time. In the original studies of Bancroft et al\* on postoperative thrombophlebitis, all the patients who developed this complication had a lower than normal prothrombin time in the series of patients studied by him and his co-workers. We have plenty of cases here of patients who have had infarcts following treatment by anticoagulants with a prothrombin level above normal, although it is not common and we do not expect it.

The character of this woman's pain is interesting, and the onset is described as being fairly sharp and fairly sudden, but it does not give the impression of the onset of mesenteric thrombosis. There are at least two types of thrombosis with which I am familiar: thrombosis of the mesenteric artery and thrombosis of the venous system, which produce very different pictures. When the mesenteric thrombosis involves the arterial system, the pain is more excruciating than it is in almost any other disease. These patients are precipitated into shock from this pain. They have a weak pulse, and are grav, restless and sweating, and most patients who develop that difficulty are in the arteriosclerotic age group, and they are in a pretty hopeless state usually when they enter the hospital. In this type of thrombosis of the mesenteric vessels one almost invariably finds a high white-cell count. That is one of the helpful differential diagnostic points. It is not at all uncommon to find a count well into the forty thousands. Also this condition is progressive, although one may rarely find a favorable situation and a satisfactory outcome following resection of the involved small intestine. The mortality in this disease is extremely high.

In venous thrombosis, however, the onset is a little more insidious and is apt not to give as high a white-cell count, but even in that situation the patient should not be completely afebrile and in as good condition as this patient apparently was. It is possible for a venous thrombosis of the mesentery to carry on over a period of days as this patient did prior to the time that operation seemed indi-

cated. I am inclined to think, having tried my best to pin this on some thrombotic mechanism of the vascular system within the abdomen, that perhaps it was not present in this case — that this woman had something else to account for her symptoms.

The commonest cause of epigastric distress, followed by nausea and vomiting, and pain settling in the right lower quadrant, is acute appendicitis. There are some features of the story that make one wonder if that was not really the cause of this disturbance. She had the proper white-cell count, the proper ratio of polymorphonuclear cells, and the only out about it, which might not be an out at all, is the apparent relief of pain on the third hospital day, with a recurrence twenty-four hours later. The fact that she was afebrile and had a normal pulse and so forth is somewhat in favor of some other very mild inflammatory affair or some mechanical effect. The reason I was interested in these shadows — you may not see them but they are present in the first films — is that I thought they could be in the course of the ureter. It is not too uncommon to have a Dietl's crisis mimic other situations in the abdomen. We recently had a patient sent into the hospital with what appeared to be full-blown acute intestinal obstruction. A plain film of the abdomen, instead of showing dilated gas-filled loops of bowel as suspected, showed a great many stones in the right kidney pelvis, with one or two down the course of the ureter. The urologist helped us out and passed the catheter up the patient's ureter and dislodged the stones and the symptoms of intestinal obstruction were immediately relieved. So it is possible that this woman under discussion could have had a ureteral stone.

Our attention is called to this spot in the ileum that looks atypical. We are carefully told in the history that this is not intestinal obstruction from the character of the peristaltic sounds heard through the stethoscope. I will be surprised if it turned out to be the site of this patient's difficulty, since I would not expect to find barium passing through the area so readily, also I believe the symptomatology would be different. It is obvious that the woman did not have intussusception. Intussusception of the small bowel is common enough, but it gives perfectly typical symptoms of small-bowel obstruction, which I am sure this woman did not have. Because an operation was performed — and I do not know whether anyone would consider cystoscopy an operation or not — I suppose that this

\*Bancroft, F. W., Kugelmass, I., and Stanley-Brown, M. Evaluation of blood clotting factors in surgical diseases. *Ann. Surg.* 90:161-189, 1929.

dilated loops of small bowel, although some loops contain air

DR ALLEN There is a small shadow to the right of the spinal column. Does that have any significance at all?

DR McCORT I do not know the significance of the small calcification in the right lower quadrant.

DR ALLEN Is it anywhere near the course of the ureter?

DR McCORT It seems a little bit lateral. I cannot rule out a ureteral calculus without a urogram, but it may be a calcification in a mesenteric lymph node.

The films of the gastrointestinal tract were taken at the time the barium was ingested, and no abnormality is demonstrated in the stomach or duodenum. This film was taken six hours after the barium was administered, and the stomach is completely empty. The greater portion of the barium is present in the lower small bowel and ascending colon. A narrowed area, several centimeters in length, is present in the terminal ileum. This might bear further investigation to determine whether it is a tumor or inflammatory stricture.

DR ALLEN Is that in the ileum?

DR McCORT Yes.

DR ALLEN This patient is interesting from many points of view, and since I have no clear-cut idea as to what brought her in here the last time, I think I am justified in reviewing some of the points of the past history. In the first place it appears that this woman developed her original thrombophlebitis at the age of fifteen. This is unusual because although we do see this complication following injuries to the lower extremities in young people, such as burns and fractures, it is rare to have it occur as a complication of an appendectomy or any such operation as that. Without a doubt she had a rather fulminating attack of bilateral femoral phlebitis at that time. It is common to have in these patients a recurrence of their thrombophlebitis following childbirth or operation, and she proceeded to behave in this characteristic fashion. The story brings out a good many of the methods of examination and treatment of chronic thrombophlebitis that we used in previous years but now are not using at all. For instance, before this woman had an interruption of the femoral vein, she had phlebograms made of the venous system. That was thought to be quite important at one time in this hospital. It is rarely, if ever, thought necessary now.

DR BENJAMIN CASTLEMAN It was done in 1943.

DR ALLEN Another point is that she had an operation devised by Dr Linton several years ago of interruption of the communicating veins between the superficial and deep systems. This was preceded by a lumbar sympathectomy, probably done because she was said to have some difficulty with her arterial circulation as well, since it is recorded that no pulsations in the arteries were felt below the femoral veins. This operation of interruption of communicating veins between the superficial and deep systems has been fairly well abandoned now for a better procedure, which consists of stripping out the superficial system, the long saphenous and short saphenous veins if necessary, and interruption of the superficial femoral vein just below the profunda. These procedures are more apt to succeed in preventing recurrent illnesses from the lymphedema and ulceration that is so common as an aftermath of deep thrombophlebitis.

There is nothing much to say about some of these previous admissions other than what I have brought out, except that I should emphasize that we have done in this hospital very few interruptions of the vena cava. We have felt that many of the patients that might be subjected to this form of treatment actually do better with a procedure of less magnitude, that is, bilateral interruption of the femoral veins with removal of the thrombi, if present, and treatment with anticoagulants afterward. I think somewhere in the neighborhood of fifteen vena cava interruptions only have been done here during the time when we have had approximately 3000 patients under treatment, either prophylactically or therapeutically, for thrombophlebitis and pulmonary embolism. Interruption of the vena cava should be reserved, we believe, for those patients who are having septic infarcts arising from the pelvic veins. It is wise to interrupt also the ovarian or spermatic vein, as the case may be, provided these veins are also thrombosed. Although vena-cava interruption is a safe operation so far as life and death are concerned, it leaves these patients, as a rule, more handicapped than some of the less radical procedures that we have used.

Coming down to the final admission, the fifth admission, which is the present illness, it would be a natural supposition that the abdominal discomfort that this patient had might in some way be associated with her great tendency to thrombose her blood vessels. It is interesting that the pro-

thrombin level at the time of the second admission was 27 seconds, with a normal of 22 seconds, and on the last admission it was still a little higher than normal, 18 seconds. It is a fairly well understood fact throughout the country that we do not often have thrombophlebitis or thrombosis of blood vessels occur in persons who have a higher than normal prothrombin time. In the original studies of Bancroft et al\* on postoperative thrombophlebitis, all the patients who developed this complication had a lower than normal prothrombin time in the series of patients studied by him and his co-workers. We have plenty of cases here of patients who have had infarcts following treatment by anticoagulants with a prothrombin level above normal, although it is not common and we do not expect it.

The character of this woman's pain is interesting, and the onset is described as being fairly sharp and fairly sudden, but it does not give the impression of the onset of mesenteric thrombosis. There are at least two types of thrombosis with which I am familiar: thrombosis of the mesenteric artery and thrombosis of the venous system, which produce very different pictures. When the mesenteric thrombosis involves the arterial system, the pain is more excruciating than it is in almost any other disease. These patients are precipitated into shock from this pain. They have a weak pulse, and are gray, restless and sweating, and most patients who develop that difficulty are in the arteriosclerotic age group, and they are in a pretty hopeless state usually when they enter the hospital. In this type of thrombosis of the mesenteric vessels one almost invariably finds a high white-cell count. That is one of the helpful differential diagnostic points. It is not at all uncommon to find a count well into the forty thousands. Also this condition is progressive, although one may rarely find a favorable situation and a satisfactory outcome following resection of the involved small intestine. The mortality in this disease is extremely high.

In venous thrombosis, however, the onset is a little more insidious and is apt not to give as high a white-cell count, but even in that situation the patient should not be completely afebrile and in as good condition as this patient apparently was. It is possible for a venous thrombosis of the mesentery to carry on over a period of days as this patient did prior to the time that operation seemed indi-

cated. I am inclined to think, having tried my best to pin this on some thrombotic mechanism of the vascular system within the abdomen, that perhaps it was not present in this case — that this woman had something else to account for her symptoms.

The commonest cause of epigastric distress, followed by nausea and vomiting, and pain settling in the right lower quadrant, is acute appendicitis. There are some features of the story that make one wonder if that was not really the cause of this disturbance. She had the proper white-cell count, the proper ratio of polymorphonuclear cells, and the only out about it, which might not be an out at all, is the apparent relief of pain on the third hospital day, with a recurrence twenty-four hours later. The fact that she was afebrile and had a normal pulse and so forth is somewhat in favor of some other very mild inflammatory affair or some mechanical effect. The reason I was interested in these shadows — you may not see them but they are present in the first films — is that I thought they could be in the course of the ureter. It is not too uncommon to have a Dietl's crisis mimic other situations in the abdomen. We recently had a patient sent into the hospital with what appeared to be full-blown acute intestinal obstruction. A plain film of the abdomen, instead of showing dilated gas-filled loops of bowel as suspected, showed a great many stones in the right kidney pelvis, with one or two down the course of the ureter. The urologist helped us out and passed the catheter up the patient's ureter and dislodged the stones and the symptoms of intestinal obstruction were immediately relieved. So it is possible that this woman under discussion could have had a ureteral stone.

Our attention is called to this spot in the ileum that looks atypical. We are carefully told in the history that this is not intestinal obstruction from the character of the peristaltic sounds heard through the stethoscope. I will be surprised if it turned out to be the site of this patient's difficulty, since I would not expect to find barium passing through the area so readily, also I believe the symptomatology would be different. It is obvious that the woman did not have intussusception. Intussusception of the small bowel is common enough, but it gives perfectly typical symptoms of small-bowel obstruction, which I am sure this woman did not have. Because an operation was performed — and I do not know whether anyone would consider cystoscopy an operation or not — I suppose that this

\*Bancroft, F. W., Kugelmass, L. V. and Stanley-Brown, M. Evaluation of blood clotting factors in surgical diseases. *Ann. Surg.* 90:161-189, 1929.

dilated loops of small bowel, although some loops contain air

DR ALLEN There is a small shadow to the right of the spinal column Does that have any significance at all?

DR McCORT I do not know the significance of the small calcification in the right lower quadrant

DR ALLEN Is it anywhere near the course of the ureter?

DR McCORT It seems a little bit lateral I cannot rule out a ureteral calculus without a urogram, but it may be a calcification in a mesenteric lymph node

The films of the gastrointestinal tract were taken at the time the barium was ingested, and no abnormality is demonstrated in the stomach or duodenum This film was taken six hours after the barium was administered, and the stomach is completely empty The greater portion of the barium is present in the lower small bowel and ascending colon A narrowed area, several centimeters in length, is present in the terminal ileum This might bear further investigation to determine whether it is a tumor or inflammatory stricture

DR ALLEN Is that in the ileum?

DR McCORT Yes

DR ALLEN This patient is interesting from many points of view, and since I have no clear-cut idea as to what brought her in here the last time, I think I am justified in reviewing some of the points of the past history In the first place it appears that this woman developed her original thrombophlebitis at the age of fifteen This is unusual because although we do see this complication following injuries to the lower extremities in young people, such as burns and fractures, it is rare to have it occur as a complication of an appendectomy or any such operation as that Without a doubt she had a rather fulminating attack of bilateral femoral phlebitis at that time It is common to have in these patients a recurrence of their thrombophlebitis following childbirth or operation, and she proceeded to behave in this characteristic fashion The story brings out a good many of the methods of examination and treatment of chronic thrombophlebitis that we used in previous years but now are not using at all For instance, before this woman had an interruption of the femoral vein, she had phlebograms made of the venous system That was thought to be quite important at one time in this hospital It is rarely, if ever, thought necessary now

DR BENJAMIN CASTLEMAN It was done in 1943

DR ALLEN Another point is that she had an operation devised by Dr Linton several years ago of interruption of the communicating veins between the superficial and deep systems This was preceded by a lumbar sympathectomy, probably done because she was said to have some difficulty with her arterial circulation as well, since it is recorded that no pulsations in the arteries were felt below the femoral veins This operation of interruption of communicating veins between the superficial and deep systems has been fairly well abandoned now for a better procedure, which consists of stripping out the superficial system, the long saphenous and short saphenous veins if necessary, and interruption of the superficial femoral vein just below the profunda These procedures are more apt to succeed in preventing recurrent illnesses from the lymphedema and ulceration that is so common as an aftermath of deep thrombophlebitis

There is nothing much to say about some of these previous admissions other than what I have brought out, except that I should emphasize that we have done in this hospital very few interruptions of the vena cava We have felt that many of the patients that might be subjected to this form of treatment actually do better with a procedure of less magnitude, that is, bilateral interruption of the femoral veins with removal of the thrombi, if present, and treatment with anticoagulants afterward I think somewhere in the neighborhood of fifteen vena cava interruptions only have been done here during the time when we have had approximately 3000 patients under treatment, either prophylactically or therapeutically, for thrombophlebitis and pulmonary embolism Interruption of the vena cava should be reserved, we believe, for those patients who are having septic infarcts arising from the pelvic veins It is wise to interrupt also the ovarian or spermatic vein, as the case may be, provided these veins are also thrombosed Although vena-cava interruption is a safe operation so far as life and death are concerned, it leaves these patients, as a rule, more handicapped than some of the less radical procedures that we have used

Coming down to the final admission, the fifth admission, which is the present illness, it would be a natural supposition that the abdominal discomfort that this patient had might in some way be associated with her great tendency to thrombose her blood vessels It is interesting that the pro-

# The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established 1828

Official Organ of

THE MASSACHUSETTS MEDICAL SOCIETY

and

THE NEW HAMPSHIRE MEDICAL SOCIETY

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND

PUBLISHED WEEKLY UNDER THE JURISDICTION OF THE

COMMITTEE ON PUBLICATIONS

Richard M Smith M.D. *Chairman*

James P O'Hare, M.D. Conrad Wesselhoeft M.D.

Oliver Cope M.D. John Fallon M.D.

Joseph Garland M.D. *EDITOR*

ASSOCIATE EDITORS

Thomas H. Lanman M.D. Donald Munro M.D.

Henry Jackson Jr M.D.

Clara D Davies *EXECUTIVE EDITOR*Robert O Leary *ASSISTANT EDITOR*

EDITORIAL BOARD

C. Guy Larc, M.D.

Henry R. Viets M.D.

Robert M. Green M.D.

Dwight O'Hara M.D.

Fletcher H. Colby M.D.

Robert L. Goodale M.D.

Clement L. Jones M.D.

Harvey R. Morrison M.D.

Maxwell Finland M.D.

James M. Faulkner M.D.

Carroll B. Larson M.D.

Francis D. Moore M.D.

C. Stuart Welch M.D.

Vernon P. Williams M.D.

Benjamin Castleman M.D.

Hugh R. Leavell M.D.

**SUBSCRIPTION TERMS:** \$7.00 per year in advance, postage paid, for the United States (medical students \$4.00 per year). Canada, \$8.00 per year (Boston funds) \$9.50 per year for all foreign countries belonging to the Postal Union.

MATERIAL should be received not later than noon on Thursday three weeks before date of publication.

THE JOURNAL does not hold itself responsible for statements made by any contributor.

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts. Telephone KE 6-2074.

NEW ENGLAND ADVERTISING REPRESENTATIVE: Edwin B. Tyler, 89 State Street, Boston, Massachusetts. Telephone LA 3-5516.

## PHYSICIAN OF AYSGARTH

THE general practitioner, having suffered somewhat of an eclipse in the Age of Specialism, is returning to the favor that he merits. He has had special sections devoted to his calling in important medical associations, and an academy has been founded to which he may aspire. He has been the recipient of spontaneous tributes such as was accorded him by Miss Mary Ellen Chase in her address published in the *Journal* a month ago. Perhaps his next danger will be the risk of turning into that paradoxical paragon, the general specialist!

Miss Chase's tribute, however, was to a breed of physician somewhat more and somewhat less than the general practitioner. It was to the physicians who represent the essence of general practice—those rugged individualists, the country doctors

Of such basic fiber is Dr William N. Pickles, of Aysgarth, Yorkshire, whose Cutter Lecture on Preventive Medicine appears in this issue of the *Journal*. Dr Pickles also, in his life and his accomplishments, illustrates not so much the difference between the general practitioner and the specialist, as he does the advantages to be found in country practice over the limitations imposed by practice in the city.

This comparison is not a new one, and the idea is one to which many medical men take kindly, here as abroad. Physicians everywhere have been imbued with reverence for Withering and the Shropshire foxglove bells, and for Edward Jenner, who recorded the temperature of hibernating hedgehogs for John Hunter while mentally incubating his own great contribution to medicine. They remember with respect Crawford W. Long, of Georgia, and Ephraim McDowell, the backwoods ovariologist, and a host of other country doctors whose services have been equally faithful if less eventful.

Dr Pickles is a present example of one who has taken advantage of the peculiar opportunities afforded him as a country doctor to gather knowledge and to acquire wisdom and, by virtue of his intimate acquaintance with his people, to observe the character of disease and trace its spread through a familiarly known population.

Perhaps the secret of his success is best expressed by his own thoughts as he looked down upon his Yorkshire valley from an adjacent hilltop one summer evening:

Our attractive little lake seemed to lie at my feet, and one by one I made out most of our gray villages with their pall of smoke. And as I watched the evening train creeping up the valley, with its pauses at our three stations, I had this strange thought, that there was hardly a man, woman or child in all those villages of whom I did not know even the Christian name and with whom I was not on terms of friendship.

A graduate of London University in 1910 and a member of the Royal College of Physicians of London, Dr Pickles is a country practitioner and medical officer of health for the Aysgarth Rural District. He is the author of *Epidemiology in Country Practice*, published in 1939 and occupies the unique position for a rural health officer of being called

woman had a laparotomy, and my opinion is that acute appendicitis was probably the reason for the exploration

DR ALFRED KRANES Would the fact that the appendix was supposed to have been removed many years previously alter your opinion on that?

DR ALLEN Is it in the history? I read it and completely forgot it during my discussion of her interesting story

DR KRANES The appendix may still be there

DR ALLEN But probably not

DR CASTLEMAN Why not make another choice?

DR ALLEN I will come back to ureteral colic as a second choice

DR CASTLEMAN Dr Hardy, will you tell us what Dr Linton thought about this case?

DR IRAD B HARDY To bring you up to date briefly about the previous operation, it is of interest that following vena-cava ligation she did, as Dr Allen mentioned, have some disability in that prior to operation she had been quite a golfer and since the ligation she has never been able to make eighteen holes without fatigue Also of interest, since interruption of the femoral veins, the legs have been well That point did not seem clear in the record She had no further ulcerations for some time, and it does not appear that she will On admission to the hospital the idea was certainly in the back of Dr Linton's mind that the process in the abdomen might be another manifestation of venous thrombosis since she had shown such a tendency to it At about the time the gastrointestinal series was reported negative, it was realized that an intravenous pyelogram should precede everything and while planning that procedure, she began to get sicker and complained more of abdominal pain Finally on the fifth or sixth hospital day it appeared necessary to explore her as an emergency without the benefit of getting her more adequately prepared in the way of antibiotics or a Miller-Abbott tube However, a Levine tube was passed, and the patient was explored in the middle of the night

#### CLINICAL DIAGNOSIS

Mesenteric venous thrombosis?

DR ALLEN'S DIAGNOSIS

Ureteral stone

ANATOMICAL DIAGNOSIS

*Mesenteric venous thrombosis*

#### PATHOLOGICAL DISCUSSION

DR HARDY A loop of terminal ileum about a foot in length was found to be involved with venous mesenteric thrombosis, and the mesentery was involved over a great extent In doing the resection to remove all the obviously involved mesentery, it became questionable whether the blood supply to the right colon had not become jeopardized, so that resection of the terminal ileum plus a right colectomy and an ileotransverse colostomy were performed The patient did well for a few days after operation and then went into a peculiar state of peripheral vascular insufficiency with low blood pressure and cold and clammy upper extremities The legs remained dry and fairly warm The cause of the condition was uncertain There was no evidence of intraperitoneal irritation The heparin and penicillin she had been getting were omitted, and strangely enough her chart rapidly improved and she got out of the state of peripheral shock The temperature, which had risen to 104°F, and the pulse came down Since then she has rapidly improved and is doing very well now We are considering the possibility of trying heparin-sensitivity tests on her but not too soon The clotting time is being maintained at what we think is a satisfactory level We were interested to know whether it was possible for heparin, which she was getting, to play a part in the postoperative picture At the present time large maintenance doses of dicumarol are keeping the prothrombin time at a satisfactory level

DR CASTLEMAN The specimen received showed an adherent thrombus in the ileocolic vein and most of its tributaries There was infarction of all the terminal ileum, but microscopically the ascending colon was viable The ordinary example of mesenteric venous thrombosis involves the larger veins, such as the superior mesenteric The absence of involvement here of the larger veins might account for the minimal symptoms that she had before the final episode preoperatively I believe this is the first case I have seen in which there was spontaneous thrombosis of a vein smaller than the superior or inferior mesenteric I reviewed the sections of the femoral veins removed a couple of years ago, and they showed intimal sclerosis, there was also a little intimal sclerosis in the ileocolic vein I am still at a loss to explain this unusual condition

sion After the war he studied medicine, taking his degree at the University of Toronto. He served an internship in England, practiced general medicine in Canada and studied human relations at Yale, returning then to England to study psychiatry.

During the second World War he was appointed director-general of the Medical Services of the Canadian Army and helped to develop the Pulhems system for determining aptitudes. In November, 1944, he became Canada's first deputy minister of health in the newly organized Department of National Health and Welfare. Two years later he resigned this post to become executive secretary of the Interim Commission of the World Health Organization.

In 1945 Dr. Chisholm was cited in connection with the Albert A. and Mary Lasker Award for "safeguarding the mental health of Canadian soldiers as a psychiatrist, soldier, philosopher, and administrator."

Dr. Chisholm is to be congratulated on his election, our friends and neighbors across the border are to be congratulated on the selection of a native son for this eminent position.

---

## POSTGRADUATE MEDICAL EDUCATION IN CONNECTICUT

EXPANSION of facilities for postgraduate medical education in Connecticut was recently announced by President Seymour of Yale University. In co-operation with the Connecticut State Medical Society, the University is inaugurating a program to provide for short and long refresher courses for Connecticut physicians and to assist small hospitals in training resident physicians who are preparing for various medical specialties. Dr. William R. Willard, associate professor of public health, has been named assistant dean in charge of postgraduate medical education.

The expanded program is an extension of already successful co-operation between the University and the State Society that has made possible year-round operation of an institute of occupational medicine and hygiene, a joint endeavor with various state mental hospitals on the part of the Univer-

sity and the Clinical Congress of the Society, held at Yale each fall, which attracts from 600 to 800 physicians to its sessions. Like the Postgraduate Lecture Course of the Massachusetts Medical Society, the Connecticut program offers physicians an opportunity to keep abreast of the latest advances in therapy and public health. Members of the medical profession in Connecticut and elsewhere will watch the development of the program with great interest.

---

## MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

### CHANGE IN RATE FOR CRIPPLED-CHILDREN CARE

On or after October 1, the all-inclusive per diem rate paid by the Department of Public Health to hospitals for care of crippled children will be increased to \$10.00. Until recently, when the Department of Public Health and the Department of Education were successful in increasing the amount, the rate paid had been \$8.00.

In the past year in an attempt to set a standard rate for payments based upon actual cost to hospitals for services given, a study was made by the Department of Public Health in conjunction with the Departments of Welfare, Mental Health, Correction and Education and with the Industrial Accident Board. A plan, satisfactory to the hospitals rendering the services and to the Commonwealth as a purchasing agent, was drawn up by an unpaid commission composed of the heads of the departments previously mentioned with the co-operation of the Veterans Administration. The plan was incorporated in Senate Bill 430 (1948), and was presented before the recent legislature. However, this bill was not passed.

The defeat of the bill left the Department of Public Health in the position of paying for hospital services of certain programs at a rate not only below posted hospital charges but also below actual costs to the hospitals. In the care of crippled children and rheumatic-fever patients the department has been limited in reimbursements to all-inclusive per diem rates of \$8.00. Reports from some hospitals of Greater Boston have shown that all-inclusive per diem cost for these patients approximates \$16.00. The result is that certain hospitals are subsidizing crippled-children programs to the extent of \$8.00 a day for each case.

The Department of Public Health hopes that this increase in rate will to some extent lighten the financial burden carried by the hospitals.

repeatedly in consultation by the principal health authorities in England and Scotland

In 1935 he lectured on "Epidemiology in Country Practice" before the Royal Society of Medicine, he gave the Milroy Lecture before the Royal College of Physicians in 1942 and the Finlayson Lecture of the University of Glasgow in 1946. He studied the incubation period of epidemic hepatitis years before epidemic hepatitis acquired its current importance, and was the first to recognize the presence of Bornholm disease in Great Britain, and to describe its clinical and epidemiologic behavior.

He has developed to a high degree the pastoral qualities of the physician, at the same time making so fruitful a study of rural epidemiology that his influence has spread over the United Kingdom. What more can be said of anyone than that he tilled well the soil whereon he was placed?

## BLUE SHIELD AND THE PREMATURE INFANT

ELSEWHERE in this issue of the *Journal* a Blue Shield release appears concerning the definition of obstetric services as they apply to the "routine" care of the premature infant. The point around which discussions may revolve is the statement that "during confinement of the mother, Blue Shield does not cover routine care rendered by other than the physician who accomplished the delivery." This statement implies that care of the premature infant may be a part of the routine care of the confinement and is not chargeable to Blue Shield as a legitimate added expense.

Criticism of the assumption that the care of a premature infant may in any case be routine has been the result, notably on the part of the *Norfolk Medical News*, which raises the question, in its issue of June 8, 1948, whether the care of the premature baby should ever be classified as other than a medical emergency. This classification was apparently so intended by the Massachusetts Department of Public Health when it sponsored Section 67A of Chapter 111 of the General Laws, providing for the reporting of the birth of a premature infant elsewhere than in a hospital and the transportation of such an infant to a hospital suitably equipped for its care.

The matter requires further clarification in order that the financial responsibility of Blue Shield may be fixed and criticism reduced to a minimum. Obviously an acceptable definition of prematurity should first be established, and weight is the simplest factor on which to base this classification. Five and a half pounds, or 2500 gm, has been used as such a standard, the incidence of births at this weight or less being from 5 to 6 per cent of the total. If 5 pounds is accepted as the standard the incidence is nearer 4 per cent. The group weighing from 5 to 5½ pounds and the group weighing less than 5 pounds at birth are approximately equal, with a very low mortality rate for the former. On this basis Massachusetts law defines prematurity as of 5 pounds or less and in New York, although 5½ pounds is accepted as the standard for prematurity, special care in premature centers is not offered unless the baby at birth weighs 4 pounds or less. The sound suggestion has been made that for Blue Shield purposes a birth weight of 4½ pounds or less be accepted as the criterion for prematurity.

Individual infants will vary greatly as to the amount of care required to start them safely on their way, but it should be accepted that the majority of premature infants as defined above will require special oversight and that only a very small minority, if any, should be considered as suitable candidates for the routine attention accorded the newborn. For practical purposes such care may be considered as part of the routine of an obstetric case only if it can be given safely by the physician who made the delivery, at the hospital where the delivery took place and then only during the period of confinement of the mother.

## DIRECTOR-GENERAL OF WORLD HEALTH ORGANIZATION

DR BROCK CHISHOLM, a Canadian, has been elected the first director-general of the World Health Organization, the *News Letter* of the Organization reports. Dr Chisholm, born in Oakville, Canada, in 1897, entered the Canadian Army during World War I as a private, later receiving a commis-

## NOTICES (Concluded from page 452)

NOVEMBER 4-6 American Society of Anesthesiologists Page 418  
 issue of September 9  
 NOVEMBER 8-12 American Public Health Association Page 420 issue  
 of March 18  
 NOVEMBER 10-13 Association of Military Surgeons of the United  
 States Page 722 issue of May 13  
 NOVEMBER 20-23 American Academy of Pediatrics Annual Meeting  
 Chalfonte-Haddon Hall Hotel Atlantic City New Jersey  
 DECEMBER 7-9 Southern Surgical Association Annual Meeting  
 Page 543 issue of April 8  
 DECEMBER 9 and 10 New York State Society of Anesthesiologists  
 Page 54 issue of July 1  
 FEBRUARY 4 1949 American Board of Obstetrics and Gynecology Inc  
 Page 244 issue of August 5  
 MARCH 28-APRIL 1 1949 American College of Physicians Page 158  
 issue of July 22  
 MAY 16-19 1949 American Urological Association Biltmore Hotel  
 Los Angeles  
 NOVEMBER 11-17 1949 Third Inter-American Congress of Radiology  
 Page 158 issue of July 22

## DISTRICT MEDICAL SOCIETIES

## NORFOLK

SEPTEMBER 28 Specialty Night

## SUFFOLK

OCTOBER 9 Fall Dinner

## Firm, Natural Support Need Never Be Sacrificed for ANY Fashion

A functional garment, properly fitted, will mold  
a figure to the fashion's new requirements with-  
out causing displacement of organs

### EVYLYN L. WEIGEL

25 HUNTINGTON AVE MASSACHUSETTS AVE., ROUTE 111  
 BOSTON 16, MASS WEST ACTON, MASS  
 KENMORE 6-2718 ACTON 504-3

## Washingtonian Hospital

41-43 WALTHAM STREET, BOSTON, MASS

Incorporated 1859

Conditioned Reflex, Psychotherapy, Semi-Hospitalization  
For Rehabilitation of Male Alcoholics

Treatment of Acute Intoxication and Alcoholic Psychoses  
Included

Outpatient Clinic and Social-Service Department for  
Male and Female Patients

JOSEPH THIMANN, M D, Medical Director

Visiting Psychiatric and Neurologic Staff  
Consultants in Medicine Surgery and the Other Specialties  
Telephone HA 6-1750

## Valleyhead Hospital

CONCORD, MASSACHUSETTS

For the treatment of psychoneuroses, alcoholism mild  
mental disorders and chronic diseases Pleasant pastoral  
setting near historic Concord Accepted modern therapies  
used Complete occupational and recreational facilities  
available including outdoor swimming pool and tennis  
court

S GAGNON, M D  
Superintendent

J BUTLER TOMPEINS M D  
Director of Clinical Psychiatry

J P THORNTON, M D  
Consultant in Neuro-  
psychiatry

IRVING KAUFMAN, M D  
Psychiatrist

Post Office Box 151 Concord Mass Tel Concord 1600

## Tablets Ferglate-B with C

High in vitamin B complex content to quicken hemo-  
globin response to iron therapy

## EACH TABLET CONTAINS

Ferrons Gluconate (5 grains)	0.375 gm	Pyridoxine HCl	0.15 mg
Thiamin HCl	3 mg	Calcium Pantothenate	0.5 mg
Riboflavin	2 mg	Ascorbic Acid	30 mg
Nicotinamide	20 mg	Yeast-Liver Base	q.s.

## INDICATIONS

Iron deficiency and nutritional anemias as a source of iron and  
B complex factors

Write Department N12 for Professional  
Sample and Literature

### KENMORE PHARMACAL CO.

500 COMMONWEALTH AVENUE  
BOSTON 15 MASS

## THE CHANNING HOME

For the MEDICAL and SURGICAL treatment of  
Pulmonary Tuberculosis in Women

Established 1857

198 PILGRIM ROAD BOSTON 15 MASS

Our endowment permits variations in charges for patients  
board There are no physicians fees  
Those patients suitable for treatment with STREPTO-  
MYCIN will receive the drug without cost, out of funds  
supplied by the Research Grants Division of United States  
Public Health Service.

Good nursing care and food are emphasized

Address all applications to  
ELIZABETH H PELTON, Superintendent

**Zemmer**  
PHARMACEUTICALS

A complete line of laboratory  
controlled ethical pharmaceuticals

Chemists to the Medical Profession for 44 years  
NE 9-48

**The Zemmer Company**

Oakland Station • PITTSBURGH 13 PA

## BLUE CROSS - BLUE SHIELD

### OBSTETRIC COVERAGE

The Blue Shield subscriber certificate defines obstetric services in part as "routine care of a full term or premature newborn, including circumcision when undertaken during confinement of the mother and when provided by the physician who accomplished the delivery." In another section, routine care, including circumcision, of a full-term or premature newborn infant is excluded when undertaken during the confinement of the mother by any physician other than the one who accomplished its delivery. As applied to premature infants these provisions mean that

During confinement of the mother, Blue Shield does not cover routine care rendered by other than the physician who accomplished the delivery.

After confinement of the mother, Blue Shield covers routine care rendered by any participating physician.

During and after confinement of the mother, Blue Shield covers other than routine care rendered by any participating physician.

Experience with these provisions has demonstrated that the question of whether there is such a thing as routine care of a premature infant is essentially academic because, even with the exclusion of coverage during confinement of the mother, most premature infants remain in the hospital in excess of the maximum number of benefit days provided by Blue Shield.

### MISCELLANY

#### NEW FOUNDATION

The Arthritis and Rheumatism Foundation has been organized to promote a united nation-wide attack on arthritis and other rheumatic diseases according to a release from W. Paul Holbrook, M.D., Tucson, Arizona, its president. The new Foundation is sponsored by the American Rheumatism Association in co-operation with the National Arthritis Research Foundation, The Detroit Fund for Crippling Diseases, and others.

"The organization," the release continues, "has been created to unite the efforts of lay and medical leaders in developing a new voluntary health agency, comparable in the field of rheumatism, to such agencies as the National Tuberculosis Association, The National Foundation for Infantile Paralysis and the American Cancer Society."

Its main objectives include the making of a nation-wide survey of what can and should be done to combat the problem of arthritis, arousing the public and the medical profession to the need for action in this field, and the financing of a program designed to accomplish those ends.

### NOTICES

#### NORFOLK DISTRICT MEDICAL SOCIETY

The scientific meeting of the Norfolk District Medical Society will be held at 8 p.m. on Tuesday, September 28, at the Boston Medical Library, 8 Fenway, Boston, entitled "Specialty Night."

#### PROGRAM

The Relief of Common Eye Disorders Seen in General Practice Dr. Edwin B. Dunphy  
The Relief of Common Ear, Nose and Throat Disorders Seen in General Practice Dr. Leighton F. Johnson  
Dermatology in Relation to General Practice Dr. Chester N. Frazier

#### SOUTH BOSTON MEDICAL SOCIETY

The next meeting of the South Boston Medical Society will be held on Monday, October 4, at 9 p.m., in the auditorium of the Carney Hospital. The speaker will be Dr. Frank H. Lahey.

#### SUFFOLK DISTRICT MEDICAL SOCIETY

The fall dinner of Suffolk District Medical Society will be given at the Harvard Club of Boston on Saturday, October 9, at 7 p.m. The Honorable Christian A. Herter, United States Congress, will speak on "The Effect of Foreign Policy on Domestic Questions."

Members of the Massachusetts Medical Society, wives and friends are cordially invited.

#### UROLOGY AWARD

The American Urological Association offers an annual award of \$1000 (first prize of \$500, second prize \$300 and third prize \$200) for essays on the result of some clinical or laboratory research in urology. Competition is limited to urologists who have been in such specific practice for not more than five years and to residents in urology in recognized hospitals. All interested should write to the secretary, Dr. Thomas D. Moore, 899 Madison Avenue, Memphis, Tennessee. Essays must be in his hands before February 15, 1949. The first-prize essay will appear on the program of the forthcoming meeting of the American Urological Association to be held at the Biltmore Hotel, Los Angeles, May 16 to 19.

#### SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, SEPTEMBER 23

FRIDAY, SEPTEMBER 24

\*9:00 a.m.-12:00 p.m. Combined Medical and Surgical Staff Roundtable.  
Peter Bent Brigham Hospital.

TUESDAY, SEPTEMBER 28

\*12:15-1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.  
\*1:30-2:30 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.  
8:00 p.m. Norfolk District Medical Society. Boston Medical Library.

WEDNESDAY, SEPTEMBER 29

\*12:00 p.m.-1:00 p.m. Clinical Conference. (Children's Hospital).  
Amphitheater. Peter Bent Brigham Hospital.

\*Open to the medical profession.

SEPTEMBER 18 College of American Pathologists Page 418 issue of September 9  
SEPTEMBER 20-23 American Hospital Association Page 310 issue of February 26.  
SEPTEMBER 22 New England Conference of Industrial Physicians and Surgeons Page 244 issue of August 5  
SEPTEMBER 28 Norfolk District Medical Society Notice above.  
SEPTEMBER 29 Mississippi Valley Medical Editors' Association Page 170 issue of January 29  
OCTOBER 1 and 2 American Society of Anesthesiologists, Inc. Page 352 issue of September 2  
OCTOBER 1-MAY 20 Metropolitan State Hospital Page 418 issue of September 9  
OCTOBER 4 South Boston Medical Society Notice above  
OCTOBER 6-9 American Board of Ophthalmology Page 170 issue of January 29  
OCTOBER 9 Suffolk District Medical Society Notice above.  
OCTOBER 14 The Practical and Clinical Sides of the Management of the Rh Problem in Pregnancy Dr. William C. Moloney. Penetucket Association of Physicians 8:30 p.m. Haverhill  
OCTOBER 15 American Trudeau Society Page 418 issue of September 9  
OCTOBER 18-22 American College of Surgeons Page 417 issue of September 9  
OCTOBER 27 New England Obstetrical and Gynecological Society Annual Meeting Hotel Somerset Boston  
NOVEMBER 1-3 American Clinical and Climatological Association Page 582 issue of April 15  
NOVEMBER 3 and 4 Annual Meeting of National Committee for Mental Hygiene Inc. Page 282 issue of August 12.

(Notices concluded on page xvii)

# NOTICES (Concluded from page 452)

NOVEMBER 4-6 American Society of Anesthesiologists Page 418  
 issue of September 9  
 NOVEMBER 8-12 American Public Health Association Page 420 issue  
 of March 18  
 NOVEMBER 10-15 Association of Military Surgeons of the United  
 States Page 722 issue of May 15  
 NOVEMBER 20-23 American Academy of Pediatrics Annual Meeting  
 Chalfonte Haddon Hall Hotel Atlantic City New Jersey  
 DECEMBER 7-9 Southern Surgical Association Annual Meeting  
 Page 543 issue of April 8  
 DECEMBER 9 and 10 New York State Society of Anesthesiologists  
 Page 34 issue of July 1  
 FEBRUARY 4 1949 American Board of Obstetrics and Gynecology Inc  
 Page 244 issue of August 5  
 MARCH 28-APRIL 1 1949 American College of Physicians Page 158  
 issue of July 22  
 MAY 16-19 1949 American Urological Association Biltmore Hotel  
 Los Angeles  
 NOVEMBER 11-17 1949 Third Inter American Congress of Radiology  
 Page 158 issue of July 22

## DISTRICT MEDICAL SOCIETIES

### NORFOLK

SEPTEMBER 28 Specialty Night

### SUFFOLK

OCTOBER 9 Fall Dinner

## Firm, Natural Support Need Never Be Sacrificed for ANY Fashion

A functional garment, properly fitted, will mold  
 a figure to the fashion's new requirements with-  
 out causing displacement of organs

### EVYLYN L. WEIGEL

25 HUNTINGTON AVE MASSACHUSETTS AVE, ROUTE 111  
 BOSTON 16, MASS WEST ACTON, MASS  
 KENMORE 6-2718 ACTON 504-3

## Washingtonian Hospital

41-43 WALTHAM STREET, BOSTON, MASS

Incorporated 1859

Conditioned Reflex, Psychotherapy, Semi-Hospitalization  
 For Rehabilitation of Male Alcoholics

Treatment of Acute Intoxication and Alcoholic Psychoses  
 Included

Outpatient Clinic and Social-Service Department for  
 Male and Female Patients

JOSEPH THIMANN, M D, Medical Director

Visiting Psychiatric and Neurologic Staff  
 Consultants in Medicine Surgery and the Other Specialties  
 Telephone HIA 6-1750

## Valleyhead Hospital

CONCORD, MASSACHUSETTS

For the treatment of psychoneuroses, alcoholism mild  
 mental disorders and chronic diseases Pleasant pastoral  
 setting near historic Concord Accepted modern therapies  
 used Complete occupational and recreational facilities  
 available including outdoor swimming pool and tennis  
 court

S GAGNON, M D  
 Superintendent

J BUTLER TOMPKINS, M D  
 Director of Clinical Psychiatry

J P THORNTON, M D  
 Consultant in Neuro-  
 psychiatry

IRVING KAUFMAN, M D  
 Psychiatrist

Post Office Box 151, Concord, Mass Tel Concord 1600

## Tablets Ferrogate-B with C

High in vitamin B complex content to quicken hemo-  
 globin response to iron therapy

### EACH TABLET CONTAINS

Ferrous Gluconate (5 grains)	0.375 gm	Pyridoxine HCl	0.15 mg
Thiamin HCl	3 mg	Calcium Pantothenate	0.5 mg
Riboflavin	2 mg	Ascorbic Acid	30 mg
Niacinamide	20 mg	Yeast-Liver Base	qs

### INDICATIONS

Iron deficiency and nutritional anemias as a source of iron and  
 B complex factors

Write Department N12 for Professional  
 Sample and Literature

### KENMORE PHARMACAL CO.

500 COMMONWEALTH AVENUE  
 BOSTON 15, MASS

## THE CHANNING HOME

For the MEDICAL and SURGICAL treatment of  
 Pulmonary Tuberculosis in Women

Established 1857

198 PILGRIM ROAD, BOSTON 15, MASS

Our endowment permits variations in charges for patients  
 board There are no physicians fees

Those patients suitable for treatment with STREPTO-  
 MYCIN will receive the drug without cost, out of funds  
 supplied by the Research Grants Division of United States  
 Public Health Service

Good nursing care and food are emphasized

Address all applications to  
 ELIZABETH H PELTON, Superintendent

**Zemmer**  
**PHARMACEUTICALS**

A complete line of laboratory  
 controlled ethical pharmaceuticals

Chemists to the Medical Profession for 44 years  
 NE 9-48

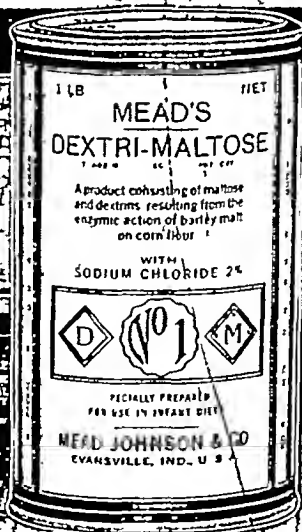
**The Zemmer Company**

Oakland Station • PITTSBURGH 13, PA

# BACKGROUND

The use of cow's milk, water and carbohydrate mixtures represents the one system of

infant feeding that consistently, for over three decades, has received universal pediatric



recognition. No carbohydrate employed in this system of infant feeding enjoys so rich and enduring a background of authoritative clinical experience as Dextri-Maltose.

# The New England Journal of Medicine

Copyright 1948 by the Massachusetts Medical Society

Volume 239

SEPTEMBER 23, 1948

Number 13

## FACTORS FAVORING SUCCESSFUL TRANSMETATARSAL AMPUTATION IN DIABETES\*

HOWARD F. ROOT, M.D.†

BOSTON

ALTHOUGH the emergency character of infectious or early gangrenous lesions of the toes and feet of diabetic patients has long been recognized by most physicians, a new aspect of this problem is presented by the demonstration that in many diabetic patients a useful and serviceable foot can be preserved through the proper use of the transmetatarsal amputation.<sup>1,2</sup> Actually, in the last two years major amputations above the ankle have become less frequent at the New England Deaconess Hospital (Table 1). The danger inherent in minor lesions and the importance of teaching all older diabetic patients simple prophylactic measures appeared time and time again in the records of these 920 patients, many of whom cut a corn or drew blood by trimming a callus and walked on the foot for weeks before going to a physician for attention. Mildness of the diabetes is no protection against gangrene and, if overemphasized by the physician, gives the patient a false sense of security. Gangrene characteristically occurs in the obese, neglected diabetic patient with low insulin requirements and little or no glycosuria but with a malignant tendency to arteriosclerosis in the legs, the coronary vessels and the retinas. The injunction not to walk on a sore toe must be endlessly repeated: the insensitive foot is most dangerous and least resistant to infection.

The introduction of chemotherapy, especially penicillin, made possible control of infection to such a degree as to improve the possibility of carrying out with success conservative surgical procedures in diabetic patients. The group of patients so far operated upon have been selected with such attention to details that success has been obtained in 6 out of 7 operations. The analysis of the various factors making for success or failure in this group includes estimation of the blood supply, determination of the infection present and assessment of such factors as the duration and type of the diabetes and presence or absence of cardiac and renal complications.

It became evident early in this series that the line

separating failure and success was extremely narrow. In some patients successful healing occurred when the chances seemed remote. It was particularly true that certain patients who failed to heal promptly in the hospital did after a prolonged period at home, succeed in obtaining a thorough healing and useful foot. This paper summarizes

TABLE 1 *Types of Diabetic Amputation in 920 Cases at the New England Deaconess Hospital*

OPERATION	No. of Cases	
	1942-1945	1946-1947
Major amputation	269	84
Transmetatarsal amputation	56	95
Transmetatarsal amputation followed by thigh amputation	(11)	(14)
Toe amputation	322	94
Totals	647	273

some of the clinical data in an attempt to present criteria for the selection of patients for operation.

### CLINICAL MATERIAL

One hundred and thirty-three transmetatarsal amputations were carried out on 122 different diabetic patients in the New England Deaconess Hospital between 1944 and September, 1947, by Drs. Leland S. McKittrick, John B. McKittrick, Norman L. Wilson, Theodore C. Pratt and Clifford C. Franseen. In 22 cases failure to heal is recorded, but in 3 of these, thigh amputation was not necessary. In 1 case after a period of many months at home healing finally occurred, and in 2 cases the result was termed a failure because of recurrence of ulcerations in anesthetic feet. The remaining 19 cases that failed to heal necessitated a subsequent thigh amputation.

The failures occurred chiefly in women, numbering 17 as against 5 failures in men. This preponderance is in excess of the proportion of women in the series since there were 74 female as against 59 male patients, in the total of 133 operations. This proportion is consistent with the sex incidence of

\*From the George F. Baker Clinic, New England Deaconess Hospital. Aided by a grant from the Eaton Laboratories Fund.

†Associate in Medicine, Harvard Medical School; physician-in-chief, New England Deaconess Hospital.

diabetes in middle and later life, although the sex incidence is equal in childhood diabetes

The duration of the diabetes must be considered at the same time as the age of patients at the time of operation. Thus, the duration was greatest in the 2 men operated upon in the fourth decade, both of whom had adequate blood supply to the foot but suffered typical neurogenic anesthetic feet. The

TABLE 2 *Age and Duration of Diabetes at Time of Transmetatarsal Amputation*

AGE	MALE PATIENTS		FEMALE PATIENTS	
	NO	DURATION OF DIABETES yr	NO	DURATION OF DIABETES yr
31-40	2	17	0	0
41-50	4	13	3	14
51-60	16 (2)*	9	26 (4)	9
61-70	26 (2)	10	30 (8)	14
71-80	10 (1)	11	13 (5)	15
81-90	1	0 2	2	6
Totals	59		74	

\*Figures in parentheses indicate failure to heal

bulk of the operations were done in patients being between fifty-one and eighty years of age, totaling 52 out of 59 in men and 69 out of 74 in women. The duration of diabetes in these patients varied from nine years in the men between fifty-one and sixty years of age and fifteen years in the women between seventy-one and eighty years of age. The average duration of diabetes was ten years in the successful operations and fourteen years in the failures. It is evident that long duration of diabetes does not contraindicate this operation, although in general the longer the duration of diabetes in the patients in the older groups, the more serious the risk. The average age in the successful operations was sixty-

trauma was slight, consisting merely of the pricking of a blister that had broken or the cutting of a corn, and the commonest lesion was the infected callus with extension into the bone or joint. The lesions were described as localized or invasive according to the presence of lymphangitis or evidence of acute extending infection at the time of admission. It should be said that in this diabetic group practically all the lesions were invasive in the sense that the extension of infection from an infected corn or callus to a bone or joint with osteomyelitis, which is common in the diabetic patient, is rare in the person without the disease. To this extent it is a peculiarly invasive lesion. However, unless the lesion was accompanied by active extending invasive infection at the time of admission, it was considered to be localized. The invasive lesions numbered 62, and the localized lesions 71. In many cases in which lymphangitis or infection extended above the ankle the use of penicillin resulted in the subsidence of infection in the favorable cases to a degree that permitted the transmetatarsal amputation. The relation of invasive infection to successful operation is shown by the fact that successful operations were done in 50 cases of invasive infection. In the failures invasive infection was present in 12 out of 22 cases. In the cases of localized infection success was obtained in 61, and failure occurred in 10. It is evident therefore that success was not dependent upon the presence or the lack of the active invasive type of infection.

#### NATURE OF DIABETES

This group of patients stands out as composed of mild cases of diabetes of long duration in patients who had formerly been extremely obese. Table 3

TABLE 3 *Obesity and Weight Loss*

MAXIMUM WEIGHT	NUMBER OF CASES	AVERAGE MAXIMUM WEIGHT	AVERAGE WEIGHT AT OPERATION	AVERAGE WEIGHT LOSS	AVERAGE PERIOD OF WEIGHT LOSS	DURATION OF DIABETES AT OPERATION
lb		lb	lb	lb	yr	yr
315-225	22	245	171	75	15	11 0
224-190	52	208	147	59	17	8 5
189-150	50	170	136	34	18	13 2
Under 150	4	138	117	19	16	10 5
No data	5	—	—	—	—	—

one years, and in the failures it was sixty-five years (Table 2).

#### NATURE OF LESIONS

In this group, gangrene of one or more toes was present in 78 cases. In these 78 cases the pathological report also mentioned osteomyelitis. In another 19 cases osteomyelitis alone was recorded. In 36 cases the lesions were described as chronic ulcerations in the feet, with defective circulation or with neurotrophic disturbance of sensation. In all cases some type of trauma had been present. Often the

shows groups of the patients classified according to maximum weight. In 22 operations the maximum weight of the patient had been between 225 and 315 pounds, with an average of 245 pounds. The average maximum weight had been 208 pounds in 52 cases and 170 pounds in 50 cases. In only 4 cases had the maximum weight been less than 150 pounds. The loss of weight up to the time of the operation averaged in these different groups from 75 down to 19 pounds. The average period between the maximum weight and the time of operation showed very little variation in the different groups.

It is evident that serious foot lesions in mild diabetic patients depend in part upon an antecedent obesity and in part upon metabolic changes associated with great losses of weight due in large measure to relatively uncontrolled diabetes. The preceding treatment of diabetes in the group had as a whole been haphazard. Thus, in the successful cases, 99 patients had had no measured diet, and 21 patients among the failures had similarly had no measured diet. Actually only 13 patients in the series had been on a measured diet, and in those the period of a measured diet had been only a small part of the diabetic history. In the successful amputations insulin had been administered on the average for six years and seven months in 82 cases, and in 14 cases in this group insulin had been used for less than six months. In 15 of the successful operations no insulin had ever been used. Among the failures 20 patients out of the 22 had been taking insulin for an average of eight years and nine months. In this group two cases had taken no insulin. The striking factor here is the comparatively long period during which diabetes had existed without treatment by means of insulin. More important, however, is the fact that even though insulin had been used, the balance of diet and insulin had not been successfully or accurately maintained, with the result that glycosuria and hyperglycemia not only were present at admission but also had probably been present long before the recurrence and development of the lesion that brought about admission to the hospital.

#### CIRCULATION

The condition of the circulation, both general and local, is undoubtedly in many cases a chief factor in determining success. In the successful patients the blood pressure on admission averaged 167 systolic, 84 diastolic, whereas in the failures the value was 166 systolic, 84 diastolic. During the period of convalescence the average minimal blood pressure in the successful cases was 120 systolic, 76 diastolic, whereas in the failures the average minimal pressure was 133 systolic, 77 diastolic. Although in both groups patients showed slightly high blood pressures, the series as a whole was characterized by moderate hypertension of the systolic type, which naturally fell during rest more in the successful group than in the failures.

One might therefore suppose that a slightly greater degree of systemic hypertension was present in the failures. However, the local circulatory conditions undoubtedly were more important than the systemic blood-pressure readings. In the estimation of local circulation, presence or absence of normal palpable pulsations in the dorsalis pedis, popliteal and posterior tibial arteries was considered of chief importance. However, the appearance of the foot regarding atrophy of muscles on the affected side, the normally rapid or slow filling of the veins

after emptying, the development of rubor upon hanging the foot down, the presence of thin, shiny skin with loss of subcutaneous weight and the temperature of the foot and leg measured by palpation were taken into account. In the successful patients pulsation in the dorsalis pedis artery was absent in 76 and present in 35 cases whereas in the failures pulsation in the dorsalis pedis was absent in 21 cases. Almost the same situation was true of the pulsation in the posterior tibial artery. Pulsation of the popliteal artery is notoriously difficult to record with accuracy. A slight change in position of the patient makes the pulse easily felt one day and absent to palpation on another. However, among the successful cases the pulse was present in 91 and absent or not felt in 20 cases. It was absent in 6 of the 22 failures. If one single evidence of the character of peripheral circulation were to be relied upon the presence or absence of pulses in the dorsalis pedis vessel would probably be of greatest service provided that palpation were carried out with care and deliberation on more than one occasion and provided due allowance was made for the difficulty of feeling pulsation in a foot swollen with edema and inflammation.

In summary one may say that a deficient blood supply as indicated by absent pulsation in the dorsalis pedis, posterior tibial and popliteal arteries was a conspicuous feature in the cases in which failure occurred, and yet exception occurred in which healing proceeded successfully in spite of apparently hopelessly deficient circulation, so that some other factor must be assumed (Table 4). This factor may be humoral or in the tissue. It may be nutritional, or it may be concerned with the mechanism by which infection is controlled.

#### INFECTION

Cultures were made from the open lesions in 92 cases. *Staphylococcus aureus* was the most important single organism, but the combination of *Staph aureus* and a streptococcus occurred in 21 cases among the successful amputations and in 4 cases among the failures.

Hemolytic streptococcus alone was obtained in 7 cases. The hemolytic *Staph aureus* was obtained in 20 cases, and the *Staph aureus* in 21 cases. Other organisms such as diphtheroids, enterococcus, *Streptococcus faecalis* and *Clostridium welchii* (1 case) were reported in 16 cases. Seven of the 22 failures showed *Staph aureus*, 1 hemolytic *Staph aureus*, 3 hemolytic streptococcus and 4 a mixture of staphylococcus and streptococcus.

Unfortunately, no division of the *Staph aureus* was carried out, but it is evident that this species, in combination with other organisms, is at present the most frequent organism found in cultures obtained from open wounds. As yet no definite information is available whether the organisms are derived from outside sources or have been

carried to the lesion from within the patient's own body. The presumption is that they gain entrance into the tissue through injury and break in the skin, and that, once the skin is broken, the poor local resistance of the diabetic tissue enables the organisms to invade muscle, soft tissue and finally bone and joint spaces. The nature of the defect that makes diabetic patients so vulnerable to invasive infection by these organisms is a matter of speculation. For many years repeated studies have failed to disclose in the blood or body fluids a mechanism directly related to the staphylococcus. In animals made diabetic the study of staphylococcal lesions is not easy because many animals do not develop staphylococcal infections in a manner comparable with that of human beings. It seems more likely

particularly when there has been a great loss of weight and tissue cachexia. Recently, the relation of vitamins and the disturbances of nutrition associated with avitaminosis has been intensively studied, and particularly in experimental diabetes attention has been given to the effect of thiamine chloride deficiency. As yet, however, no clear picture of the mechanism by which diabetic tissues lose the power of resisting invasion by the staphylococcus and streptococcus has been presented.

#### *Anesthetic Feet*

Other factors in this group of patients may be emphasized. In 24 of the successful cases various degrees of anesthesia of the toes, foot or even of the lower leg were present, whereas in 2 of the failures

TABLE 4 *Factors Affecting 133 Transmetatarsal Amputations among 122 Diabetic Patients*

RESULT OF OPERATION	NO. OF CASES	PATIENTS TAKING INSULIN FOR MORE THAN 6 MO.	PATIENTS TAKING INSULIN FOR LESS THAN 6 MO.	PATIENTS NOT TAKING INSULIN	DURATION OF DIABETES	AVERAGE AGE	AVERAGE BLOOD PRESSURE	
							ON ADMISSION	AFTER REST
Success	111	92	14	15	37	57	164/84	120/76
Failure	22	15	2	2	10	61	166/84	136/77
					14	65		

that the resistance to such organisms is a matter of tissue resistance rather than a humoral mechanism. Patients with diabetes of long duration are well known to show a variety of tissue changes,

this factor was prominent. Deficient sensation in diabetic feet has been a matter of clinical observation for many years. It is associated with the loss of reflexes and sometimes with changes in the cen-

TABLE 4 (Continued)

RESULT OF OPERATION	NO. OF CASES	CASES OF INVASIVE INFECTION	CASES OF LOCALIZED INFECTION	PATIENTS WITH HEMOGLOBIN ABOVE 14 GM.	PATIENTS WITH HEMOGLOBIN BELOW 14 GM.	PATIENTS WITH <i>Staph aureus</i> INFECTION	PATIENTS WITH HEMOLYTIC <i>Staph aureus</i> INFECTION	PATIENTS WITH STAPHYLOCOCCAL AND STREPTOCOCCAL INFECTION
Success	111	50	61	41	70	14	19	21
Failure	22	12	10	9	15	7	1	4

which are measurable both by pathological techniques and by clinical methods. It is also well known that normal glycogen may be greatly reduced in content in diabetic acidosis as well as in states of diabetic malnutrition. Although the level of glucose may increase in normal tissue and in the skin of diabetic patients not under good control, at the same time the glycogen content of the diabetic skin is greatly reduced. The concentration of glycogen is directly affected and increased when adequate insulin and dietary treatment is carried out. Similar changes in the lipid content of diabetic tissues—notably, liver, kidneys and nerve tissues—have been recorded. An increase in the lipid content of the blood except the cholesterol content occurs under conditions of diabetic maladjustment, par-

tral nervous system indicated by an increase of protein in the cerebrospinal fluid. The importance of the finding of anesthesia lies in the fact that these feet healed readily after surgery and will remain healed so long as the patient is in bed or spending only a short period on his feet. Continued use of the feet in walking results sooner or later in pressure areas, ulcerations and infection, and the resistance to infection of this group of patients seems even lower than that in the group as a whole. Frequently associated with this anesthesia, which usually is not accompanied by any serious impairment of blood supply, there may be an increase in the protein of the cerebrospinal fluid and a well marked increase in capillary fragility. In this group the spinal-fluid protein was above 50 mg per 100

cc in 24 of the successful cases and 5 of the failures. It was below 50 mg in 18 successful cases and 4 failures. Albuminuria, hypertension and retinitis were common. In 36 of the successful cases and 12 of the failures hemorrhages and exudates were present in the evegrounds. Serious impairment of vision was common. However, in 37 cases hemorrhages and exudates were not noted although it must be said that in many of these cases the examinations were not carried out by an ophthalmologist.

PREVIOUS LESIONS

In 51 patients of this series there had been previous infections of the streptococcus and staphylococcus type, including ulcerations, carbuncles and boils. In 56 cases amputations of a toe or in a

This group is often described as made up of patients with mild diabetes. If one takes as evidence of mildness the amount of insulin required and glycosuria present, this statement may be true. Actually, in this group the average maximum insulin dosage was 31 units for successful cases and 48 units for the failures, and at discharge, after a prolonged period of hospital treatment, the average was 17 units for the successful cases and 24 units for the failures. One may say, therefore, that the failures represented a somewhat severer type of diabetes, however, even this conclusion is not safe since the difference in the insulin dosage is slight and readily accounted for on the basis of more serious infection in the cases of failure. The important point, however, is to recognize the fact that

TABLE 4 (Continued)

BLOOD SUGAR			AVERAGE GLYCOSURIA ON ADMISSION	AVERAGE ALBUMIN IN URINE	AVERAGE AMOUNT OF INSULIN IN HOSPITAL		PATIENTS WITH MEASURED DIET	PATIENTS WITH UNMEASURED DIET	AVERAGE DIET AT DISCHARGE	
ON ADMISSION mg/100 cc	MAXIMUM mg/100 cc	ON DISCHARGE mg/100 cc			MAXIMUM units	ON DISCHARGE units			CARBOHYDRATE gm	cal
178	239	131	1.5	92	31	17	12	99	164	1764
183	266	142	1.9	93	48	24	1	21	159	1652

few cases of a leg had previously been performed. This group, therefore, consisted of patients in whom by and large the arteriosclerotic process had been in evidence for a considerable period, and the ampu-

the severity of diabetes in this group of patients is not to be measured by the glycosuria or the requirement of insulin dosage. Actually, a better measure is some assessment of the effect of diabetes

TABLE 4 (Continued)

PATIENTS WITH PULSATION IN DORSALIS PEDIS ARTERY	PATIENTS WITH NO PULSATION IN DORSALIS PEDIS ARTERY	PATIENTS WITH NO PULSATION IN POSTERIOR TIBIAL ARTERY	PATIENTS WITH NO PULSATION IN POPLITEAL ARTERY	PATIENTS WITH ANESTHETIC FEET	PATIENTS WITH SPINAL FLUID PROTEIN ABOVE 50 MG. PER 100 CC.	PATIENTS WITH RETINITIS	PATIENTS WITHOUT RETINITIS
35 1	76 21	73 21	20 6	24 2	24 5	36 12	33 4

tation through the transmetatarsal area was in many cases done as a matter of desperation to save one foot when the other had already been amputated. The frequency of these infections suggests again the well known fact that, although in the course of healing one assumes that local immunity has developed and antibodies occur, not only is there no persisting immunity but also these patients seem to represent a group in which a specific vulnerability to the organisms continues. As a practical consequence the teaching given to diabetic patients should emphasize all precautions, not merely directed against trauma but particularly designed to prevent and control infections whenever any break of the skin has permitted the entry of the organisms.

in producing loss of weight, malnutrition, vascular disease, impairment of nerve supply and finally and most important of all, the destruction of the normal resistance against invasive infection by the staphylococcus and the streptococcus.

FOLLOW-UP STUDY

A follow-up summary to April, 1948, of all patients undergoing transmetatarsal amputations at the New England Deaconess Hospital is presented in Table 5. The striking improvement in the selection of patients is shown by the fact that in 1944 and 1945, 45 out of 56 operations were successful, 10 failed to heal and required thigh amputations and 1 patient died of coronary occlusion. In the second period, 1946-1947 only 14 failures

occurred in 95 operations, and in 1948 only 1 unsuccessful operation was performed in 19. A single postoperative death occurred in the total of 170 operations.

Examination of the patients or a doctor's report in 1948 revealed that of the 45 patients who left the hospital in 1944 and 1945 with a healed transmetatarsal amputation 30 are still healed and walking, 4 walk with some limitation, 5 of the patients

foot is a useful foot and stands the strain of walking for a long time.

SUMMARY

An analysis of 133 transmetatarsal amputations in 122 cases of diabetes at the New England Deaconess Hospital is presented. The danger of infections or early gangrene resulting from cutting of corns or trimming of callus among diabetic

TABLE 5 Results of Follow-up Study in 170 Transmetatarsal Amputations

PERIOD	TOTAL OPERATIONS	SUCCESSFUL OPERATIONS	UNSUCCESSFUL OPERATIONS*	DEATH OF PATIENTS	CONDITION OF PATIENT AT LAST EXAMINATION†						NO DATA AVAILABLE
					PATIENTS HEALED AND WALKING	PATIENTS WITH LIMITED WALKING	PATIENTS WALKING WITH PROSTHETIC APPLIANCE	PATIENTS WITH IPSOLATERAL THIGH AMPUTATIONS	DEATHS FROM CORONARY OCCLUSION AND OTHER COMPLICATIONS		
1944-1945	36	4	10	1	30	4	5	—	12		4
1946-1947	95	81	14	—	70	5	14	2	5		1
January-April 1948	19	18	1	—	18	—	1	—	—		—

\*Followed by thigh amputation  
†1948

who required thigh amputation in 1944 and 1945 are walking with a prosthetic appliance, and the other 5 are included among the 12 patients who died of coronary occlusion and other vascular complications after discharge from the hospital. In the period 1946-1947 out of 81 successful operations 70 patients are still healed and walking, 5 more have limited walking, 14 who suffered a thigh amputation are still walking with a prosthetic appliance and 3 are dead. One of the most striking facts is that in only 2 cases out of 144 patients who left the hospital with a healed transmetatarsal amputation has a subsequent thigh amputation become necessary on the same side. In these cases trauma to the leg led to gangrene at the level of the ankle in 1 and at the level of the shin in the other. The deficiency of the blood supply was so great that thigh amputation followed. However, if the patient once succeeds in healing a transmetatarsal amputation the

patients is stressed. All persons with diabetes should be constantly warned against walking on a sore toe.

Failure to heal occurred in 22 of the amputations, and 19 patients required subsequent thigh amputation (failures occurred chiefly among female patients). In all cases trauma, usually slight, was followed by gangrene. Most of the patients had mild diabetes and had once been overweight. The blood pressures among the failures were higher than those among the successful cases.

Results have steadily improved since 1944, owing to selection of patients and the introduction of chemotherapy and penicillin.

81 Bay State Road

REFERENCES

1 McKinnick, L. S. Recent advances in care of surgical complications of diabetes mellitus. *New Eng J Med* 235:929-932, 1946.  
2 Joslin, E. P., Root, H. F., White, P., Marble, A. and Bailey, C. C. *The Treatment of Diabetes Mellitus*. Eighth edition. 861 pp. Philadelphia: Lea & Febiger, 1946. Pp. 700-702.

## BRONCHIAL ADENOMA\*

CARLTON R. SOLDER, M.D.,† AND J. W. KINGSLEY, JR. M.D.‡

BOSTON

**B**RONCHIAL adenoma was first recognized sixty-five years ago, and yet it received little mention in the literature until relatively recently. Since the publication of Reisner's<sup>1</sup> article in 1928 several excellent clinical and pathological descriptions of this tumor have been written. The increasing awareness of bronchial adenoma has led to its more frequent recognition and to a more thorough understanding of the altered respiratory physiology and of the pulmonary complications to which it predisposes. The recent advances in thoracic surgery have broadened the therapeutic approach to these tumors, as well as to other types of pulmonary lesions. The purpose of this communication is to review the literature and to present our experience with bronchial adenoma.

The incidence of bronchial adenoma has been stated to be approximately 6 per cent of all primary bronchial tumors.<sup>2</sup> It comprised 12 per cent of 278 neoplasms diagnosed bronchoscopically by Clerf and Bucher.<sup>3</sup> Of 217 histologically proved primary lung tumors encountered at the Lahey Clinic since 1930, 15 were bronchial adenomas, an incidence of 6.9 per cent. Adams<sup>4</sup> has discussed some of these cases in a previous report. It is of interest to note that the diagnosis has been confirmed in 9 cases during the past three years, whereas only 6 cases of bronchial adenoma were discovered over the preceding fifteen years. For ease of description the cases have been numbered in the order in which they were diagnosed, and the pertinent features of each are summarized in Table I.

The origin of bronchial adenoma remains unsettled. It appears that most adenomas arise in the submucosa of the bronchial wall, probably from the bronchial glands or ducts. From this point of origin growth progresses into the bronchial lumen as well as extrabronchially. Brunn and Goldman<sup>5</sup> stated that extrabronchial extension occurs in 90 per cent of cases, however, this was definitely found in only 7 of the cases.

Because of the uncertain origin and variable morphology of these tumors, numerous terms have been suggested for bronchial adenoma. Nevertheless, it is believed that the use of this designation is desirable until the situation is clarified.

With few exceptions bronchial adenomas are situated in a primary bronchus, where they can be readily visualized through the bronchoscope. In the 15 cases reported herein, the tumor was seen by the bronchoscopist in 12. In Case 8 the growth

was in a segmental bronchus of the left upper lobe, where it could not be demonstrated. In Case 13 there was definite narrowing of the right-lower-lobe bronchus from external pressure without evidence of intrabronchial growth. At operation the latter was found to arise in the dorsal division of the right-lower-lobe bronchus and to possess an extra-bronchial portion several times larger than that within the lumen. In Case 5 bronchoscopy was not performed.

When seen bronchoscopically an adenoma appears as a rounded, pink or reddish-purple mass, the surface of which is often bosselated. The tumors are usually attached by a broad base but rarely have a distinct pedicle that permits the entire mass to move with respiration or instrumentation (Case 3). Not infrequently blood vessels can be seen on the surface of the tumor. As a rule, there is no visible ulceration. Adenomas are notorious for profuse bleeding following manipulation, and death has been reported from aspiration of blood after biopsy.<sup>6</sup> Instrumentation did not cause serious bleeding in any of our cases.

If an adenoma is satisfactorily visualized, its distinctive appearance usually differentiates it from carcinoma. Whereas carcinoma often produces fixation of the bronchus, this almost never occurs in the presence of adenoma. Carcinomas are frequently ulcerated, and although they may bleed freely at biopsy this is seldom troublesome. Microscopical examination of biopsy material is essential in the differential diagnosis but is not without its shortcomings. In the first place, the forceps may not penetrate the tumor deeply enough to obtain characteristic cells, and secondly, squamous metaplasia of the surface epithelium or distortion of the cells may lead to an erroneous diagnosis of carcinoma. Serial sections minimize the possibility of error.

Histologically bronchial adenomas have been divided into two main types: carcinoid and mixed tumor, or cylindroma. The latter is considered by some investigators to possess greater malignant potentialities than the more common carcinoid type.<sup>7,8</sup> Womak and Graham<sup>9</sup> prefer the term "mixed tumor" for all adenomas because of their resemblance to mixed tumors of the salivary glands and the occasional presence of bone and cartilage. The cellular structure of the carcinoid type is comparable to that of appendiceal carcinoids, parathyroid adenomas and basal-cell carcinoma.<sup>10</sup>

Differences of opinion regarding the potential malignancy of bronchial adenoma have interfered with the adoption of uniform therapy. Foster-

\*From the Department of Internal Medicine, Lahey Clinic.

†Member, Department of Internal Medicine, Lahey Clinic.

‡Fellow in Internal Medicine, Lahey Clinic.

Carter,<sup>11</sup> Jackson et al.<sup>12</sup> and Clerf and Bucher<sup>3</sup> concluded that the tumors are essentially benign. On the other hand, Wessler and Rabin<sup>13</sup> found evidence to the liver has been described by Anderson<sup>15</sup> and by Holley.<sup>16</sup> Laff and Neuburger<sup>7</sup> found malignant change with spread to the opposite lung thirteen

TABLE 1 Summary of Cases

CASE No	SEX	AGE	DURATION	SYMPTOMS	PHYSICAL FINDINGS	ROENTGENOLOGIC FINDINGS	BRONCHOSCOPIC FINDINGS
1	F	33	4 yr	Cough sputum hemoptysis recurrent fever sweats and pleurisy	Diminished breath sounds rales over right lower lobe	Atelectasis right lower lobe no filling of dorsal division right lower lobe bronchus on bronchography	Tumor mass right lower lobe bronchus
2	F	34	1 yr	Cough hemoptysis and chest discomfort	Negative	Soft tissue mass lower pole of right hilus	Tumor mass right lower-lobe bronchus
3	F	23	2½ yr	Cough wheeze chest discomfort, chills fever and weight loss	Diminished breath sounds right lower and middle lobes increased breath sounds right upper lobe	Obstructive emphysema right lung	Right main bronchus almost completely occluded by pedunculated tumor which could be moved 1 cm. but bleeding
4	M	30	6 yr	Cough sputum pressure in chest and hemoptysis	Diminished breath sounds over right lower lobe	Soft-tissue mass right hilus	Tumor mass in right lower-lobe bronchus active bleeding on biopsy
5	F	38	5 yr	Cough sputum pneumonia three times	Negative	Infiltration and bronchiectasis right lower lobe bronchogram done	No bronchoscopy done
6	M	39	6 yr	Cough sputum hemoptysis repeated pneumonia	Diminished resonance and breath sounds left lower lobe	Atelectasis and bronchiectasis left lower lobe	Tumor mass obstructing left-lower-lobe bronchus
7	M	41	2 yr	Vague abdominal distress and hemoptysis	Negative	Questionable mass right hilus	Tumor mass at junction of right middle and lower-lobe bronchi
8	F	29	2½ yr	Cough dyspnea and chest discomfort	Inspiratory lag on left	Tumor and segmental atelectasis bronchiectasis left upper lobe	No tumor seen
9	F	51	8 mo	Repeated hemoptyses	Negative	Mass right hilus partial atelectasis right lower lobe	Tumor mass within right lower-lobe bronchus extending into middle-lobe bronchus
10	M	42	3 yr	Cough and repeated hemoptyses	Negative	Negative	Pedunculated tumor right main bronchus encroaching upon carina
11	M	13	1 yr	Cough wheeze dyspnea chest discomfort repeated pneumonia and weight loss	Diminished breath sounds and resonance left lower lobe	Atelectasis left lower lobe	Tumor left main bronchus
12	M	37	16 mo	Cough hemoptysis and chest discomfort	Negative	Infiltration midportion of left lung field	Tumor left upper lobe bronchus extending to lower-lobe bronchus
13	F	49	4 yr	Cough sputum, pleurisy and severe hemoptysis	Diminished breath sounds and resonance right lower lobe	Tumor mass right hilus atelectasis right lower lobe	Narrowing of right lower lobe bronchus from external pressure no tumor visible within bronchus
14	F	47	18 mo	Cough purulent sputum hemoptysis repeated pneumonia and weight loss	Diminished breath sounds and resonance left lower lobe	Atelectasis left lower lobe	Tumor obstructing left-lower lobe bronchus and extending into upper lobe bronchus
15	M	32	8 mo	Cough sputum wheeze dyspnea severe hemoptysis once	Wheeze over left lower lobe when patient was lying on left side rhonchi	Negative	Tumor mass arising in left main bronchus extending into upper lobe bronchus and almost completely filling lower lobe bronchus

of malignancy in 2 cases. Adams, Steiner and Bloch<sup>14</sup> reported 5 cases, 2 with distant metastases, which they considered to be malignant. Metastasis years after the original diagnosis of cylindroma. Lymph-node involvement was present in 5 of 10 cases reported by Chamberlain and Gordon.<sup>17</sup>

Graham and Womack<sup>18</sup> believe that some adenomas become malignant with loss of their original identity. Local infiltration by tumor cells has been

with tumor cells present in two hilar lymph nodes<sup>19</sup>

From these facts one must conclude that bronchial adenoma is a potentially malignant neoplasm

TABLE 1 (Continued)

CASE No	TREATMENT	PATHOLOGY	RESULTS OF FOLLOW UP STUDY	COMMENT
1	Local removal and electrocoagulation twice removal of right lower and middle lobes	Carcinoid type with invasion and infiltration of wall large extrabronchial portion bronchiectasis	Patient well 6½ yr after lobectomy	Despite repeated examinations and removal of recurrent growth pressure from extrabronchial portion led to bronchostenosis and bronchiectasis
2	X-ray therapy local removal and electrocoagulation	Infiltrating carcinoid type	Patient well after 6½ yr	—
3	Local removal electrocoagulation of base.	Infiltrating carcinoid type	Patient well after 4½ yr	—
4	Removal of right middle and lower lobe	Low grade adenocarcinoma arising from adenoma, with involvement of 2 hilar lymph nodes	Patient well after 4 yr	Seropositive congenital syphilis present
5	Removal of right lower lobe	Infiltrating carcinoid type at orifice of right lower lobe bronchus with large extrabronchial extension bronchiectasis	Patient well after 2½ yr	Diagnosis not made preoperatively
6	Removal of left lower lobe	Infiltrating carcinoid type bronchiectasis	Patient well after 2 yr	—
7	Removal of right middle and lower lobes	Infiltrating carcinoid type with ossification of stroma	Patient well after 2 yr	—
8	Removal of left upper lobe	Tumor in segmental bronchus left upper lobe carcinoid type bronchiectasis	Patient well after 20 mo	—
9	Removal of right middle and lower lobes	Infiltrating carcinoid type	Patient well after 14 mo	—
10	Local removal and electrocoagulation twice	Infiltrating carcinoid type	Patient well after 7 mo	—
11	Partial removal pneumonectomy (left) elsewhere.	Infiltrating carcinoid type	No follow-up study	—
12	Recurrence 2 months after local removal and electrocoagulation pneumonectomy (left)	Infiltrating carcinoid type, with ossification of stroma	Dysphagia after 5 mo	Pressure on esophagus by bronchial stump
13	Removal of right, middle and lower lobes	Tumor dorsal division of right lower lobe bronchus infiltrating carcinoid type with large extrabronchial extension	Patient well after 6 mo	Immediate operation because of severe hemoptysis
14	Removal of left lung	Infiltrating carcinoid type bronchiectasis left lower lobe.	Patient well after 5 mo	—
15	Removal of left lung	Infiltrating carcinoid type	—	Patient operated on too recently for follow up observations

a frequent finding and was detected in 14 cases. In Case 4 the pathological diagnosis was "low-grade adenocarcinoma arising from bronchial adenoma

The grade of malignancy is apparently low, inasmuch as there are no cases on record in which death has resulted from sudden rapid growth of the tumor

Carter,<sup>11</sup> Jackson et al.<sup>12</sup> and Clerf and Bucher<sup>3</sup> concluded that the tumors are essentially benign. On the other hand, Wessler and Rabin<sup>13</sup> found evidence

to the liver has been described by Anderson<sup>14</sup> and by Holley.<sup>16</sup> Laff and Neuburger<sup>7</sup> found malignant change with spread to the opposite lung thirteen

TABLE 1 Summary of Cases

CASE No	SEX	AGE	DURATION	SYMPTOMS	PHYSICAL FINDINGS	ROENTGENOLOGIC FINDINGS	BROSCOPIC FINDINGS
1	F	33	4 yr	Cough sputum hemoptysis recurrent fever sweats and pleurisy	Diminished breath sounds rales over right lower lobe	Atelectasis right lower lobe no filling of dorsal division, right lower lobe bronchus, on bronchography	Tumor mass right lower lobe bronchus
2	F	34	1 yr	Cough hemoptysis and chest discomfort	Negative	Soft tissue mass lower pole of right hilus	Tumor mass right lower lobe bronchus
3	F	23	2½ yr	Cough wheeze chest discomfort chills fever and weight loss	Diminished breath sounds right lower and middle lobes increased breath sounds right upper lobe	Obstructive emphysema right lung	Right main bronchus almost completely occluded by pedunculated tumor which could be moved 1 cm but bleeding
4	M	30	6 yr	Cough sputum pressure in chest and hemoptysis	Diminished breath sounds over right lower lobe	Soft tissue mass right hilus	Tumor mass in right lower lobe bronchus active bleeding on biopsy
5	F	38	5 yr	Cough sputum pneumonia three times	Negative	Infiltration and bronchiectasis right lower lobe bronchogram done	No bronchoscopy done
6	M	59	6 yr	Cough sputum hemoptysis repeated pneumonia	Diminished resonance and breath sounds left lower lobe	Atelectasis and bronchiectasis left lower lobe	Tumor mass obstructing left lower-lobe bronchus
7	M	41	2 yr	Vague abdominal distress and hemoptysis	Negative	Questionable mass right hilus	Tumor mass at junction of right middle and lower-lobe bronchi
8	F	29	2½ yr	Cough dyspnea and chest discomfort	Inspiratory lag on left	Tumor and segmental atelectasis bronchiectasis left upper lobe	No tumor seen
9	F	51	8 mo	Repeated hemoptyses	Negative	Mass right hilus partial atelectasis right lower lobe	Tumor mass within right lower-lobe bronchus extending into middle-lobe bronchus
10	M	42	3 yr	Cough and repeated hemoptyses	Negative	Negative	Pedunculated tumor right main bronchus encroaching on carina
11	M	13	1 yr	Cough wheeze dyspnea chest discomfort repeated pneumonia and weight loss	Diminished breath sounds and resonance left lower lobe	Atelectasis left lower lobe	Tumor left main bronchus
12	M	37	16 mo	Cough hemoptysis and chest discomfort	Negative	Infiltration midportion of left lung field	Tumor left upper lobe bronchus extending to lower-lobe bronchus
13	F	49	4 yr	Cough sputum pleurisy and severe hemoptysis	Diminished breath sounds and resonance right lower lobe	Tumor mass right hilus atelectasis right lower lobe	Narrowing of right lower lobe bronchus from external pressure no tumor visible within bronchus
14	F	47	18 mo	Cough purulent sputum hemoptysis repeated pneumonia and weight loss	Diminished breath sounds and resonance left lower lobe	Atelectasis left lower lobe	Tumor obstructing left lower lobe bronchus and extending into upper lobe bronchus
15	M	32	8 mo	Cough sputum wheeze dyspnea severe hemoptysis once	Wheeze over left lower lobe when patient was lying on left side rhonchi	Negative	Tumor mass arising in left main bronchus extending into upper-lobe bronchus and almost completely filling lower lobe bronchus

of malignancy in 2 cases. Adams, Steiner and Bloch<sup>14</sup> reported 5 cases, 2 with distant metastases, which they considered to be malignant. Metastasis

years after the original diagnosis of cylindroma. Lymph-node involvement was present in 5 of 10 cases reported by Chamberlain and Gordon.<sup>17</sup>

of atelectasis. There may be a noticeable disparity in the size and expansion of the two hemithoraces. Compensatory emphysema of the uninvolved lobes is not uncommon in cases with complete occlusion of the bronchus. The fact that in 6 patients physical examination of the chest was negative serves to emphasize the fact that abnormal physical signs are not essential to a diagnosis of bronchial adenoma.

ROENTGENOLOGIC FINDINGS

Roentgenograms of the chest reveal abnormalities in the majority of cases of adenoma of the bronchus, however special technics are frequently necessary to establish a reasonably exact diagnosis. Most observers have mentioned atelectasis as the most common finding followed by inflammatory

infiltrations of these findings in 4 cases (Fig 3 and 4). Obstructive emphysema was present in 1 patient



FIGURE 1 Plain Film in Case 4 Showing a Rounded Soft-Tissue Mass at the Lower Pole of the Right Hilum



FIGURE 2 Inflammatory Infiltration of the Majority of the Left-Lower Field in Case 12

(Fig 5). Chest roentgenograms were normal in 2 cases. Overexposed (grid or Bucky) films are valu-



FIGURE 3 Tumor Mass Superior atelectasis and Bronchectasis of the Left Upper Lobe in Case 8. The adenoma was resected and a bronchogram

able in detecting intraluminal tumors which as a rule are less readily discernible than extrabronchial

infiltration, a visible tumor mass and obstructive emphysema. It must be emphasized that none of these findings are diagnostic of bronchial adenoma. Whether present singly or in combination they indicate nothing more than mechanical interference with normal bronchial function. The visible tumor mass produced by an adenoma cannot be differentiated from other types of bronchial tumors by roentgenologic study alone. Final diagnosis must rest upon the bronchoscopic and histopathological appearance.

Atelectasis alone was demonstrated in 3 cases; a tumor mass (Fig 1) in 3; inflammatory infiltration (Fig 2) or bronchiectasis in 2; and various combinations of these findings in 4 cases (Fig 3 and 4). Obstructive emphysema was present in 1 patient.

with widespread metastases — a common finding in the usual type of bronchiogenic carcinoma

### CLINICAL CONSIDERATIONS

#### *Age and Sex*

Adenoma of the bronchus is largely a disease of the younger age groups. Sixty per cent of the 15 patients were under 40 years of age, the converse of the age distribution of bronchiogenic carcinoma

TABLE 2 *Age and Sex Distribution*

AGE	NO OF PATIENTS	FEMALE PATIENTS	MALE PATIENTS
11-20	1	0	1
21-30	3	2	1
31-40	3	3	2
41-50	4	2	2
51-59	2	1	1
Average age		38.0	36.3

The age range was from 13 to 59 years, with an average of 37.15 years (Table 2). Eight patients (53 per cent) were women.

#### *Duration of Symptoms*

It is not uncommon to discover bronchial adenoma as the cause of respiratory symptoms of several years' standing. The duration of symptoms among these patients varied from 8 months to 6 years, with an average of 2.7 years. This parallels the experience of others.

#### *Symptoms*

**Cough and sputum.** Cough, the commonest symptom of bronchial adenoma, was the initial symptom in 7 and was present in 13 patients. At the outset the cough is likely to be mild, but with growth of the tumor the bronchial irritation increases and the cough becomes more distressing. This symptom may be most troublesome at night or when the patient assumes a particular position. The presence of sputum depends largely upon the degree of bronchial obstruction produced by the adenoma. Early, therefore, sputum may be absent or mucoid in character owing to the increased bronchial secretion. When bronchial obstruction and infection supervene, with or without actual bronchiectasis or abscess, the sputum tends to become purulent. Sputum was present to some degree in 8 of the patients in this series.

**Hemoptysis.** Hemoptysis is one of the outstanding manifestations of adenoma of the bronchus. It occurred one or more times in 11 of the 15 patients, in 3 it was the initial symptom. In Case 13 hemoptysis was of such severity and persistence as to necessitate prompt surgical intervention. Typically, the bleeding is sudden in onset, brisk and fairly abrupt in cessation. In the female patients hemoptysis was not related to the menses. It seems likely

that in most cases bleeding results from the rupture of a blood vessel on the surface of the adenoma since, as mentioned above, the tumors are almost never found to be ulcerated. The presence of bronchiectasis constitutes another possible source of hemorrhage.

**Wheeze.** Wheeze was an outstanding complaint of 3 patients, 2 of whom were referred to the clinic with a presumptive diagnosis of bronchial asthma. One extremely important feature of the wheeze accompanying bronchial adenoma is its tendency to be localized to a definite area. In addition, it may be transient and vary with change of position, this is especially true of the pedunculated adenoma as exemplified by Case 3. Wheeze tends to disappear as the bronchus becomes completely obstructed.

**Dyspnea.** Although as a rule not extreme, dyspnea may be distinctly troublesome. This complaint was present in 4 cases. Moderate diminution of vital capacity may result from atelectasis or obstructive emphysema. If the latter is of sufficient degree to produce mediastinal shift, the function of the sound lung will be compromised. Dyspnea is often more pronounced with partial than with complete bronchial obstruction.

**Chest discomfort.** Varying degrees of chest discomfort occur fairly frequently in association with bronchial adenoma. In general, this is mild and is often described as a feeling of fullness or pressure in the chest. The most severe type of pain encountered is due to pleuritis. Six patients complained of mild chest pain.

**Pulmonary infection.** Patients with bronchial adenoma are prone to develop pulmonary sepsis. Often there is a history of recurrent bouts of pneumonia involving the same lobe, or of slowly resolving pneumonia. Bronchial obstruction may, in addition to producing pneumonitis, lead to bronchiectasis or abscess formation. In other cases the clues to the underlying process are less obvious, the clinical manifestations being limited to fever, either intermittent or continuous, sweats and, not infrequently, weight loss. Four patients had recurrent episodes of pneumonia. Two others had repeated chills and fever. Pleurisy was present in 2 cases. Three patients lost from 12 to 25 pounds in weight.

### PHYSICAL FINDINGS

Abnormal findings on physical examination are in direct proportion to the degree of bronchial obstruction and the extent of pulmonary involvement distal to the tumor. In the presence of partial obstruction of a bronchus decreased resonance and distant breath sounds, with or without wheeze, may be detected over the involved lobe. Rales or rhonchi will be added in the presence of pneumonitis or bronchiectasis. Obstructive emphysema develops distal to adenomas that permit ingress of air but occlude the bronchus during expiration. With complete bronchial obstruction the findings are those

carina. It may be employed to promote bronchial drainage prior to surgical resection, thereby reducing the degree of infection.

Surgical resection holds the advantage of removing not only the entire tumor but also the infected portion of the lung. Bronchiectasis in itself is an indication for resection, regardless of whether or not the tumor can be completely removed bronchoscopically. In addition, surgical resection precludes the possibility of malignant degeneration, which, although relatively infrequent, cannot be entirely discounted. It might be argued that resection is too radical for sessile adenomas without demonstrable extrabronchial tumor or infection, and yet the probability of later complications after local removal is sufficiently great to make lobectomy or pneumonectomy the preferred method of treatment.

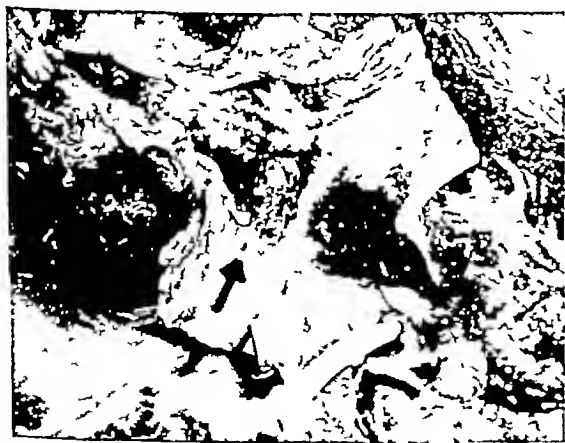
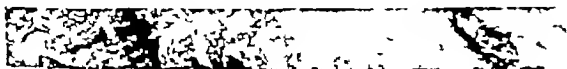


FIGURE 6 Surgical Specimen in Case 15 Showing a Small Adenoma in situ at the Bifurcation of the Left Main Bronchus. The tumor mass arose in the main bronchus, extended into the upper-lobe bronchus and almost completely occluded the lower-lobe bronchus. A portion of the adenoma had previously been removed for biopsy.

This is especially true today with the great reduction in mortality and morbidity that has resulted from improved surgical technic and from the use of antibiotics.

In 3 patients of the present series the adenomas were removed bronchoscopically without a recurrence to date. Case 2 was treated by local removal prior to the evolution of the present policies of treatment, there has been no recurrence after six and a half years. The adenoma in Case 3 had a distinct pedicle, which rendered bronchoscopic removal practicable, this patient has remained well for four and a half years. In Case 10 the tumor arose in the

right main bronchus and encroached upon the carina, electrocoagulation was carried out without recurrence after seven months. Another patient (Case 1) was bronchoscoped seven times over a six-year period, although the endobronchial portion of the tumor was successfully obliterated, extra-bronchial growth produced progressive broncho-



FIGURE 7 Bronchial Adenoma in Case 15, Showing Intra-luminal Growth and Infiltration of the Bronchial Wall, with Replacement of the Normal Glandular Structure ( $\times 11\frac{1}{2}$ ).

stenosis, bronchiectasis developed, and lobectomy became necessary. In Case 12 the tumor involved both the left-upper-lobe and the left-lower-lobe bronchi, therefore, it was decided that trial by local removal was justified in an attempt to avert pneumonectomy. The growth recurred within two months, and pneumonectomy was performed without further delay. In Case 15 the tumor was located at the bifurcation of the left-upper-lobe and left-lower-lobe bronchi (Fig 6), pneumonectomy was done without trial of local removal. Infiltration of the bronchial wall by tumor cells is shown in Figure 7.

The left lung was removed in 3 cases. Two lobes were resected in 5 patients, and a single lobe in 3. The remaining patient underwent pneumonectomy elsewhere and has been lost to follow-up observation. There were no operative deaths. Five months after removal of the left lung the patient in Case 12 developed difficulty in swallowing, barium studies revealed distortion of the esophagus by the bronchial stump, without obstruction. The other 10 patients have been completely relieved of their symptoms and have remained well for from six months to six and a half years postoperatively, except 1 (Case 15), who was operated on too recently to be included in the follow-up report.

#### SUMMARY AND CONCLUSIONS

Bronchial adenoma constituted 6.9 per cent of all pathologically proved primary bronchial tumors.

masses. Fluoroscopy and roentgenograms taken during forced expiration aid in discovering obstructive emphysema and should therefore be utilized whenever partial bronchial obstruction is suspected. Body-section roentgenography, as advocated by Lowry and Rigler,<sup>2</sup> has not been employed in this clinic.

Bronchography occasionally proves of value and was employed in 2 cases. The chief indications for

biopsy material usually establish the diagnosis. The main points of differentiation from bronchiogenic carcinoma have been discussed. Bacteriologic studies of bronchial secretions are important in ruling out tuberculosis, however, the two conditions can coexist. An intrabronchial foreign body can be distinguished in most cases by the history of aspiration.

#### TREATMENT

Therapy of bronchial adenoma has been almost entirely confined to local removal and to surgical resection. Irradiation has been given a limited trial but has proved of questionable value. This form of treatment was employed in Case 2 with temporary decrease in cough and hemoptysis, but without



FIGURE 4 Tumor Mass at the Right Hilum in Case 9, Producing Partial Atelectasis of the Right Lower Lobe

lipiodol studies are to determine the site of a suspected tumor when bronchoscopy fails to do this, and to ascertain the presence of bronchiectasis. When the latter is being sought, it may be necessary to remove a portion of the adenoma prior to bronchography to obtain satisfactory filling. In Case 1 bronchograms showed obstruction of the dorsal division of the right-lower-lobe bronchus. In Case 5 bronchiectasis was demonstrated, but the tumor mass, which was largely extrabronchial, was not apparent.

#### DIAGNOSIS

Bronchial adenoma should be considered as a diagnostic possibility in every young patient who presents a history of chronic cough, hemoptysis and repeated pulmonary infections. Likewise, the possibility of adenoma should be entertained in the presence of atelectasis, localized wheeze, obstructive emphysema or unilateral bronchiectasis. The prime requisite to the diagnosis is to suspect bronchial adenoma and to obtain bronchoscopy. Visualization of the tumor and microscopic study of



FIGURE 5 Obstructive Emphysema of the Right Lung in Case 3, Produced by the Valve-like Action of a Pedunculated Bronchial Adenoma

Note the low position of the right leaf of the diaphragm and shift of the heart to the left

visible change in the tumor itself, which was later removed by electrocoagulation.

Bronchoscopic removal affords good results in selected cases, specifically those in which the adenoma has a distinct pedicle and no extrabronchial extension, and in which irreversible pulmonary damage has not occurred. Local removal is the only possible approach to adenomas that involve the

It is believed that these experiences may be of value to others who wish to develop similar facilities

In May, 1946, a tentative plan for the treatment of selected psychiatric patients in the House of Mercy Hospital, Pittsfield, Massachusetts, was embarked on. The plan was formulated with the co-operation of the hospital medical director, Dr Reo J Marcotte, who recognized the responsibility the hospital would assume, but also recognized the service that could be performed for the benefit of the community. The House of Mercy Hospital is a general hospital of 200-bed capacity. It is the largest of three in the City of Pittsfield, which has a population of about 55,000. There is also an additional population of 75,000 in the county. The neuropsychiatric program was started without any significant expense to the hospital. In the Outpatient Department, several rooms that had not previously been fully utilized were designated as the "treatment area." The nurses assigned to the Outpatient Department plan their schedule so that they are available for treatments, which are given at approximately the same time each morning. A male attendant is also available at such treatment periods. Personnel of this type are especially necessary when electric convulsive therapy is administered. In the treatment area, subcoma insulin and sodium amytal interviews are also carried out. Subcoma insulin treatments are supervised by the same nurses. Patients are treated on an inpatient or outpatient basis. Inpatients who have improved are often discharged, and treatment is continued on an outpatient basis.

This psychiatric program is carried on without assistance from hospital interns or residents. Although it would be desirable to have such doctors participate in the program there has been a marked shortage of house officers in the smaller general hospitals. Medical supervision of the program depends entirely on myself, the only physician taking part in the program. I spend all my mornings in the hospital, and in this way all treatments can be properly supervised.

The success of the plan for the management of psychiatric patients depends largely on selection. Since there are no locked facilities, a significant number of patients must be rejected. It is apparent that disturbed, overactive, unco-operative and some paranoid patients cannot be accepted for treatment. In the psychotic group of patients, depressions comprise the largest number. Psychotic patients are accepted for treatment when it appears that they can be helped by electric shock therapy. Psychoneurotic patients are accepted when psychotherapy in a hospital setting is considered advantageous, and when it is believed that somatic treatment will be of value. The largest number of these patients have severe anxiety tension states and have been difficult to manage on the basis of office treatment. Such patients are treated with psycho-

therapy and subcoma insulin. Patients with conversion states are hospitalized and are treated with psychotherapy, aided by sodium amytal interviews.

Table 1 presents a report of the patients treated during the year 1947. It is realized that the numbers are not impressive. However, the figures should be considered in relation to the size of the community. No attempt is made to evaluate the somatic treatments used, since these have been adequately discussed elsewhere.

It can be seen that a higher percentage of psychotic patients were treated as outpatients. This was often due to the patient's inability to co-operate

TABLE 1 *Inpatients and Outpatients Treated during 1947*

DIAGNOSIS		No OF CASES
Inpatients		
Psychoneurosis		42
Psychosis		14
		56
Outpatients		
Psychoneurosis		8
Psychosis		20
		28
Total		84

in a general hospital. It would probably have been better to institutionalize several of these patients. However, neither the patient nor the family was able to make such a decision. To refuse treatment to such patients would have meant that they would merely remain at home.

The management of psychiatric patients in a general hospital, without locked facilities, has significant advantages. Patients are treated without legal commitment or certification. At an early date the family and patient can more readily accept the psychiatric diagnosis and the indicated treatment. Relatives are reassured when they realize that the patient is to be treated in the same hospital where he would receive care for pneumonia or appendicitis. This minimizes any question of social stigma. In this community it means that the patient does not have to be removed to some other city, since there are no other psychiatric hospital facilities in Pittsfield. Patients who are treated on an outpatient basis spend only short periods away from their home setting.

These advantages not only are important in their social implications but also include significant economic elements. Since the patient remains in the community, time and money are not spent in traveling to visit him. Hospitalization insurance has recently been liberalized and gives definite benefits to the psychiatric patient. In this community a large industrial organization has liberalized its hospitalization policy and allows both inpatient and outpatient treatment of psychiatric patients. Blue Shield in Massachusetts makes extra allowances to the physician for the

encountered at the Lahey Clinic over a period of eighteen years. Adenomas can usually be visualized bronchoscopically, and their characteristic appearance in most cases serves to differentiate them from carcinoma. Bronchial adenoma is a potentially malignant tumor, but the malignancy is of a low grade.

Sixty per cent of bronchial adenomas occurred in patients less than forty years of age. The incidence was slightly greater in female patients. A history of chronic cough, hemoptysis and repeated pulmonary infections, or findings of atelectasis, localized wheeze, obstructive emphysema or unilateral bronchiectasis are indications for bronchoscopy on a suspicion of adenoma.

Inasmuch as surgical resection removes the infected lung tissue as well as the entire tumor and prevents malignant degeneration, it is the treatment of choice in the majority of cases. Local removal may suffice for pedunculated adenomas without extrabronchial extension and without irreparable parenchymal destruction, however, the possibility of recurrence necessitates repeated bronchoscopic examinations.

## REFERENCES

1. Reissner D. Intrabronchial polypoid adenoma: report of case. *Arch Surg* 16:1201-1213 1928.
2. Lowry T. and Rigler L. G. Adenoma of bronchus: clinical and roentgenologic study with report of seven cases. *Radiology* 43:213-222 1944.
3. Clerf L. H. and Bucher C. J. Adenoma (mixed tumor) of bronchus: study of 35 cases. *Ann Otol & Laryng* 51:836-850 1942.
4. Adams R. Primary lung tumors. *J A M A* 130:547-553 1944.
5. Brunn H. and Goldman A. Bronchial adenoma. *Am. J. Sur* 54:179-192 1941.
6. Case records of the Massachusetts General Hospital (Case 15322). *New Eng. J. Med* 237:198-201 1947.
7. Laff H. I. and Neuhaeuser K. T. Bronchial adenoma with metastasis. *Arch Otolaryng* 40:487-493 1944.
8. McDonald J. R., Moersch H. J. and Tinney W. S. Cylindroma of bronchus: report of 6 cases. *J. Thoracic Surg* 14:445-451 1947.
9. Womack N. A. and Graham E. A. Mixed tumors of lung, so-called bronchial or pulmonary adenoma. *Arch Path* 26:165-168 1938.
10. Moersch H. J., Tinney W. S. and McDonald J. R. Adenoma of bronchus. *Surg Gynec & Obst* 81:551-558 1945.
11. Foster Carter A. F. Bronchial adenoma. *Quart J Med* 10:139-144 1941.
12. Jackson C. L., Konzelmann F. W. and Norn C. M. Bronchial adenoma. *J Thoracic Surg* 14:98-105 1945.
13. Weisler H. and Rabin, C. B. Benign tumors of bronchus. *Am J W Sc* 183:164-180 1932.
14. Adams W. E., Steiner P. F. and Bloch R. G. Malignant adenoma of lung: carcinoma like tumors with long clinical course. *Surgery* 11:503-526 1942.
15. Anderson W. M. Bronchial adenoma with metastasis to liver. *J Thoracic Surg* 12:351-360 1943.
16. Holley S. W. Bronchial adenomas. *Mil Surgeon* 99:578-584 1946.
17. Chamberlain J. M. and Gordon J. Bronchial adenoma treated by pulmonary resection: case reports. *J Thoracic Surg* 14:144-149 1945.
18. Graham E. A. and Womack N. A. Problem of so-called bronchial adenoma. *J Thoracic Surg* 14:106-119 1945.

## PSYCHIATRY IN A GENERAL HOSPITAL OF A SMALL CITY\*

SAMUEL M. TARNOWER, M.D.†

PITTSFIELD, MASSACHUSETTS

PSYCHIATRY is slowly becoming part of general hospital organization. This branch of medicine was preceded by neurology, which is concerned with more obvious physical disease and usually does not involve overt abnormalities of behavior. The patient with a psychiatric diagnosis is not welcome in a general hospital. His diagnosis meets the resistance of outmoded attitudes. His illness is still not devoid of some social stigma. Hospital personnel are too apt to associate memories of excitements and unco-operative behavior with psychiatric disorders. To circumvent such conditions, psychiatric patients are admitted daily to general hospitals with nonpsychiatric diagnoses. Bennett<sup>1</sup> reports that in 1940 there were 4302 general hospitals in the United States, more than 90 per cent of which did not permit the admission of a patient with a known psychiatric diagnosis.

In spite of such resistant attitude toward psychiatric patients, some definite progress has been made. Many hospitals offer psychiatric consultation. However, only hospitals with locked pavilions offer any active or complete treatment. Such locked pavilions are few in number and are usually limited

to large hospitals or those associated with teaching institutions. Heldt's<sup>2,3</sup> reports on the psychiatric division of the Henry Ford Hospital were notable and early exceptions. It is of interest that at the Henry Ford Hospital, psychotic patients were admitted even though locked facilities were not available. However, a full-time psychiatric staff cared for these patients.

With the advent of shock therapies, new opportunities for treatment of psychiatric disorders have been offered to the average general hospital. Selected patients, even though suffering from major disorders, can fit into the hospital setting for a reasonable period. Fetterman<sup>4</sup> has emphasized the value and feasibility of treating psychiatric patients in a general hospital. During a recent visit to the Royal Victoria Hospital in Montreal, I was able to view an entire building, the Alan Memorial, devoted to the treatment of neurosis and psychosis without the aid of locked wards. In the Army, small hospitals often had to care for psychotic patients. In civilian medicine the smaller general hospitals have made practically no attempt to care for the psychiatric patient. My experiences in developing a practical degree of psychiatric service in a general hospital of a small city are reported below.

\*From the House of Mercy Hospital.  
†Neurologist and psychiatrist, House of Mercy Hospital, instructor in neurology and psychiatry, Albany Medical College.

The peritoneal cavity was explored through a transverse incision and a tense cystic mass (Fig 1) exposed. This proved to be a thin-walled, unilocular cyst measuring more than 12 by 10 by 5 cm and under tension. Its attachment was immediately proximal to the fimbriated end of the left fallopian tube. There was a little gas and meconium in the large bowel, the small bowel being collapsed and compressed by the mass of the cyst. The cyst was removed intact, and its color changed from a light blue, before removal, to a pinkish yellow after removal. The intestinal tract from stomach to rectosigmoid was examined and considered normal. The wound was closed.

Review of the anesthesia chart revealed an immediate improvement in pulse, color and amplitude of respiration after delivery and removal of the cyst.

The patient's weight at birth was 6 pounds, 6 ounces. Immediately after operation it was 6 pounds, including the dressing. Convalescence was delayed by low serum protein with edema, which was corrected and she was discharged

resembles the fimbriated end of a fallopian tube. There is also noted a nipple of tissue surrounded by a silk suture. On section there is revealed an estimated 150 cc. of clear yellow fluid with the odor of formalin. The inner lining is smooth and glistening with prominent blood-vessel markings, and there are several small cystic nodules opposite the cylindrical structure on the external surface described above. They measure 0.2 to 0.5 cm in diameter and contain a clear yellow fluid. The wall is of uniform thickness throughout.

Microscopical examination revealed two sections stained by hemotoxylin and eosin and two Giemsa-stained sections,

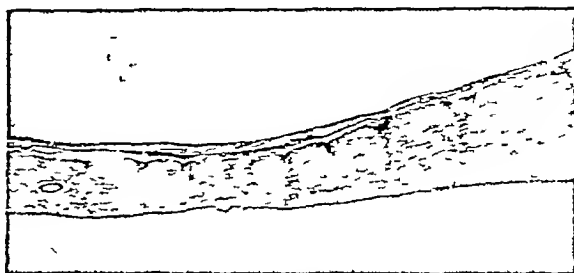


FIGURE 2

which include the fallopian tube and a segment of the cyst wall. The mucosa of the fallopian tube is drawn into its usual folds. The muscularis is moderately cellular and somewhat edematous. The cyst wall is largely composed of fine strands of connective tissue, which are loosely interwoven. The lining of the cyst is composed of from three to eight layers of flattened cells with elongated nuclei resembling fibroblasts, with a moderate number of cells with round tense nuclei resembling granulosa cells. Nowhere in the section is there an evidence of inflammation or neoplasm (Fig 2).

The diagnosis was follicular cyst of ovary and fallopian tube.

The estrogenic assays made in the Fearing Research Laboratory gave the following result: the cyst fluid was found to contain 50 international units of estrogenic activity per cubic centimeter. No ketonic estrogen was demonstrable, 80 per cent of the total activity went into the estradiol fraction. This division of estrogenic material is similar to that found in follicular cysts of the ovary in older persons, which however, contain more estrogenic activity (25 to 450 international units per cubic centimeter).

### SUMMARY

The case of a thirty-four-hour-old infant from whom a gigantic follicular cyst of the ovary was successfully removed is presented.

A report of the histologic examination and assay of contents of the cyst is made.

A review of the literature reveals only 1 case of successful operation in a newborn infant for a similar lesion.

### REFERENCES

1. Doran, A. H. G. Large ovarian tumours in seven months child. *Tr. Path. Soc. London* 40:200-205, 1839.
2. Haines, C. E., and Edgerly, W. S. Torsion of pedicle of ovarian cyst in young children. *W. Rec.* 144:121-125, 1936.
3. Benjamin, D. Torsion of ovarian cysts in children: report of case with recovery. *Am. J. Surg.* 53:500-502, 1941.
4. Bullfomonte, J. C. Large ovarian cyst in newborn child. *Am. J. Surg.* 55:175, 1942.



FIGURE 1

34 days after operation, weighing 7 pounds 4 ounces. In October, 1947, she was considered to be in good condition and developing normally.

The specimen was immediately photographed. It was then covered with gauze, soaked in physiologic saline solution and placed in a container with ice. The specimen was taken to the Fearing Research Laboratory, Free Hospital for Women, Brookline, Massachusetts, where Drs. O. Watkins Smith and George V. Smith were consulted about a possible assay of the cyst fluid. The intact cyst weighed 340 gm. It was aspirated, and approximately 300 cc. of fluid removed for assay. The removed fluid was partially replaced by a solution of formalin, and the needle puncture area was ligated. The specimen was examined in the Department of Pathology, Children's Hospital, Boston. The microscopical slides were reviewed by Drs. George V. Smith and Arthur T. Hertig, who concurred in the microscopical diagnosis made by the Children's Hospital Laboratory.

The pathological report was as follows:

The specimen consists of a roughly spherical fluctuant translucent, formalin-fixed mass weighing 340.7 gm and measuring 12 by 10 by 5 cm. The external surface is smooth and glistening and is mottled purple red in color. Through the wall are seen numerous fine vascular markings. Along one edge there is a tubular structure measuring 2.5 by 3.0 cm. One edge is closed by a silk suture, and the other re-

administration of shock therapy. In all, these changes have brought the economics of a psychiatric disorder close to that of other medical and surgical diseases.

It is recognized that this plan has definite disadvantages. Suicidal attempts are always a potential danger. Fortunately, there have been no such accidents in the hospital. However, there have been three unsuccessful suicidal attempts in patients receiving electric shock therapy on an out-patient basis. It can be seen that the plan often places an unusual responsibility on the family. Inpatients do not have the advantage of a planned occupational-therapy program.

### SUMMARY AND CONCLUSIONS

The general hospital of the smaller cities can offer treatment for psychiatric patients.

A description is given of the development of the program for treatment of psychoneurosis and psy-

choses in the House of Mercy Hospital, Pittsfield, Massachusetts.

A program for psychiatric treatment can be carried out under the supervision of one psychiatrist.

The success of the program is largely dependent on the selection of patients.

Treatment of the psychiatric patient in a general hospital has significant medical, social and economic advantages.

74 North Street

### REFERENCES

1. Bennett, A. E. Psychiatry is good business in general hospital. *Mod Hosp* 67:43-45, 1946.
2. Heldt, T. J. Functioning of division of neuropsychiatry in general hospital. *Am J Psychiat* 74:59-481, 1927.
3. *Idem*. Treatment of mental diseases in general hospital. *Am Inst State J Med* 30:63-71, 1930.
4. Fetterman, J. L. Plan for improving treatment of psychiatric patients in general hospitals. *Dis Nerv Syst* 8:220-225, 1947.

## CLINICAL NOTE

### GIANT OVARIAN CYST IN A NEWBORN INFANT\*

LIEUTENANT WILLIAM I. NEIKIRK (MC), U.S.N.R.,†  
AND  
HENRY W. HUDSON, JR., M.D.‡

OVARIAN cysts producing symptoms in early life are rare, and in the newborn infant almost unknown. Symptoms are almost invariably the result of torsion. Diagnosis is seldom made prior to operation. Doran,<sup>1</sup> in 1888, described the post-mortem appearance of a seven-month premature infant who survived birth by a few minutes as follows:

The abdomen was distended, the subcutaneous veins were prominent. The integuments above the level of the umbilicus were discolored through ecchymosis.

In 1936 Haines and Edgerly<sup>2</sup> made a review and reported cases of cysts being removed for abdominal symptoms but not for symptoms suggesting intestinal obstruction. A similar review was presented by Benjamin<sup>3</sup> in 1941.

In 1942 Bulfamonte<sup>4</sup> described a case quite similar to that reported below.

\*From the Surgical and Pediatric Services, United States Naval Hospital, Chelsea, Massachusetts.

The opinions or assertions contained herein are the private ones of the writers and are not to be construed as official or reflecting the views of the Navy Department or the naval service at large.

†Resident in pediatrics, United States Naval Hospital, Chelsea.

‡Instructor in surgery, Harvard Medical School, associate surgeon, Children's Hospital, Boston; surgeon, Mt. Auburn Hospital, Cambridge; consulting surgeon, United States Naval Hospital, Chelsea.

### CASE REPORT

A female infant was born, at term, on April 22, 1947, at 8:15 a.m. The mother had been greatly impressed by the large amount of amniotic fluid when the membranes ruptured spontaneously 2 hours before birth. She estimated the amount as several times greater than that with any of her previous seven pregnancies. No abnormality of the infant was noted by the two physicians present at delivery, nor by a physician who saw the baby at 10 a.m. because of cyanosis relieved by aspiration of mucus. The infant went to breast 12 hours after delivery and every 4 hours thereafter, and the mother noted that little or nothing was taken and that the infant was continuously spitting "saliva," which at the end of the first 24 hours of life was yellow stained.

On April 23 at 8 a.m. physical examination revealed the abdomen to be markedly distended, and several engorged veins were noted over the upper part. The percussion note was tympanic over the upper abdomen and dull in the flanks and over the lower abdomen. Peristaltic sounds were audible only in the right upper quadrant and faintly in the right flank. No mass was made out, but a sense of increased resistance was observed in the left lower quadrant. No fluid wave was demonstrated. The examiner was unable to introduce his little finger into the anus. No meconium had been passed.

Examination of the blood was not significant except that the white-cell count was 19,100. X-ray examination was reported as showing moderate distention of the stomach and numerous loops of small bowel and parts of the large bowel. These gas-filled loops lay primarily in the right upper quadrant and the right posterior gutter. The left anterior portion of the abdomen was occupied by a fairly homogeneous shadow without any evidence of identifying characteristics. The descending colon and sigmoid contained a small amount of gas. An attempt to outline the large bowel by injection of lipiodol showed only the distal 10 cm. The oil could not be introduced beyond this point, presumably because of a considerable amount of meconium rather than an organic lesion. The general impression was one of almost complete intestinal obstruction, probably resulting from an intrinsic lesion or anomaly of development. Distention increased rapidly, and by 4:30 p.m. was extreme. Cyanosis was noted. The superficial veins of the abdominal wall were greatly dilated. About 1 cm. below the xiphoid a line of demarcation was apparent, below which the skin was dusky, the legs were definitely cyanotic. Venous obstruction and intestinal obstruction seemed evident. A catheter was passed into the stomach, but little or no air obtained. Operation was performed 34 hours after birth. Various diagnoses, all concerned with possible causes of intestinal obstruction, were entertained.

§The possible association of hydramnios and anomalies of the intestinal tract in the fetus is recognized by various authorities.

The peritoneal cavity was explored through a transverse incision and a tense cystic mass (Fig 1) exposed. This proved to be a thin-walled, unilocular cyst measuring more than 12 by 10 by 5 cm and under tension. Its attachment was immediately proximal to the fimbriated end of the left fallopian tube. There was a little gas and meconium in the large bowel, the small bowel being collapsed and compressed by the mass of the cyst. The cyst was removed intact, and its color changed from a light blue, before removal, to a pinkish yellow after removal. The intestinal tract from stomach to rectosigmoid was examined and considered normal. The wound was closed.

Review of the anesthesia chart revealed an immediate improvement in pulse, color and amplitude of respiration after delivery and removal of the cyst.

The patient's weight at birth was 6 pounds, 6 ounces. Immediately after operation it was 6 pounds, including the dressing. Convalescence was delayed by low serum protein with edema, which was corrected, and she was discharged



FIGURE 1

34 days after operation, weighing 7 pounds 4 ounces. In October, 1947, she was considered to be in good condition and developing normally.

The specimen was immediately photographed. It was then covered with gauze, soaked in physiologic saline solution and placed in a container with ice. The specimen was taken to the Fearing Research Laboratory, Free Hospital for Women, Brookline, Massachusetts, where Drs O Watkins Smith and George V Smith were consulted about a possible assay of the cyst fluid. The intact cyst weighed 340 gm. It was aspirated, and approximately 300 cc of fluid removed for assay. The removed fluid was partially replaced by a solution of formalin, and the needle puncture area was ligated. The specimen was examined in the Department of Pathology, Children's Hospital, Boston. The microscopical slides were reviewed by Drs George V Smith and Arthur T Hertig, who concurred in the microscopical diagnosis made by the Children's Hospital Laboratory.

The pathological report was as follows:

The specimen consists of a roughly spherical fluctuant, translucent, formalin-fixed mass weighing 340.7 gm and measuring 12 by 10 by 5 cm. The external surface is smooth and glistening and is mottled purple red in color. Through the wall are seen numerous fine vascular markings. Along one edge there is a tubular structure measuring 2.5 by 3.0 cm. One edge is closed by a silk suture, and the other re-

sembles the fimbriated end of a fallopian tube. There is also noted a nipple of tissue surrounded by a silk suture. On section there is revealed an estimated 150 cc of clear yellow fluid with the odor of formalin. The inner lining is smooth and glistening with prominent blood-vessel markings, and there are several small cystic nodules opposite the cylindrical structure on the external surface described above. They measure 0.2 to 0.5 cm in diameter and contain a clear yellow fluid. The wall is of uniform thickness throughout.

Microscopical examination revealed two sections stained by hemotoxylin and eosin and two Giemsa-stained sections,

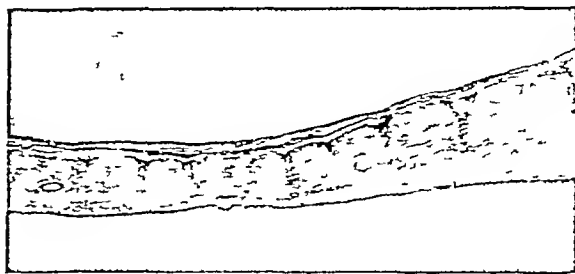


FIGURE 2

which include the fallopian tube and a segment of the cyst wall. The mucosa of the fallopian tube is drawn into its usual folds. The muscularis is moderately cellular and somewhat edematous. The cyst wall is largely composed of fine strands of connective tissue, which are loosely interwoven. The lining of the cyst is composed of from three to eight layers of flattened cells with elongated nuclei resembling fibroblasts, with a moderate number of cells with round, tense nuclei resembling granulosa cells. Nowhere in the section is there an evidence of inflammation or neoplasm (Fig 2).

The diagnosis was follicular cyst of ovary and fallopian tube.

The estrogenic assays made in the Fearing Research Laboratory gave the following result: the cyst fluid was found to contain 50 international units of estrogenic activity per cubic centimeter. No ketonic estrogen was demonstrable, 80 per cent of the total activity went into the estradiol fraction. This division of estrogenic material is similar to that found in follicular cysts of the ovary in older persons, which, however, contain more estrogenic activity (25 to 450 international units per cubic centimeter).

#### SUMMARY

The case of a thirty-four-hour-old infant from whom a gigantic follicular cyst of the ovary was successfully removed is presented.

A report of the histologic examination and assay of contents of the cyst is made.

A review of the literature reveals only 1 case of successful operation in a newborn infant for a similar lesion.

#### REFERENCES

1. Doran, A. H. G. Large ovarian tumours in seven months child. *Tr Path. Soc. London* 40:200-203, 1889.
2. Haines, C. E., and Edgerly, W. S. Torsion of pedicle of ovarian cyst in young children. *N. Rec* 144:121-125, 1936.
3. Benjamin, D. Torsion of ovarian cysts in children: report of case with recovery. *Am. J. Surg* 53:500-502, 1941.
4. Bullamonte, J. C. Large ovarian cyst in newborn child. *Am. J. Surg* 55:175, 1942.

## MEDICAL PROGRESS

## METHEMOGLOBINEMIA AND SULFHEMOGLOBINEMIA\*

CLEMENT A. FINCH, M.D.†

BOSTON

THE appearance of severe cyanosis may alarm the patient and presents a diagnostic problem to the attending physician. Recognition of the cause of the cyanosis and the specific blood pigment involved permits the separation of conditions connoting serious underlying disease from those of benign origin. An increased amount of reduced hemoglobin in cardiac or pulmonary disease is frequently responsible for mild cyanosis. The more intense degrees of cyanosis seen clinically are due to abnormal pigments within the red cell—methemoglobin and sulfhemoglobin. The relative capacity of each of these pigments to produce cyanosis is shown by the fact that about 5 gm. of reduced hemoglobin per 100 cc. of blood is required to produce recognizable cyanosis,<sup>1</sup> whereas 1.5 gm. of methemoglobin and less than 0.5 gm. of sulfhemoglobin have comparable effects. Rarely, cyanosis is produced by intravascular hemolysis with the formation of methemoglobin and methemalbumin<sup>2</sup> in the plasma. In such cases, the associated anemia, hemoglobinuria and side effects of the toxic agent are conspicuous, and the cyanosis is relatively mild. The presence of hemoglobin and its derivatives in the plasma differentiates this group from intracellular cyanosis, although combined reactions may occur. This discussion is limited to abnormal pigments within the red cell that produce cyanosis.

## INTRACELLULAR METHEMOGLOBIN

Hemoglobin iron is normally ferrous, and in its role as an oxygen carrier is oxygenated and de-oxygenated without change in valence. In methemoglobin the iron has been oxidized from the ferrous to the ferric form.<sup>3</sup> The change is an easily reversible one and in itself is not accompanied by any red-cell damage or destruction.<sup>4-7</sup> Methemoglobin is unable to transport oxygen and should therefore be regarded as a pigment that is temporarily inert.

## Identification

When methemoglobinemia is suspected, blood should first be drawn into a tube containing heparin or oxalate and centrifuged. If the plasma is clear, hemolysis and abnormal serum pigments are excluded as a cause of cyanosis. The whole blood may then be shaken in air for fifteen minutes. Nor-

mally, the blood becomes bright red as all pigment is converted to oxyhemoglobin. If it remains dark, abnormal intracellular pigments are present. The blood should then be diluted ten to one hundred times with water and examined with a hand spectroscope. The dark band of methemoglobin is seen at 630 millimicrons (Fig. 1). The band disappears immediately after two or three drops of 5 per cent potassium cyanide are added, differentiating it from the sulfhemoglobin band at 618, which remains fixed.<sup>8,9</sup> The same bands may be seen through the earlobe of the patient. Methemoglobin may be determined quantitatively by gasometric means<sup>10</sup> or colorimetrically.<sup>11</sup> Horecker<sup>12,13</sup> has described its absorption spectrum in the infrared and devised a method for its measurement in this range. In all quantitative determinations in the visible range, the importance of controlling the pH is shown by the spectrophotometric studies of Austin and Drabkin.<sup>14</sup> Blood should be examined within one or two hours of withdrawal since in most cases intracellular methemoglobin on standing spontaneously reverts to the ferrous form.<sup>15</sup>

*Hemoglobin-Methemoglobin Equilibrium of the Erythrocyte*

The relation between hemoglobin and methemoglobin is more clearly understood by a comparison of its equilibrium in three systems—that is, in water, in plasma and within the erythrocyte (Fig. 2). Under aerobic conditions an aqueous hemoglobin solution is progressively converted to methemoglobin. In plasma, free hemoglobin is only partially converted to methemoglobin.<sup>16,17</sup> By means of certain reducing substances the plasma appears to be able to maintain the equilibrium at somewhat over 50 per cent ferrous hemoglobin. In contrast, the normal erythrocyte contains at most only 1 or 2 per cent of methemoglobin.<sup>10,18-20</sup> The question then arises regarding how hemoglobin within the erythrocyte is maintained in the ferrous form.

Although devoid of a nucleus, the red cell energetically reduces methemoglobin by an enzymatic process in which glucose and lactate are the principal substrates.<sup>21-28</sup> The presence of methemoglobin activates this process since the resting oxygen consumption and glucose utilization of the red cell are only slight, whereas in the presence of methemoglobin there is an appreciable

\*From the Medical Clinic, Peter Bent Brigham Hospital, and the Department of Medicine, Harvard Medical School.

†Associate in medicine, Harvard Medical School; associate in medicine, Peter Bent Brigham Hospital.

increase. Methemoglobin offers an available source of oxygen for carbohydrate breakdown and in the process is itself reduced. It appears that hexose monophosphate, reduced pyridine nucleotide and perhaps Kiese's "methemoglobin reductase" are involved in this reduction. Since with lysis of the red cell the phosphorylating mechanism breaks down and pyridine nucleotide is destroyed, the system can operate only in the intact cell. Clinical states of methemoglobinemia can be caused either by dysfunction of this reconversion mechanism, with-

librium between oxidized and reduced hemoglobin within the erythrocyte it would be anticipated that much larger amounts of oxidants would be needed to produce successive increments of methemoglobin. Indeed in animals it is almost impossible

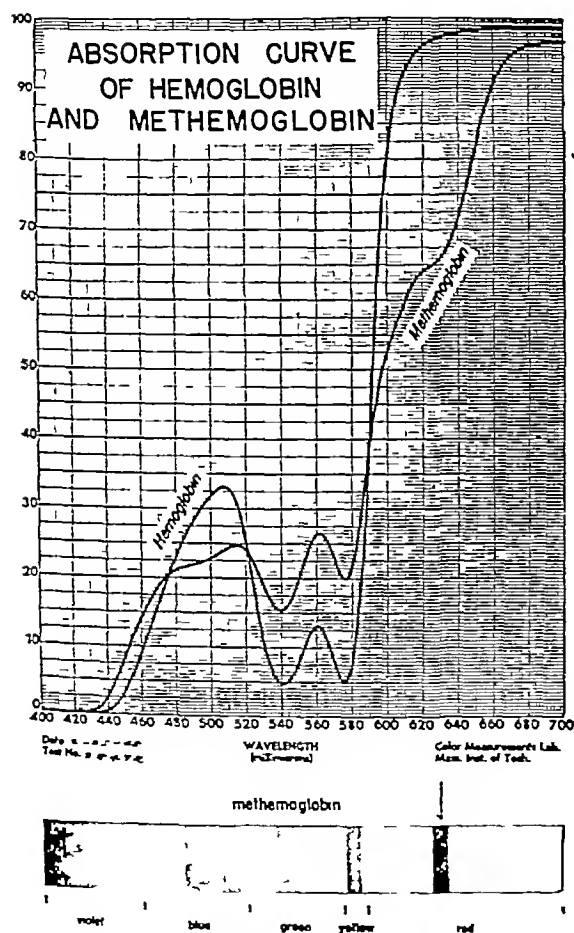


FIGURE 1 Spectrophotometric Absorption of Methemoglobin. In the upper portion the percentage transmission of a solution of oxymethemoglobin is compared with a solution of both methemoglobin and oxymethemoglobin. The decreased transmission (or increased light absorption) of the methemoglobin solution at 500 and 630 millimicrons is evident. Below is a spectrum as visualized through a hand spectroscop (adjusted to the wavelength-scale above) in which the typical band of methemoglobin in the red is shown by an arrow.

out which circulating hemoglobin would be at the mercy of the plasma oxidation-reduction potential, or by the action of oxidants which produce methemoglobin more rapidly than the cell mechanism is able to reduce it (Fig 2). With the existing equi-

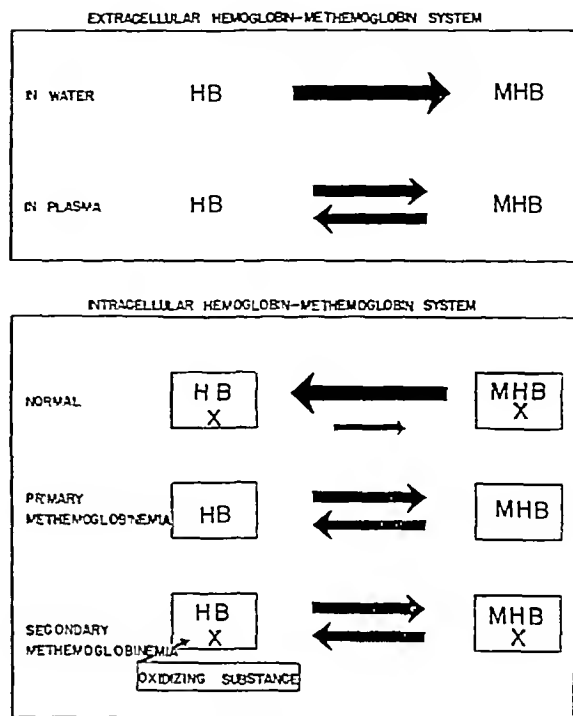


FIGURE 2 Hemoglobin (HB) and Methemoglobin (MHB) Equilibria

X represents the normal-functioning methemoglobin reconversion system of the erythrocyte. The arrows designate the nature of the equilibria under different conditions. Blood hemolyzed in water is progressively and completely converted to methemoglobin. It is apparent that in respect to the hemoglobin-methemoglobin equilibrium the red cell in congenital methemoglobinemia is similar to hemoglobin suspended in plasma. In both methemoglobin is found in amounts slightly below 50 per cent. Although the red-cell mechanism (X) maintains a ratio of about 99 HB/MHB, oxidizing substances may temporarily displace this equilibrium.

to displace this equilibrium to the lethal point with certain aniline derivatives<sup>29-31</sup>

### Physiologic Effects of Methemoglobinemia

Symptoms from methemoglobinemia are attributable to the anoxia produced by the lowered oxygen capacity of the blood or to side effects of the agent producing methemoglobinemia. At concentrations of 20 per cent methemoglobin, working subjects complained of mild fatigue and showed abnormally high blood lactic acid levels.<sup>32</sup> In dogs with methemoglobin concentrations over 40 per cent, a compensatory increase in cardiac output has been observed.<sup>33</sup> A shift in the oxygen dissociation curve to the left has been shown to occur in

drug-induced methemoglobinemia, seriously handicapping the unloading of oxygen in the tissues<sup>24, 25</sup> Despite this, levels of 30 to 50 per cent methemoglobin may occur without producing severe symptoms.<sup>5</sup> The lethal concentration of methemoglobin in dogs is about 85 to 90 per cent.<sup>36</sup> The exact level at which coma and death supervene in man is not known.

### Treatment of Methemoglobinemia

Methemoglobin in the body may be reconverted to hemoglobin by reducing substances, by the nor-

role in red-cell metabolism was the observation of Harrop and Barron<sup>40</sup> that red-cell respiration and carbohydrate utilization are increased greatly by methylene blue. In tissue respiration methylene blue is able to substitute for the cytochrome enzymes. Mammalian red cells lack these enzymes. Since the dye accelerates red-cell respiration and methemoglobin reduction to a state comparable to that found in nucleated avian erythrocytes, it may be postulated that it acts as a more efficient oxidation-reduction transport system than that present in the mammalian erythrocyte. Methylene blue reverts methemoglobin at a rate far greater than that of the normal cell mechanism, as shown in Figure 3.<sup>39, 41-43</sup>

The misleading statement is sometimes made that methylene blue may either reduce methemoglobin or produce it depending on the dose employed. However, over a dosage range of a fraction of a milligram to 10 mg per kilogram of patient's body weight, methylene blue acts to revert methemoglobin to hemoglobin and *clinically significant amounts of methemoglobin are not produced*.<sup>44-46</sup> Doses of 500 mg administered intravenously during ten minutes in man have produced symptoms of nausea, precordial and abdominal pain, dizziness and headache, and mental confusion for as long as twelve hours.<sup>47</sup> Larger doses up to 7 gm administered slowly have been given without symptoms but have produced anemia in man.<sup>46</sup> Still larger doses in animals have produced hemolytic anemia, pulmonary edema and death.<sup>48, 49</sup> In the usual therapeutic dose of 1 or 2 mg per kilogram of body weight, given over a five-minute period, however, no such reactions have been reported.

Specific treatment for methemoglobinemia has been discussed elsewhere.<sup>39</sup> After the pigment has been identified, 1 mg of methylene blue per kilogram of body weight in adults and 2 mg in infants may be injected intravenously slowly over a period of five minutes.\* If cyanosis has not disappeared within an hour, a second dose of 2 mg per kilogram of body weight should be given. Methylene blue may also be given orally in doses of 3 to 5 mg per kilogram.

### CLINICAL METHEMOGLOBINEMIA

#### Primary Methemoglobinemia

In the literature at least 16 established cases of congenital methemoglobinemia have been reported,<sup>50-61</sup> in 8 of which there was a familial incidence. In 5 other cases information regarding the congenital aspect was incomplete.<sup>62-65</sup> Symptoms consisting of fatigue, exertional headaches and reduced exercise tolerance are surprisingly mild. I have seen 1 patient with a methemoglobin level of 40 per cent who was able to indulge in strenuous

\*For intravenous injection 1 per cent solutions are prepared by Parke Davis and Co. and by William H. Rover Incorporated. The usual adult dose is 7 cc.

### RATE OF METHEMOGLOBIN REVERSION

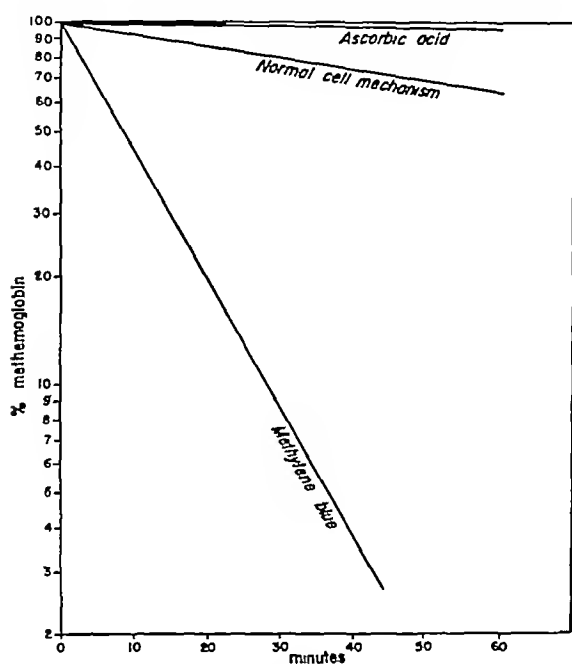


FIGURE 3 Various Reversion Rates Calculated from Data Presented Elsewhere.<sup>39</sup>

The ordinant represents the percentage of the initial level of methemoglobin, usually between 2 and 5 gm per 100 cc in the patients studied.

mal cell-reconversion mechanism or by catalysis of this normal mechanism.

Ascorbic acid<sup>27</sup> and glutathione<sup>28</sup> are effective as reducing agents, although the only one used clinically has been ascorbic acid. This substance reduces methemoglobin slowly in vivo and even in large doses does not approach the speed of the normal cell-reconversion system.<sup>39</sup> This material is of little value, therefore, in conditions in which the normal cell-reconversion mechanism may have been exceeded—that is, in secondary methemoglobinemia (Fig. 3).

Methylene blue brings about reversion of methemoglobin not by its own reduction capacity but through acceleration of the normal cell-reconversion mechanism. Perhaps the first suggestion of its

activity without symptoms. This remarkable tolerance to methemoglobinemia may be explained by its chronicity by the secondary polycythemia compensating for inert pigment and by the normal oxygen-dissociation curve in contrast to secondary methemoglobinemia.<sup>5</sup> Reports indicate that without treatment the majority of these patients tend to reach equilibrium at about 40 per cent methemoglobinemia.

In blood drawn from these patients, methemoglobin shows no tendency to revert to hemoglobin spontaneously. The biochemical lesion, a failure of the normal reconversion mechanism, represents a congenital defect of the erythrocyte. Methemoglobin accumulates slowly until a point of equilibrium is reached. In 1 patient studied it was produced at the rate of 3 per cent of the total pigment a day.<sup>5</sup> The ascorbic acid of the serum is decreased in these patients despite adequate diets,<sup>55-59-61</sup> and the plasma has little or no capacity to reduce methemoglobin.<sup>60</sup> This suggests that reducing substances are being expended in the reduction of methemoglobin to hemoglobin. These reducing substances may be regarded as a secondary line of defense of the body against pigment oxidation. Patients may be adequately treated with either ascorbic acid or methylene blue. Lian<sup>55</sup> first described the efficacy of ascorbic acid in congenital methemoglobinemia, and this has been verified by others.<sup>5, 56, 59-61</sup> In doses of 100 to 500 mg a day by mouth the methemoglobin levels are reduced to 8 to 10 per cent of the total pigment. This might be anticipated since the rate of reconversion by ascorbic acid is considerably greater than the spontaneous methemoglobin accumulation in these patients.<sup>39</sup> Methylene blue is likewise effective in a daily dosage of 100 to 300 mg by mouth.<sup>5</sup>

Secondary Methemoglobinemia

*That due to drugs.* Certain drugs or their degradation products have the capacity of converting hemoglobin to methemoglobin. These drugs preferentially oxidize hemoglobin, and reducing substances in the body such as glutathione and ascorbic acid offer no protection against this oxidation.<sup>66</sup> Some of these drugs are listed in Table I. It seems probable that the amino and nitro groups of these compounds are responsible for the methemoglobinemia. Nitrites, sulfonamides and aniline derivatives are perhaps the most important drugs in the production of methemoglobinemia.

Nitrites produce methemoglobin rapidly and quantitatively within limits when studied in vitro or in vivo, although the exact chemical interaction is not clear.<sup>78</sup> The many ways in which nitrites gain access to the blood stream have presented numerous clinical problems. Cyanosis may be produced by excessive use of amyl nitrite or nitroglycerin, or by inhalation of nitrous gases as reported in arc welders.<sup>79</sup> Ingested nitrates may be converted to

nitrites by intestinal bacteria, and, after absorption from the intestine produce methemoglobin. Cases have been reported in infants drinking well water that had high concentration of nitrates,<sup>80-82</sup> from the use of bismuth subnitrates in the treatment of diarrhea,<sup>83, 84</sup> from ammonium nitrate used as a diuretic<sup>85</sup> and from food high in nitrates.<sup>86</sup> Methemoglobin is especially prone to occur after nitrate ingestion in patients with ulcerative lesions of the bowel.

Sulfonamides — particularly sulfanilamide, but also prontosil, sulfathiazole and sulfapyridine — frequently produce both methemoglobin and sulfhemoglobin.<sup>87-94</sup> No report has been found of this

TABLE I *Amino and Nitro Compounds Producing Methemoglobinemia\**

AROMATIC DRUGS	ALIPHATIC AND INORGANIC DRUGS
Aniline	Sodium nitrite
Anilinoethanol	Hydroxylamine
Phenacetin	Dimethylamine
Acetanilid	Nitroglycerin
Methylacetanilide	Amyl nitrite
Hydroxylacetanilide	Ethyl nitrite
Prontosil	Bismuth subnitrate
Sulfanilamide	Ammonium nitrate
Sulfapyridine	
Sulfathiazole	
Phenylenediamine	
Aminophenol	
Toluenediamine	
Alphanaphthylamine	
Paraminopropiophenone	
Phenylhydroxylamine	
Tolylhydroxylamine	
Nitrobenzene	
Dinitrobenzene	
Trinitrotoluene	
Nitrosobenzene	
Paranitraniline	

\*Based on various reports in the literature.<sup>39, 40, 41</sup>

type of cyanosis due to sulfadiazine or sulfamerazine. Rimington and Hemmings<sup>95</sup> have attempted to correlate the porphyrinuric action of these drugs with their methemoglobin production capacity.

Aniline dyes are particularly dangerous because of their ability to penetrate the intact skin,<sup>96-99</sup> producing methemoglobinemia through the action of breakdown products — that is, phenylhydroxylamine and aminophenol. Contact with dyed blankets, laundry marks on diapers and freshly dyed shoes has produced methemoglobinemia. A single washing of the dyed article will prevent this. Recently several cases of methemoglobinemia have been observed in children swallowing colored crayons.<sup>100</sup> Owing to their extensive use phenacetin and acetanilid are two of the more common drugs producing methemoglobinemia.<sup>101</sup>

Associated red-cell damage varies considerably from one drug to another and even with the same drug from one patient to another. The over-all picture is best represented as a spectrum with methemoglobin formation at one end and extensive red-cell destruction at the other. Nitrites cause chiefly methemoglobinemia although Heinz bodies and anemia have been described in chronic poison-

drug-induced methemoglobinemia, seriously handicapping the unloading of oxygen in the tissues<sup>34, 35</sup> Despite this, levels of 30 to 50 per cent methemoglobin may occur without producing severe symptoms.<sup>5</sup> The lethal concentration of methemoglobin in dogs is about 85 to 90 per cent.<sup>36</sup> The exact level at which coma and death supervene in man is not known.

### Treatment of Methemoglobinemia

Methemoglobin in the body may be reconverted to hemoglobin by reducing substances, by the nor-

role in red-cell metabolism was the observation of Harrop and Barron<sup>40</sup> that red-cell respiration and carbohydrate utilization are increased greatly by methylene blue. In tissue respiration methylene blue is able to substitute for the cytochrome enzymes. Mammalian red cells lack these enzymes. Since the dye accelerates red-cell respiration and methemoglobin reduction to a state comparable to that found in nucleated avian erythrocytes, it may be postulated that it acts as a more efficient oxidation-reduction transport system than that present in the mammalian erythrocyte. Methylene blue reverts methemoglobin at a rate far greater than that of the normal cell mechanism, as shown in Figure 3.<sup>39, 41-43</sup>

The misleading statement is sometimes made that methylene blue may either reduce methemoglobin or produce it depending on the dose employed. However, over a dosage range of a fraction of a milligram to 10 mg per kilogram of patient's body weight, methylene blue acts to revert methemoglobin to hemoglobin and *clinically significant amounts of methemoglobin are not produced*<sup>44-46</sup> Doses of 500 mg administered intravenously during ten minutes in man have produced symptoms of nausea, precordial and abdominal pain, dizziness and headache, and mental confusion for as long as twelve hours.<sup>47</sup> Larger doses up to 7 gm administered slowly have been given without symptoms but have produced anemia in man.<sup>48</sup> Still larger doses in animals have produced hemolytic anemia, pulmonary edema and death.<sup>48, 49</sup> In the usual therapeutic dose of 1 or 2 mg per kilogram of body weight, given over a five-minute period, however, no such reactions have been reported.

Specific treatment for methemoglobinemia has been discussed elsewhere.<sup>39</sup> After the pigment has been identified, 1 mg of methylene blue per kilogram of body weight in adults and 2 mg in infants may be injected intravenously slowly over a period of five minutes.\* If cyanosis has not disappeared within an hour, a second dose of 2 mg per kilogram of body weight should be given. Methylene blue may also be given orally in doses of 3 to 5 mg per kilogram.

### CLINICAL METHEMOGLOBINEMIA

#### Primary Methemoglobinemia

In the literature at least 16 established cases of congenital methemoglobinemia have been reported,<sup>50-61</sup> in 8 of which there was a familial incidence. In 5 other cases information regarding the congenital aspect was incomplete.<sup>62-66</sup> Symptoms consisting of fatigue, exertional headaches and reduced exercise tolerance are surprisingly mild. I have seen 1 patient with a methemoglobin level of 40 per cent who was able to indulge in strenuous

### RATE OF METHEMOGLOBIN REVERSION

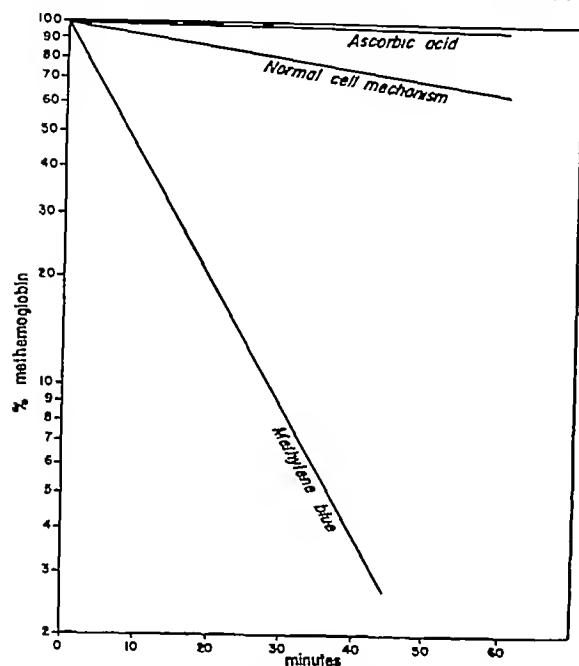


FIGURE 3 Various Reversion Rates Calculated from Data Presented Elsewhere<sup>39</sup>

The ordinant represents the percentage of the initial level of methemoglobin, usually between 2 and 5 gm per 100 cc in the patients studied.

mal cell-reconversion mechanism or by catalysis of this normal mechanism.

Ascorbic acid<sup>37</sup> and glutathione<sup>38</sup> are effective as reducing agents, although the only one used clinically has been ascorbic acid. This substance reduces methemoglobin slowly in vivo and even in large doses does not approach the speed of the normal cell-reconversion system.<sup>39</sup> This material is of little value, therefore, in conditions in which the normal cell-reconversion mechanism may have been exceeded—that is, in secondary methemoglobinemia (Fig. 3).

Methylene blue brings about reversion of methemoglobin not by its own reduction capacity but through acceleration of the normal cell-reconversion mechanism. Perhaps the first suggestion of its

\*For intravenous injection 1 per cent solutions are prepared by Parke Davis and Co. and by William H. Rorer, Incorporated. The usual adult dose is 7 cc.

excreted<sup>25</sup> Inhalation of amyl nitrite is even more rapid in its antidotal action

### SULFHEMOGLOBINEMIA

Sulfhemoglobin is an abnormal pigment, not found in the body under ordinary circumstances. It exists exclusively inside the red cell except in cases of sulfhemoglobinemia with associated hemolysis.<sup>115</sup> The exact nature of sulfhemoglobin is unknown, but available evidence indicates that there is a closed porphyrin ring with no increase in easily split iron.<sup>126</sup> It is to be distinguished from choleglobins.<sup>127</sup> The latter are open ring structures and a biproduct of sulfhemoglobin formation by hydrogen sulfide *in vitro*. They have not been demonstrated in man. It is possible that the transformation to sulfhemoglobin is the result of displacement of one of the N atoms in the pyrrole ring by sulfur.<sup>128</sup> Although it has not been prepared in pure form, its spectrum shows a strong band at 618 (Fig. 4), which has been the basis of spectroscopic and colorimetric methods of identification.<sup>8, 11, 129</sup> It can be qualitatively identified with a hand spectroscope since its band is unaffected by potassium cyanide, but is dispersed by hydrogen peroxide.<sup>2, 8, 9</sup>

The formation of sulfhemoglobin does not indicate cell damage, but does represent an irreversible change in hemoglobin pigment. In workers who became cyanotic from exposure to trinitrotoluene, the disappearance of sulfhemoglobin was identical to the disappearance rate of transfused normal erythrocytes as determined by Ashby counts.<sup>130</sup> The life span of the involved cells was not altered. Thus, whereas methemoglobin due to drugs rapidly reverts, sulfhemoglobinemia is a stable compound cleared from the blood over as long as three or four months. Although hemoglobin is rendered inert as an oxygen carrier, it seems unlikely that sufficient amounts of sulfhemoglobin are ever produced clinically to endanger the life of the patient.

### CLINICAL SULFHEMOGLOBINEMIA

#### That Due to Drugs

Drugs causing sulfhemoglobinemia include the group described above as methemoglobin producers (Table 1). There are frequent reports of its production by the earlier sulfonamide derivatives,<sup>91</sup> by phenacetin and acetanilid<sup>101</sup> and by aniline.<sup>97</sup> Oxidizing agents, such as phenylhydrazine, hydroxylamine and paraminophenol, catalyze the production of sulfhemoglobin *in vitro*.<sup>8</sup> Similarly, the clinical conditions necessary to produce sulfhemoglobin are an oxidizing drug and either constipation or a sulfur-containing medication.<sup>131</sup> It should not be inferred that methemoglobin is an intermediary leading to sulfhemoglobinemia, since cases of congenital methemoglobinemia have not had sulfhemoglobinemia. Once formed, there is no way to rid the blood stream of sulfhemoglobin other than by actually removing blood. Treatment consists

of removing the drug and intestinal conditions causing the disorder.

#### Enterogenous Sulfhemoglobinemia

In reviewing cases of enterogenous cyanosis, one is impressed by the greater frequency of cases of sulfhemoglobinemia<sup>115, 132-142</sup> and by the predominance of constipation in these patients as compared

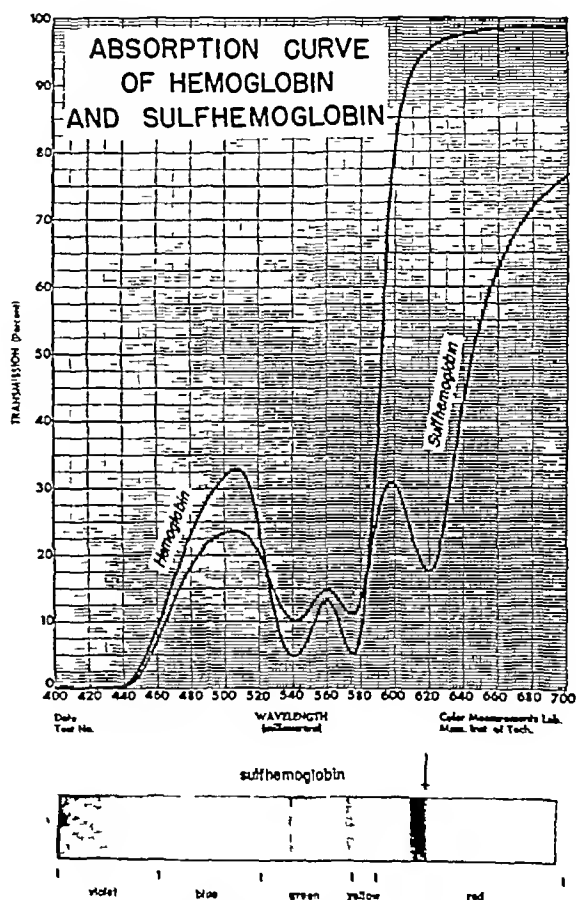


FIGURE 4 Spectrophotometric Absorption of Sulfhemoglobin

In the upper portion the percentage transmission of a solution of oxyhemoglobin is compared with that of a solution of sulfhemoglobin and hemoglobin. There is a strong absorption of the sulfhemoglobin solution at 620 millimicrons. The greater intensity of sulfhemoglobin is seen by a comparison with Figure 1. Both solutions had approximately the same amount of abnormal pigment. The absorption band of sulfhemoglobin in the red of the spectrum as seen in the hand spectroscope is shown below.

with diarrhea in patients with enterogenous methemoglobinemia. The importance of disturbed bowel function is well shown by the case of a nine-year-old boy reported by van den Bergh<sup>110</sup> with a rectal stricture and cyanosis for two years. After operation with relief of the obstruction the cyanosis disappeared. Symptoms are identical to those with enterogenous methemoglobinemia, the only clinical differentiation being the much slower rate of dis-

ing Phenylhydrazine, on the other hand acts in vivo to produce only red-cell destruction. Some drugs, — for example, the sulfonamides, — which produce predominantly methemoglobinemia, on some occasions cause extensive cell destruction.<sup>102, 103</sup> Drugs such as potassium chlorate and arsine<sup>104</sup> produce massive hemolysis but also methemoglobinemia. It appears that methemoglobin formation secondary to drugs may be regarded as a mild and reversible form of cell injury and that more severe cell damage frequently occurs and should always be looked for.

The rapidity of methemoglobin production of these various drugs is dependent upon their metabolism within the body and on their excretion. Although the effect of intravenous nitrite is expended within an hour nitrobenzene does not produce its maximum effect for twelve to fifteen hours.<sup>105</sup> The duration of action of the drug is of importance in anticipating the duration of the methemoglobinemia produced. As pointed out above, the reversion mechanism of the erythrocyte will, within a few hours, convert methemoglobin back to hemoglobin unless there is some oxidant acting in the opposing direction.

In drug-induced methemoglobinemia, the capacity of the normal red-cell reconversion mechanism may be assumed to have been exceeded, and substances that act less rapidly than this normal mechanism, as ascorbic acid does, have no place in its therapy (Fig 3).<sup>39, 43</sup> On the other hand, methylene blue is extremely effective as evidenced by numerous reports in the literature.<sup>42, 43, 91, 106</sup> Should the cyanosis not respond to methylene blue, one must suspect either that a large quantity of oxidizing substance is present, which is still able to displace the equilibrium despite the action of methylene blue, or that some other pigment, such as sulfhemoglobin is present. It has been suggested, on the basis of observations in vitro, that in some cases methemoglobin may be produced indirectly by drugs through the destruction of erythrocyte catalase, thus rendering the erythrocyte vulnerable to oxidation.<sup>107</sup> This awaits clinical verification.

#### *Enterogenous Methemoglobinemia*

Since the reports of Stokvis<sup>108</sup> and Talma<sup>109</sup> in 1902, the term enterogenous cyanosis has appeared repeatedly in the literature. Some justification for the acceptance of this as a clinical syndrome is the similarity of the case reports.<sup>110-114</sup> The patients usually have abdominal pain with diarrhea, or constipation. There are attacks of slate-blue cyanosis accompanied by headache, often shortness of breath, dizziness, collapse and syncope, van den Bergh<sup>111</sup> demonstrated nitrite-producing bacteria in the stools and nitrites in the blood of such patients. It was postulated that because of the gastrointestinal disease, there was an abnormal pro-

duction and absorption of nitrites. As pointed out by van Lier,<sup>52</sup> however, many of these patients were taking aniline derivatives for headache, and, at the time of these early reports, the capacity of these drugs to produce methemoglobinemia was not appreciated. Certainly, some of the cases may have been due to drugs, the intestinal lesions being contributory but not causative.<sup>52, 115-117</sup> In contrast to primary methemoglobinemia, anemia is frequently present in this group, and indicanuria is found. Van den Bergh noted an increase in cyanosis shortly after meals and suggested a milk diet and enemas, which resulted in improvement in several cases. Under the heading of enterogenous cyanosis cases have been reported of both methemoglobinemia and sulfhemoglobinemia, often not distinguished spectroscopically in the reports. It seems likely that the two occur together more often than reports indicate.<sup>112, 114</sup> For convenience, enterogenous methemoglobinemia and enterogenous sulfhemoglobinemia are discussed separately in this paper. It will be apparent, however, that their separation is artificial. It is not difficult to distinguish the two pigments in detailed case reports, since methemoglobin is quickly reverted to normal and therefore shows a rapidly changing blood level whereas sulfhemoglobin gradually disappears from the circulating blood over a period of two or three months.

#### *Methemoglobinemia and Hemolytic Anemia*

Two cases that have recently been observed showed both acquired hemolytic anemia and intracellular methemoglobinemia.<sup>116, 119</sup> The absence of gastrointestinal disease and of drug intake excludes the types of secondary methemoglobinemia mentioned above. The patients' erythrocytes also functioned normally in reverting methemoglobin. Although no cause has been discovered, it is conceivable that some endogenous substance is responsible for both oxidation of the hemoglobin and red-cell destruction.

#### *Therapeutic Use of Methemoglobin*

Methemoglobin is of no value in carbon monoxide poisoning but is useful in combating cyanide. Cyanide produces paralysis of tissue respiration by combining with cytochromes. It is possible to reduce its toxicity by the production of methemoglobin, for which cyanide has an even greater affinity. When methemoglobin is produced prophylactically, animals are protected against several times the lethal dose of cyanide.<sup>120-122</sup> Even when given after exposure to cyanide, methemoglobin may successfully compete with the ferricytochrome oxidase for the cyanide ion.<sup>124</sup> The usual therapeutic regime consists of 0.5 gm of sodium nitrite intravenously over five to ten minutes, followed by 25 gm of sodium thiosulfate intravenously for ten minutes. The latter combines with the cyanide to form thiocyanate, which is relatively nontoxic and is

53. Lian C, Framusan P and Sassier Methemoglobinemia congenitale et familiale. Action favorable de l'acide ascorbique. *Bull et Ann Soc med d Hop de Paris* 2:1194-1203 1939
56. Denny J, Murdoch, E T and Rogan J J Familial idiopathic methaemoglobinemia with note on treatment of two cases with ascorbic acid. *Brit M J* 1:721-725 1945
57. King E, J Gilchrist M. and White J C. Case of methaemoglobinemia. *Biochem J* 38:1111 1944
58. Graybiel A, Lilienthal J L, Jr. and Riley R L. Report of case of idiopathic congenital (and probably familial) methemoglobinemia. *Bull Johns Hopkins Hosp* 76:155-162 1945
59. Barcroft H, Gibson Q H, Harrison D C., and McMurray J. Familial idiopathic methaemoglobinemia and its treatment with ascorbic acid. *Clin Sci* 5:145-157 1945
60. Sievers R. F. and Ryon J B. Congenital idiopathic methemoglobinemia favorable response to ascorbic acid therapy. *Arch Int Med* 76:299-307 1945
61. King E J, White J C. and Gilchrist, M. Case of methaemoglobinemia treated by ascorbic acid and methylene blue. *J Path & Bact.* 59:181-188 1947
62. Slosse A. and Wybauw R. Un cas de methemoglobinemie idiopathique. *Ann et Bull Soc roy d sc med et nat de Brux* 70:205-214 1912
63. Litarczek G, Aubert H, Cosmulesco I, Comanescu A. and Litarczek S. Sur un cas de cyanose autotoxique par methemoglobinemie intraglobulaire. *Sarg* 4:185-202 1950
64. Leiner G., and Vinibek H. Ein Fall von intraglobularer Methaemoglobinämie. *Wochschr* 48:1347 1955
65. Beasley E H, Rhea L J. and Mills E S. Familial idiopathic methaemoglobinemia. *Quart J Med* N S 7:525-530 1958
66. Floren W. and Heite H J. Über die Wirkung methämoglobinbildender Gifte auf einige körpereigene reduzierende Stoffe. *Arch f exper Path u Pharmacol* 197:338-352 1941
67. Pulna B. Studien über Methämoglobinbildung. VII. Wirkungen von Salpeter und Salpeterminerale auf das Blut. *Arch f exper path u Pharmacol* 200:324-334 1942
68. Anderson A. Acute paratraniline poisoning. *Brit J Indust Med* 3:245 1946
69. Bannon J H, Escher D J W. and Balrelander M. Effect of continuous administration of p-aminopropiophenone on blood in man. *Federation Proc* 5:5 1946
70. Jung F. Studien über Methämoglobinbildung der Kreisprozess Phenylhydroxylamin-Nitrosobenzol. *Arch f exper Path. u Pharmacol* 195:208-217 1940
71. Knaz, G. Studien über Methämoglobinbildung. VIII. Vergiftung von Meerschweinchen mit m-Dinitrobenzol. *Arch f exper Path u Pharmacol* 199:508-520 1942
72. Leoder S D. Nitrobenzene poisoning: report of unusual case in child. *Arch Pediat* 49:245-250 1952
73. Von Ischutz, B. Jr. Studien über Methämoglobinbildung. VI. Mitteilung. *Arch f exper Path u Pharmacol* 193:351-356 1939
74. Duvour M. and Goldberg R. La methemoglobine et les poisons methemoglobinisants. *Paris med* 73:561-566 1929
75. Petersen C. Studien über Methämoglobinbildung. VI. Ortho-Aminophenol und Nitrosobenzol. *Arch f exper Path u Pharmacol* 198:675-682 1941
76. Lester D. Formation of methemoglobin II. Repeated administration of acetanilide and acetophenone. *J Pharmacol & Exper Therap* 77:160-164 1943
77. Bass A D, Frost L H. and Salter W T. 2-Aminioethanol — industrial hazard production of methemoglobin. *J A M A* 123:761-763 1945
78. Greenberg L A, Lester D. and Haggard H W. Reaction of hemoglobin with nitrate. *J Biol Chem* 151:665-671 1945
79. McCord C. P. Harold G C. and Meek S F. Chemical and physiological investigation of electric arc welding fumes. Coated welding rods. *J Indust Hyg & Toxicol* 23:200-215 1941
80. Faucett R L. and Miller H C. Methemoglobinemia occurring in infants fed milk diluted with well water of high nitrate content. *J Pediat* 29:595-596 1946
81. Medovy H, Guest W C. and Victor M. Cyanosis in infants in rural areas (well-water methaemoglobinemia). *Canad M J* 55:508-508 1947
82. Comley H H. Cyanosis in infants caused by nitrates in well water. *J A M A* 129:112-116 1945
83. Roe H E. Methemoglobinemia following administration of bismuth subnitrate: report of fatal case. *J A M A* 100:523-524 1951
84. Miller G E. Bismuth subnitrate poisoning with methemoglobinemia: report of case in diabetic. *Gastroenterology* 4:430-434 1945
85. Tarr L. Transient methemoglobinemia due to ammonium nitrate. *Arch Int Med* 51:38-44 1933
86. Riggs C W. Nitrite poisoning from ingestion of plants high in nitrate. *Am J Vet Research* 6:194-197 1945
87. Vigness I, Watton C J. and Spink W W. Relation of methemoglobin to cyanosis observed after sulfanilamide administration. *J Clin Investigation* 19:83-87 1940
88. Carey B W. and Wilson J L. Methemoglobinemia following sulfanilamide and sulfapyridine therapy in infants and children. *J Pediat* 17:38-43 1940
89. Hartmann A F, Perley A M. and Barnett H L. Study of some of physiological effects of sulfanilamide. II. Methemoglobin formation and its control. *J Clin Investigation* 17:699-710 1938
90. Bensley E. H. and Ross J B. Methaemoglobinemia due to sulphanilamide therapy. *Canad M J* 37:62-64 1937
91. Harris J S. and Michel H O. Formation of methemoglobin and sulfhemoglobin during sulfanilamide therapy. *J Clin Investigation* 18:507-519 1939
92. Wendel W B, Wendel N M. and Cox, W W. Methemoglobin as principal abnormal pigment in blood of humans showing cyanosis from sulfanilamide. *J Biol Chem* 131:177-185 1939
93. Campbell D. and Morgan T. Cyanosis caused by sulphonamide compounds. *Lancet* 2:123-127 1939
94. Fox, C L. and Ching J E. Occurrence of methemoglobinemia during sulfanilamide therapy. *J Clin Investigation* 19:123-127 1940
95. Remington C. and Hemmings A W. Porphyrinogenic action of drugs related to sulphanilamide: comparison with reported toxicity therapeutic efficiency and causation of methaemoglobinemia: definition of structure responsible for porphyrinogenic action. *Biochem J* 33:960-977 1939
96. Graubarth J, Bloom C J, Coleman F C. and Solomon H. Dye poisoning in nursery: review of seventeen cases. *J A M A* 128:1155-1157 1945
97. Gley P. Action sur le sang des derives de l'aniline (Methemoglobinemie et sulfhemoglobinemie). *Bull Acad de med Paris* 118:577-582 1937
98. Weinberg A A. Aniline poisoning in newborn with report of 15 cases. *Am J Obst & Gynec* 21:104-108 1951
99. Venland W. Über Vergiftungen von Säuglingen und Kindern durch Methämoglobinbildende Substanzen (Anilin Naphthalin usw.). *Med Klin* 17:905-905 1921
100. Mall F. Unpublished data
101. Gross M. *Aetiology of a critical bibliographic review* 155 pp. New Haven: Hillhouse Press 1936. Pp 25-58
102. Moeschlin S. Innenkörper-Anämien durch Entstehung von Methämoglobin infolge Drogen-Wirkung (Sulfiapyridin). *Schweiz med Wochenschr* 21:786-790 1940
103. Goldbloom A A, Greenwald L. and Reinstein H. Toxic reactions to sulfapyridine: acute hemolytic anemia, leucocytoid reaction and purpura in 3 separate cases. *J Lab & Clin Med* 27:139-147 1941
104. Kensler C J, Abels J C. and Rhoads C P. Arsine poisoning: mode of action and treatment. *J Pharmacol & Exper Therap* 88:99-108 1946
105. Cox, W W. and Wendel W B. Normal rate of reduction of methemoglobin in dogs. *J Biol Chem* 143:341-340 1942
106. Zierz, P. Zur Therapie der Sulfonamidcyanosen. *Med Klin* 36:1022 1940
107. Seide G. Über die Wirkung von Blutgiften auf die Katalase. *Biochem Zuehr* 308:175-186 1941
108. Stokvis, Zur Casus der Autotoxischen Enterogenen Cyanosen (Methaemoglobinemia (?) et Enterus Parasitana). *Internat Britte z inn Med.* 1:597-613 1902
109. Tajima S. Intraglobuläre Methämoglobinämie beim Menschen. *Beiträger klin Wochenschr* 37:863-867 1902
110. van den Bergh A A H. Enterogene Cyanose. *Deutsches Arch f klin Med* 83:86-106 1905
111. van den Bergh A A H. and Gruttenink, A. Enterogene Cyanose. *Beiträger klin Wochenschr* 43:7-10 1906
112. Waterfield R L. Alternation and subsequent combination of methaemoglobinemia and sulfhemoglobinemia in one patient. *Gus Hosp Rep* 8:265-274 1928
113. Dunaevsky M I. and Kozlovskaya M P. Case of autotoxic methemoglobinemia. *Frank delo* 22:367-370 1940
114. Henstell H. H. and Dameshek, W. Enterogenous cyanosis with methemoglobin and sulfhemoglobinemia: clinical and spectrophotometric studies. *J Clin Investigation* 15:464 1936
115. Giordano C. and Vichani E. C. Sulfhemoglobinemia. *Arch per le sc med* 64:137-220 1937
116. Miller R. C. Methemoglobinemia occurring in case of chronic ulcerative colitis. *Proc Staff Meet. Ma v Clin* 19:308-311 1944
117. Traxler P S. Methemoglobinemia or enterogenous cyanosis. *M Bull Int Adm* 20:227 1945
118. Enzer N. Eder H. and Finch C A. Unpublished data
119. Evans A S. Unpublished data
120. Chen K K, Rose C L. and Clowes G H A. Comparative values of several antidotes in cyanide poisoning. *Am J M Sc* 188:767-781 1934
121. Jandorf B J. and Bodansky O. Therapeutic and prophylactic effect of methemoglobinemia in inhalation poisoning by hydrogen cyanide and cyanogen chloride. *J Indust Hyg & Toxicol* 28:125-132 1946
122. Rose, C L., Welles J S, Fink, R D. and Chen K K. Antidotal action of p-aminopropiophenone with or without sodium thiosulfate in cyanide poisoning. *J Pharmacol & Exper Therap* 89:107-114 1947
123. Chen K K, Rose, C L. and Clowes G H A. Modern treatment of cyanide poisoning. *J Indiana M A* 37:344-350 1944
124. Albaum H. G., Tepperman J. and Bodansky O. Spectrophotometric study of competition of methemoglobin and cytochrome oxidase for cyanide in vitro. *J Biol Chem* 163:641-647 1946
125. Goodman L. and Gilman A. *The Pharmacological Basis of Therapeutics. A textbook of pharmacology, toxicology and therapeutics for physicians and medical students* 1953 pp. New York: MacMillan Co. 1941
126. Barkan G. and Walker B S. Sulfhemoglobin formation and labile iron in vitro and in vivo. *Science* 96:66-68 1942

appearance of the cyanosis. As pointed out by van Lier many patients reported had been taking aniline derivatives, which he and others<sup>52, 115, 132</sup> demonstrated to be capable of producing sulfhemoglobin in the presence of constipation.

### SUMMARY

Abnormal hemoglobin pigments may be suspected in patients by the recognizable clinical syndrome in the congenital enterogenous types, by a history of drug intake or by the very intensity of the cyanosis with minimal symptoms. The diagnosis depends on the spectroscopic identification of the abnormal pigment. Methemoglobinemia may be due to dysfunction of the normal red-cell reconversion mechanism or to conversion of hemoglobin by circulating oxidants. Treatment with methylene blue or ascorbic acid depends on the etiology of the methemoglobinemia, since ascorbic acid is effective only in congenital methemoglobinemia.

Sulfhemoglobin is formed by the action of a methemoglobin-producing drug in addition to either constipation or a sulfur-containing medication. Unlike methemoglobin, which may be reverted rapidly to hemoglobin, sulfhemoglobin once formed remains until the red cell containing it is destroyed.

### REFERENCES

- Lundsgaard, C. and Van Slyke D. D. Cyanosis. *Medicine* 2: 1-76 1923.
- Fairley, N. H. Methaemalbumin. I. Clinical aspects. *Quart J Med* 10: 95-114 1941.
- Conant J. B. Oxidation of hemoglobin and other respiratory pigments. *Harcis Lectures* 1932 33. Pp 159-183.
- Jung F. Methämoglobinbildung und Blutkörperchenresistenz. *Klin Wchnschr* 19: 1016 1940.
- Eder H. A. Fineb C. and McKeen R. W. Congenital methemoglobinemia. Chemical and biochemical study of case. *J Clin Investigation* (in press).
- Heubner W. Heinzkörperchen und Blutfarbstoff. *Klin Wchnschr* 21: 520 1942.
- Idem. Methämoglobin, Innenkörper der Erythrocyten und Anämie. *Klin Wchnschr* 20: 137-141 1941.
- Michel H. O. and Harris J. S. Blood pigments properties and quantitative determination with special reference to spectrophotometric methods. *J Lab & Clin Med* 25: 445-463 1939-40.
- Ross J. F. Hemoglobinemia and hemoglobinurias. *New Eng J Med* 233: 691-696 1945.
- Van Slyke D. D. Hiller A. Weisger J. R. and Cruz, W. O. Determination of carbon monoxide in blood and of total and active hemoglobin by carbon monoxide capacity. Inactive hemoglobin and methemoglobin contents of normal human blood. *J Biol Chem* 166: 121-148 1946.
- Evelyn K. A. and Malloy H. T. Microdetermination of oxyhemoglobin, methemoglobin and sulfhemoglobin in single sample of blood. *J Biol Chem* 126: 655-662 1938.
- Horecker B. L. Absorption spectra of hemoglobin and its derivatives in visible and near infra red regions. *J Biol Chem* 148: 173-183 1943.
- Horecker B. L. and Brackett, F. S. Rapid spectrophotometric method for determination of methemoglobin and carboxyl hemoglobin in blood. *J Biol Chem* 152: 669-677 1944.
- Austin J. H. and Drabkin D. L. Spectrophotometric studies. III. Methemoglobin. *J Biol Chem* 112: 67-115 1935.
- Heubner W. and Stuhlmann M. Studien über Methämoglobinbildung. XI. Ruckbildung im Aderlassblute. *Arch f exper Path. u. Pharmacol* 199: 1-3 1942.
- Hamilton P. B. Hiller A. and Van Slyke D. D. Renal effects of hemoglobin infusions in dogs in hemorrhagic shock. *J Exper Med* 86: 477-487 1947.
- Amberson W. R. et al. On use of Ringer-Locke solutions containing hemoglobin as substitute for normal blood in mammals. *J Cell & Comp Physiol* 5: 359-382 1934.
- Roughton, F. J. W. Darling R. C. and Root W. S. Factors affecting determination of oxygen capacity, content and pressure in human arterial blood. *Am J Physiol* 142: 708-720 1944.
- Paul W. D. and Kemp, C. R. Methemoglobin, normal constituent of blood. *Proc Soc Exper Biol & Med* 56: 55 1944.
- Drabkin D. L. and Schmidt C. F. Spectrophotometric studies. XII. Observation of circulating blood in vivo and direct determination of saturation of hemoglobin in arterial blood. *J Biol Chem* 157: 69-83 1945.
- Warburg O. and Reid A. Oxydation von Hämoglobin durch Methylblau. *Biochem Ztschr* 242: 149-158 1931.
- Warburg O. and Christian W. Über Aktivierung der Ribose durch Hexose-Mono-Phosphorsäure in roten Blutzellen und die Gärung aktivierender Fermentlösungen. *Biochem Ztschr* 242: 206-227 1931.
- Wendel W. B. Oxidations by erythrocytes and catalytic influence of methylene blue. II. Methemoglobin and effect of cyanide. *J Biol Chem* 102: 385-401 1933.
- Idem. Oxidations by erythrocytes and catalytic influence of methylene blue. I. Oxidation of lactate to pyruvate. *J Biol Chem* 102: 373-383 1933.
- Kiese M. Die Reduktion des Hämoglobins. *Biochem. Ztschr* 316: 262-294 1944.
- Gutman H. R. Jandorf B. J. and Bodansky O. Role of pyridine nucleotides in reduction of methemoglobin. *J Biol Chem* 169: 145-152 1947.
- Drabkin D. L. Maintenance of active hemoglobin—function of erythrocytes. *Federation Proc* 5: 132 1946.
- Shapov V. S. Mechanism of biologic reduction of methemoglobin in erythrocytes. *Biochimica* 3: 430-444 1938.
- Lester D. Formation of methemoglobin. I. Species differences with acetanilide and acetaphenetidine. *J Pharmacol & Exper Therap* 77: 154-159 1943.
- Lolli G. Lester D. and Rubin M. Formation of methemoglobin. II. Influence of total hemoglobin on formation of methemoglobin from acetanilide. *J Pharmacol & Exper Therap* 80: 74-77 1944.
- Clark B. B. Van Loon E. J. and Morrissey R. W. Acute experimental aniline intoxication. *J Indust Hyg & Toxicol* 25: 112, 1943.
- Tepperman J. Bodansky O. and Jandorf B. J. Effect of para-aminopropiophenone induced methemoglobinemia on oxygenation of working muscle in human subjects. *Am J Physiol* 146: 707 1946.
- Clark B. B. Van Loon E. J. and Adams W. L. Respiratory and circulatory responses to acute methemoglobinemia produced by aniline. *Am J Physiol* 139: 64-69 1943.
- Darling R. C. and Roughton F. J. W. Effect of methemoglobin on equilibrium between oxygen and hemoglobin. *Am J Physiol* 137: 56-68 1942.
- Lester D. and Greenberg L. A. Comparative anoxic effects from carbon monoxide hemoglobin and methemoglobin. *J Pharmacol & Exper Therap* 81: 182-188 1944.
- Vandenbelt J. M. Pfeiffer C. Lauser M. and Sibert M. Methemoglobinemia after administration of p-aminopropiophenone and p-aminopropiophenone. *J Pharmacol & Exper Therap* 80: 31-38 1944.
- Gibson Q. H. Reduction of methaemoglobin by ascorbic acid. *Biochem J* 37: 615-618 1943.
- Morrison D. B. and Williams E. F. Jr. Methemoglobin reduction by glutathione or cysteine. *Science* 87: 15 1938.
- Finch C. A. Treatment of intracellular methemoglobinemia. *Bull New Eng J Med* 9: 241-245 1947.
- Harrop G. A. Jr. and Barron E. S. G. Studies on blood cell metabolism. I. Effect of methylene blue and other dyes upon oxygen consumption of mammalian and avian erythrocytes. *J Exper Med* 48: 207-223 1928.
- Hauschild F. Die Wirkung des Katalysins (Thionin) bei der Methämoglobinvergiftung. *Arch f exper Path. u. Pharmacol* 184: 458-467 1936.
- Wendel W. B. Control of methemoglobinemia with methylene blue. *J Clin Investigation* 18: 179-185 1939.
- Bodansky O. and Gutmann H. Treatment of methemoglobinemia. *J Pharmacol & Exper Therap* 89: 46-56 1947.
- Sturm A. and Franke W. Chromosomenstudien. III. Vermutlich Methylenblau bzw. Chromosomen im lebenden Organismus. Methämoglobin zu bilden? *Arch f exper Path. u. Pharmacol* 186: 305-312 1937.
- Finch C. A. Unpublished data.
- Pfeiffer C. C. Gersh I., Snyder R. and Stormont R. T. *A Pharmacological Study of Methylthionine Chloride (Methylene Blue) and Toluidine Blue*. Unpublished data.
- Nadler J. E., Green, H. and Rosenbaum A. Intravenous injection of methylene blue in man with reference to its toxic symptoms and effects on electrocardiogram. *Am J Med Sc* 188: 15-21 1934.
- Nacht D. I. and Harden W. C. Toxicology and assay of methylene blue. *Ann Int Med* 71: 738-745 1933.
- Lederer J. A. Contribution à l'étude pharmacodynamique de la thionine action sur le métabolisme des hydrates de carbone et toxicité. *Arch internat de pharmacodyn et de therap* 55: 347-361 1937.
- Hitzemberger K. Autotoxische Zyanose (Intraglobuläre Methämoglobinämie). *Wien Arch. f. Inn. Med* 23: 85-96 1932.
- Dieckmann W. J. Methemoglobinemia. *Arch Int Med* 50: 574-578 1932.
- van Lier H. W. *Oer de Parhaemoglobinaemiam*. Utrecht Zuidsm. Ed 1933.
- van Thienen G. J. Methaemoglobinaemie. *Nederl tijdschr Geneesk* 77: 1086-1092 1933.
- van Heukelom S. Intraglobulaire congenitale familiale methemoglobinaemie. *Geneesk Tachr Med Indes* 77: 30-34 1937.

dyspnea and cyanosis with nausea and vomiting but no chest pain or cough. The patient was taken immediately to the operating room. The right superficial femoral vein was ligated and divided without incident. No clot was found. The vein on the left side was exposed, found to be free of clot, and was about to be opened when the patient suddenly became cyanotic and dyspneic and died.

### DIFFERENTIAL DIAGNOSIS

DR RICHARD J. CLARK. Let us go briefly over this history again. The patient apparently had indigestion for a somewhat indefinite period, which in view of later events, may reasonably have been attributable to chronic gall-bladder disease. Seven months before entry she had a briefly described illness of three weeks' duration characterized by cough and severe left pleural pain. We wonder about the possibility of bronchopneumonia or pulmonary infarction at that time. We may question a myocardial infarction in view of later events, certainly, the description is not characteristic of any such episode although it has to be borne in mind.

She soon had a severe attack of anorexia, nausea and vomiting, following which a cholecystectomy was done. There is the helpful point that the gall bladder was found to be perforated. We know that there was definite gall-bladder disease with some element of infection and that the difficulty in the gastrointestinal system was not all secondary to cardiovascular disease. We are not told whether gallstones were present or exactly what was done whether the common duct was explored, or whether or not it was drained.

At the same point in the history cardiac enlargement was noted. This is the first indication that cardiovascular disease was present. Following operation the patient did poorly and had increasing signs of gastrointestinal disturbance and apparently some evidence of decreasing cardiac reserve. There were two short episodes of fever without chills but they are not sufficiently well described to enable us to draw any definite conclusions from them. The loose bowel movements might make one wonder if there were any involvement of the pancreas along with biliary-tract disease but there is nothing in the protocol on which I can base any such diagnosis. We are told that the gastrointestinal series was negative and that two stool examinations were negative. These factors are against any intrinsic disease of the stomach or bowel. The loss of weight is explainable on the basis of the repeated gastrointestinal upsets and anorexia.

On entry there was evidence of an abnormal heart, which appeared to be in borderline failure and also of an enlarged liver. While in the hospital the patient had an irregular fever of moderate degree. On the seventh day there occurred an episode strongly suggesting pulmonary infarction.

Subsequently, in the process of bilateral femoral-vein ligation the patient died suddenly.

The problems here are threefold. What was going on in the biliary tract, what was the cardiac lesion, and what was the terminal event? So far as the biliary tract is concerned she had had persistent gastric symptoms since the cholecystectomy and showed an enlarged liver on physical examination. We are not told whether the liver was tender or anything else regarding its character. Nothing is said about clinically detectable jaundice, and there is no report of the urinary findings. She had an abnormal biphasic van den Bergh reaction of slight degree. The cephalin-flocculation reaction was insignificant, and the prothrombin time normal. Apparently she had no serious liver disturbance. We might wonder about a residual stone in the common duct, causing intermittent biliary obstruction. If so we would expect more evidence of jaundice and also a history of some abdominal pain and colic. What about hepatic abscess of some type, secondary to biliary-tract infection? Had this been present we would have expected a more fulminating course and a higher white-cell count and a febrile reaction at the time. I rule out a malignant lesion for lack of more specific evidence. Hepatic congestion, secondary to cardiac disease, is to be considered, but I doubt this because of the long-continued symptomatology without other significant evidence of congestive failure. A low-grade ascending cholangitis, which had carried on since the time of the cholecystectomy, might explain this phase of our problem most satisfactorily.

Next to consider is the cardiac lesion. May we see the films at this point?

DR STANLEY M. WYMAN. The heart is described as grossly enlarged, the borders extending to both the right and the left, more markedly toward the left. There is a faint suggestion that the left main-stem bronchus is elevated. In the lateral view there is some prominence of the upper posterior heart border, suggesting left auricular enlargement. The heart extends well to the anterior chest wall, which makes one suspect that in addition to left ventricular enlargement there is probably right ventricular enlargement. The pulmonary vascular shadows are not definitely abnormal. There is some fluid in the left costophrenic sinus laterally. The second examination, done about a week after the first, shows an area of hazy indefinite density in the right lower-lung field, seen to lie posteriorly against the chest wall. This is the shadow interpreted as being consistent with infarct.

DR CLARK. There is some unusual prominence in the region of the pulmonary conus, is there not?

DR WYMAN. The left upper border of the heart I would not interpret as being prominent. I think the pulmonary artery is probably engorged but may be overlain by the heart shadow per se. The

- 127 Lemberg R, Holden H F Legge J W, and Lockwood W H Studies on sulphaemoglobin *Australian J Exper Biol & M Sc* 20 161 167 1942
- 128 Nijveld H A W Properties and structure of sulphaemoglobin *Rec Trav Chim* 62 293 324 1943
- 129 Drabkin, D L and Austin J H Spectrophotometric studies II Preparations from washed blood cells nitric oxide hemoglobin and sulphaemoglobin *J Biol Chem* 112 51-65 1935
- 130 Jope E M Disappearance of sulphaemoglobin from blood of TNT workers in relation to dynamics of red cell destruction *Brit J Indust Med* 3 136-142 1946
- 131 Harrop G A, and Waterfield, R. L. Sulphaemoglobinemia *J A M A* 95 647 650 1930
- 132 Gibson G A and Douglas C C Microbic cyanosis *Lancet* 2 72 74 1906
- 133 West, S and Clark T W Idiopathic cyanosis due to sulphaemoglobinaemia (enterogenous cyanosis) *Lancet* 1 272 276 1507
- 134 Clarke T W and Curtis R. M Sulph hemoglobinemia, with report of first case in America *Med Rec* 78 987 991 1910.
- 135 Davis H A Case of localized intracorpuscular sulphaemoglobinaemia *Lancet* 2 1145 1912
- 136 Wallis R L M On sulphaemoglobinaemia. *Quart. J Med* 7 73-91 1913
- 137 Long W C and Spriggs E. I On sulphaemoglobinaemia. *Quart. J Med* 11 102 111, 1918
- 138 Jamieson, R A Observation upon methaemoglobinaemia or sulphaemoglobinaemia *Quart J Med* 12 81-87 1918-1919
- 139 Mason V R and Conroy F D Sulphaemoglobinaemia. *Bull Johns Hopkins Hosp* 32 391-394 1921
- 140 van den Bergh A A H and Engelkes H Über die Autotoxik intraglobuläre Sulphaemoglobinaemie *Klin Wochenschr* 119-12 1933 1922
- 141 Snapper I Over Sulphaemoglobinaemie *Nederl tydskr t geneesk* 66 2520 2526 1922
- 142 Garrod L. P. On sulphaemoglobinaemia *Quart J Med* 19-26 94 1925

## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

TRACY B MALLORY, M D, *Editor*

BENJAMIN CASTLEMAN, M D, *Associate Editor*

EDITH E PARRIS, *Assistant Editor*

### CASE 34391 .

#### PRESENTATION OF CASE

A fifty-nine-year-old woman entered the hospital because of anorexia, nausea and vomiting.

The patient was essentially well except for "indigestion" following meals until seven months before admission, when she had an illness lasting three weeks characterized by cough and severe left pleural pain. A short time following this her gall bladder was removed at a community hospital following an attack of anorexia, nausea and vomiting. The gall bladder was said to be perforated, with localized peritonitis. At that time, because of an enlarged heart and slight dyspnea on exertion, she was digitalized and continued to take the drug (one pill a day) until admission. Following operation she did not do well, being bothered by anorexia, progressive weakness, fatigue, dyspnea on exertion and afternoon ankle swelling. She had two short episodes of fever without chills and "stomach spells" occurring approximately every third day for the six months prior to admission and consisting of nausea, belching and vomiting of thick, green material. There was never any blood in the vomitus, and she never had any abdominal pain. She also noted one to three loose, watery bowel movements a day without blood, pus or cramps, the bowel habits having previously been normal and the stools formed. She lost 30 pounds of weight during the present illness.

Physical examination showed an emaciated, pale woman. The thyroid gland was not palpable. The neck veins were distended with the patient 15° above the horizontal position. The chest was emphysematous but clear. The heart seemed enlarged to percussion, the rhythm was regular, with occasional extrasystoles, and there was a Grade II systolic murmur along the left sternal border. The liver edge was felt four fingerbreadths below the costal margin.

The temperature, pulse and respirations were normal. The blood pressure was 140 systolic, 90 diastolic.

Examination of the blood revealed a red-cell count of 4,900,000, with a hemoglobin of 13 gm per 100 cc, and a white-cell count of 7500, with 74 per cent neutrophils. Two stool specimens were guaiac negative. The arm-to-tongue circulation time was 35 seconds, and the venous pressure was equivalent to 140 mm of water. An x-ray film of the chest disclosed a heart enlarged in all chambers, with a suggestion of left ventricular predominance. The lung markings were slightly increased, and there was a small amount of fluid in the left pleural sinus. An electrocardiogram showed apparent auricular fibrillation, with a rate of 85, small Q waves in Leads 2 and 3, depressed ST segments in Leads 1, 2 and CF<sub>1</sub>, flat T waves in Leads 1, 2, 3, CF<sub>1</sub> and CF<sub>2</sub>, a diphasic T wave in Lead CF<sub>1</sub>, and a tendency to low voltage. The QRS interval was 0.10 to 0.12 second. A gastrointestinal series was negative. The van den Bergh reaction was 1.4 mg per 100 cc. direct, and 1.6 mg indirect, the cephalin-flocculation test was + in twenty-four and ++ in forty-eight hours, and the prothrombin time was normal.

During the hospital stay there was an irregular fever, the temperature going as high as 101°F. During the seventh day a slight hemoptysis occurred. Fine rales were heard at the right base, and a film of the chest showed an area consistent with infarct. Heparin and dicumarol were started, but on the tenth day femoral-vein interruption was decided upon as a more permanent form of therapy. Large doses of vitamin K were given. On the following day there was a short episode of

and decided on venous ligation. We stopped the anticoagulants. On the morning of death there was an episode that seemed most likely another pulmonary infarct, so that we hurried with the venous ligation. There was no evidence at any time that she had active phlebitis in the lower extremities. We made the decision to ligate the femoral veins on a statistical basis.

DR MALLORY: Dr Means, would you like to give your opinion now or reserve it until later?

DR JAMES H. MEANS: I remember this patient very vividly and the case caused me a certain amount of emotion. I will tell you why in a moment. I took the Medical Service over the day after she came in. They had done a great deal of work on her. Dr Taylor has given an outline of what happened. They had just about disposed of the abdominal possibilities at that time, and attention was focused on the heart as probably the most important feature. I wrote, "I think the whole picture can be explained on the basis of low-grade, chronic congestive heart failure probably arteriosclerotic. I assume that is synonymous with coronary-artery disease. I suppose the indication now is to digitalize." Then I began to think more about the x-ray picture, indicating pulmonary infarction, and concluded that we ought to do something about that. Dr Dahl, as I recall, favored putting the patient on anticoagulants. She got heparin first and dicumarol afterward. We have heard so much of how to treat phlebitis that there is a great deal of confusion in the professional mind about anticoagulants versus ligation. I suppose it was because I was on dicumarol myself, having had phlebitis recently, and my medical brethren were curing me in that way, that this case was very vivid to me. We put her on these anticoagulants but I was still worried about whether she was the type of patient that should be put on anticoagulants or ligated. My thinking was conditioned a little bit by the fact that I had escaped, up to that point, getting ligation myself and I hated to wish it on her. Dr Paul D. White says here, "This is the wrong kind of patient to treat with anticoagulants." It is all right to treat a vigorous fellow like me with anticoagulants, but he advised that this bedridden cardiac patient should be ligated and I bowed to his superior wisdom. The only trouble was that we had prolonged her prothrombin time by then and we had to give her vitamin K to

shorten it. Then the surgeons took over, and she died on the table before they could ligate. I therefore think that we had grossly mismanaged this case. I felt sorry about that. I will let Dr Mallory tell us what was actually found.

DR MALLORY: Have you an opinion, Dr Zamecnik?

DR PAUL C. ZAMECNIK: I saw the patient when she first came in and was taken in by the possibility that the gastrointestinal symptoms were the most prominent feature of the history. We considered carcinoma of the stomach as a possibility. The negative gastrointestinal series then disillusioned us and caused us to pay more attention to the cardiac status.

#### CLINICAL DIAGNOSES

Pulmonary infarction  
Phlebothrombosis  
Arteriosclerotic heart disease

#### DR CLARK'S DIAGNOSES

Idiopathic myocarditis or coronary-artery disease  
Pulmonary infarcts, recent and old  
Terminal pulmonary embolism

#### ANATOMICAL DIAGNOSES

*Coronary thrombosis, recent*  
*Myocardial infarction, recent*  
*Mural thrombi, right ventricle and left auricle*  
*Pulmonary infarcts, recent and old*  
Coronary sclerosis, severe  
Cardiac hypertrophy and dilatation  
Cerebral lateral-sinus thrombosis, left

#### PATHOLOGICAL DISCUSSION

DR MALLORY: Autopsy showed no massive pulmonary embolism. There were numerous infarcts of the lung in both lower lobes of varying ages. Some of them were dense, old fibrous scars, some were of intermediate age, and one was very fresh. The heart was diffusely dilated and moderately hypertrophied. There were no valvular lesions. We found thrombi in the right ventricle and also in the left auricle. There was a large area of infarction at the apex of the heart involving the interventricular septum, and I think the right ventricular thrombi were unquestionably secondary to that. So we had an intracardiac source, as Dr

descending aorta is not remarkable. There is some calcification in the aortic arch.

DR CLARK: There is no evidence of old pleurisy on the right?

DR WYMAN: Not on the original examination. The right leaf of the diaphragm and the costophrenic angle are clear. The stomach and the duodenum appear grossly normal.

DR CLARK: There is no evidence of gallstones in the region of the gall bladder?

DR WYMAN: I do not have a film that includes the right upper quadrant adequately. I do not see any here.

DR CLARK: I gather, then, that this heart shows more generalized chamber enlargement than is ordinarily seen in coronary-artery disease. Is that correct?

DR WYMAN: Yes. It did not make me think of coronary disease primarily.

DR CLARK: The electrocardiogram as described suggests coronary disease, digitalis effect or some diffuse myocardial process. May I see a print of the tracing? This shows a normal axis with a low QRS complex in Lead 1. There are no visible P waves. The T waves throughout are low to flat. I would not consider the Q waves in Leads 2 and 3 sufficiently prominent to be significant. The QRS complexes are slightly widened.

Could this patient have had valvular heart disease? Aortic stenosis might be suggested by the Grade II systolic murmur along the left sternal border, but this alone is insufficient evidence for such a diagnosis. Viewing the x-ray films and observing suggestive left auricular enlargement we wonder about mitral disease. The murmur of mitral stenosis may be undetected, but all in all, I cannot diagnose this or any other valvular lesion.

What about hypertensive heart disease on the basis of a previously elevated blood pressure? I rule this out because of the history and the lack of any good cardiographic evidence, low voltage and absence of left-axis deviation are strong counter-evidence.

If we are to assume recurrent pulmonary infarction, could the patient have had cor pulmonale? The electrocardiogram is not in keeping, nor would this explain left-sided cardiac enlargement.

Certain rarer forms of diffuse myocardial involvement are to be considered. The generalized chamber enlargement, the continued suggestion of right-sided heart failure, the low voltage and the multiple T-wave involvement are all consistent. This patient with chronic anorexia and gastrointestinal disturbance might well have had avitaminosis, beriberi heart disease comes to mind, but in this condition the circulation time is characteristically rapid with failure, whereas here there was a prolonged circulation time. I see no good evidence for myxedema or myxedema heart in spite of the low

voltage. The distinct possibility of an idiopathic myocarditis, such as a Fiedler's, is to be seriously thought of in a situation of this type. This diagnosis is made primarily by the exclusion of other possibilities. I came here prepared to make a diagnosis of old coronary-artery disease, being influenced especially by the Q waves in Leads 2 and 3 reported in the protocol, but these we have seen to be rather insignificant. The complete lack of cardiac pain is against this diagnosis, as is the appearance of the x-ray film. I shall, therefore, put down a diffuse nonspecific myocarditis, possibly a Fiedler's, as my first bet, leaving coronary-artery disease as second choice.

Finally, let us view the pulmonary condition and terminal events. I am intrigued with the x-ray finding of fluid at the left base and none on the right. Unilateral left pleural effusion from cardiac failure has been shown to be rare unless the right pleural cavity is obliterated by adhesions. It is usually due to some local cause such as pleurisy, secondary to pulmonary infarction. Almost certainly this patient had a pulmonary infarction on the seventh hospital day and another a few days later after anticoagulant treatment, which was followed by vitamin K preparatory to venous ligation.

We are given no localizing evidence in the protocol to incriminate the legs. Obviously the Surgical Service suspected femoral phlebitis since they went ahead with ligation, and on the basis of statistics this is the most likely source for the emboli. We are told that no evidence of clot was found on opening the right vein, and this was divided. No clot was noted on the left, but death occurred before the vein was opened, presumably a clot may have slipped up from below during manipulation. A second possible source of emboli may have been from mural thrombosis in the right side of the heart, which we were told was fibrillating, but we would hardly expect such a thrombosis alone to give rise to a sudden fatal embolism. In any event I believe that we shall find evidence of multiple old and new pulmonary infarcts and that the terminal event was a massive pulmonary embolism.

DR TRACY B. MALLORY: Dr Taylor, I believe you saw this woman. Would you tell us what you thought about the case?

DR ISAAC TAYLOR: When this patient came in the question arose whether she had residual sepsis in the biliary tract or carcinoma of the stomach primarily. Because of the pulmonary infarct as described in the protocol our attention was focused in that direction. We were concerned at the same time with the treatment of congestive failure, which was brought under control. Then, as one gathers from the protocol, there was some discussion regarding how to treat this woman. She was started on anticoagulants after a couple of days on the basis of the apparently poor cardiac status, she was having a restricted life, and we changed our plans

and decided on venous ligation. We stopped the anticoagulants. On the morning of death there was an episode that seemed most likely another pulmonary infarct, so that we hurried with the venous ligation. There was no evidence at any time that she had active phlebitis in the lower extremities. We made the decision to ligate the femoral veins on a statistical basis.

DR MALLORY: Dr Means, would you like to give your opinion now or reserve it until later?

DR JAMES H. MEANS: I remember this patient very vividly, and the case caused me a certain amount of emotion. I will tell you why in a moment. I took the Medical Service over the day after she came in. They had done a great deal of work on her. Dr Taylor has given an outline of what happened. They had just about disposed of the abdominal possibilities at that time, and attention was focused on the heart as probably the most important feature. I wrote, "I think the whole picture can be explained on the basis of low-grade, chronic congestive heart failure, probably arteriosclerotic. I assume that is synonymous with coronary-artery disease. I suppose the indication now is to digitalize." Then I began to think more about the x-ray picture, indicating pulmonary infarction, and concluded that we ought to do something about that. Dr Dahl, as I recall, favored putting the patient on anticoagulants. She got heparin first and dicumarol afterward. We have heard so much of how to treat phlebitis that there is a great deal of confusion in the professional mind about anticoagulants versus ligation. I suppose it was because I was on dicumarol myself, having had phlebitis recently, and my medical brethren were curing me in that way, that this case was very vivid to me. We put her on these anticoagulants, but I was still worried about whether she was the type of patient that should be put on anticoagulants or ligated. My thinking was conditioned a little bit by the fact that I had escaped, up to that point, getting ligation myself and I hated to wish it on her. Dr Paul D. White says here, "This is the wrong kind of patient to treat with anticoagulants." It is all right to treat a vigorous fellow like me with anticoagulants, but he advised that this bedridden cardiac patient should be ligated, and I bowed to his superior wisdom. The only trouble was that we had prolonged her prothrombin time by then, and we had to give her vitamin K to

shorten it. Then the surgeons took over, and she died on the table before they could ligate. I therefore think that we had grossly mismanaged this case. I felt sorry about that. I will let Dr Mallory tell us what was actually found.

DR MALLORY: Have you an opinion, Dr Zamecnik?

DR PAUL C. ZAMECNIK: I saw the patient when she first came in and was taken in by the possibility that the gastrointestinal symptoms were the most prominent feature of the history. We considered carcinoma of the stomach as a possibility. The negative gastrointestinal series then disillusioned us and caused us to pay more attention to the cardiac status.

#### CLINICAL DIAGNOSES

Pulmonary infarction  
Phlebothrombosis  
Arteriosclerotic heart disease

#### DR CLARK'S DIAGNOSES

Idiopathic myocarditis or coronary-artery disease  
Pulmonary infarcts, recent and old  
Terminal pulmonary embolism

#### ANATOMICAL DIAGNOSES

*Coronary thrombosis, recent*  
*Myocardial infarction, recent*  
*Mural thrombi, right ventricle and left auricle*  
*Pulmonary infarcts, recent and old*  
Coronary sclerosis, severe  
Cardiac hypertrophy and dilatation  
Cerebral lateral-sinus thrombosis, left.

#### PATHOLOGICAL DISCUSSION

DR MALLORY: Autopsy showed no massive pulmonary embolism. There were numerous infarcts of the lung in both lower lobes of varying ages. Some of them were dense, old, fibrous scars, some were of intermediate age, and one was very fresh. The heart was diffusely dilated and moderately hypertrophied. There were no valvular lesions. We found thrombi in the right ventricle and also in the left auricle. There was a large area of infarction at the apex of the heart involving the interventricular septum, and I think the right ventricular thrombi were unquestionably secondary to that. So we had an intracardiac source, as Dr

Clark suggested as a remote possibility, for the pulmonary infarct

The gall bladder had been removed. We found nothing wrong with the biliary tract. The liver showed only a severe grade of chronic passive congestion. A careful search of all the ligated veins showed not the slightest trace of thrombosis above or below the ligature on either side. One other possible source of embolism is the cerebral left lateral sinus, which was extensively thrombosed, and it is conceivable, although unlikely, that the thrombus had broken loose from there. The coronary arteries showed a very old, calcified occlusion of the left descending branch, considerable sclerosis and a very fresh thrombus of the right circumflex. So death was due, I think without question, to sudden coronary occlusion, not to pulmonary embolism.

DR CLARK: How often do you see pulmonary infarcts coming from intracardiac thrombi?

DR MALLORY: We see them with significant frequency in valvular heart disease. They are quite uncommon in coronary-artery disease. Thrombi in the left ventricle, of course, are the rule in cardiac infarction, but we see them only occasionally in the right ventricle. Usually when a thrombus is present in the right ventricle it is secondary to an infarct of the interventricular septum, and thrombi will be found in both ventricles.

DR CLARK: We have recently seen 2 cases of pulmonary infarction in which the evidence was strongly suggestive of an intracardiac source of the emboli. The possibility of this mechanism is of great importance in reaching a decision regarding anticoagulant versus ligation therapy.

DR MALLORY: One can raise the point whether it is wise to give dicumarol with fresh infarction of the heart. It is quite possible that the mural thrombus, which forms over an area of infarction, tends to reinforce the cardiac wall, at that point, a process that might be prevented by the dicumarol.

DR CLARK: I have recently seen a case of myocardial infarction treated with dicumarol in which the patient died of myocardial rupture on the eighteenth day—rather later than the average rupture. Possibly the lack of mural thrombosis was the cause.

DR MEANS: Dr Clark gave a scholarly dissertation, but there is one statement that he made on which I would like to comment. He seemed to

view with some surprise the fact that nothing was found when the femoral veins were opened. I think that is common. I am sorry Dr Linton is not here but I get the impression from him that he often opens the veins when there is unquestionable thrombosis below and finds them quite empty. I do not think that the fact that they were empty is significant. Taking all the cases of pulmonary embolism with infarction, what percentage would you say come from the heart?

DR MALLORY: What would your opinion be, Dr Castleman?

DR BENJAMIN CASTLEMAN: Probably about 95 per cent.

### CASE 34392

#### PRESENTATION OF CASE

A thirty-nine-year-old salesman was admitted to the hospital because of cough and sweating.

The patient was more or less well until approximately seven months before entry, when, following a cold, he noted severe cough productive of foul sputum. The cough became progressively worse and was accompanied by night sweats and increasing dyspnea. Approximately five months after the onset of symptoms his condition became so bad that he had to stop work. He consulted a physician, who took a roentgenogram of the chest and had him admitted to a community hospital. Here he was given penicillin for ten days, after which the cough and dyspnea nearly disappeared. However, shortly before his anticipated discharge he began to have transient pain in the middle of the right side of the chest posteriorly. Since that time he had increase in cough as well as a feeling of pressure over the right side of the chest anteriorly. He never had hemoptysis.

The patient was a healthy child and had no serious illnesses. However, he stated that he had always become dyspneic on exertion and that during the past ten years he had been nervous and just "not well." Two years before entry he was found to have a duodenal ulcer by roentgenogram. He had slight abdominal pain recently and almost daily had tarry stools for an unknown length of time. He had had two "nervous breakdowns" in past years. He smoked two packages of cigarettes daily and more recently had been drinking a fair amount about every other day.

Physical examination revealed a well developed well nourished man in no acute discomfort, but having a nonproductive cough. There was an area of dullness with normal breath sounds in the mid-portion of the right side of the chest anteriorly. There was clubbing of the fingertips with questionable clubbing of the toes. The left Achilles jerk was absent.

The temperature was 98.6°F, the pulse 90, and the respirations 20 per minute.

The white-cell count was 17,600 with 75 per cent neutrophils, 2 per cent monocytes, 1 per cent eosinophils and 1 per cent basophils. The hemoglobin was 15.1 gm. The urine was normal.

An x-ray film of the chest showed an area of segmental atelectasis in the right upper lobe which involved chiefly the anterolateral portion of the lobe (Fig 1). The lung was particularly dense laterally and showed a mottled appearance more medially. A definite mass was not identified and the bronchial tree, so far as visualized on the right, was within normal limits. No definite adenopathy was observed although there was a vague density in the right paratracheal region. Comparison of the roentgenograms taken over a two-week period during the second month prior to admission showed the appearance of the lungs to be about the same, although in the present examination the lateral density was slightly greater. A gastrointestinal series was negative. There was no evidence of a filling defect or ulcer.

Three days after admission bronchoscopy was done with a report of "considerable mucopurulent sputum from the right upper lobe and moderate inflammatory changes in that orifice, mild changes in the rest of the right main bronchus, and a normal carina and left bronchial tree — the findings are consistent with inflammatory disease of the right upper lobe, no neoplasm is seen."

Smears were taken by bronchial lavage of the right main bronchus for cytologic examination. These were reported negative.

A culture of sputum was reported to have alpha-hemolytic streptococci as the predominating organism and was negative for beta streptococcus and pneumococcus. No acid-fast bacilli were seen in the sputum.

The highest temperature recorded during the week after admission was 99°F. Usually it was normal or subnormal.

On the ninth hospital day an operation was performed.

### DIFFERENTIAL DIAGNOSIS

DR ALLEN G BRALEY: Let us look at the x-ray films.

DR STANLEY M WYMAN: The minor septum is arched somewhat upward and is particularly well seen in the lateral view, having a rather high bend.



FIGURE 1

posteriorly and laterally. There is an area of rather indefinite density in this portion of the upper lobe, the density extending posteriorly and toward the hilus. There is a suggestion of a very poorly defined section of central rarefaction in this area, measuring about 3 cm in diameter. This cannot be identified in the lateral view because the film is not adequately exposed. The bronchus to the right upper lobe can be seen for a short distance and appears grossly normal. There is no appreciable fluid in either pleural cavity, but there is a suggestion of some pleural reaction overlying the right upper lobe laterally. I am not much impressed by the density described in the right mediastinum laterally. The examination on the gastrointestinal series is reported as being negative and I cannot see any gross disease. The duodenal cap is not well outlined.

DR BRAILEY Why do you say atelectasis? Why not just consolidation?

DR WYMAN The position of the septum indicates some collapse of a portion of the upper lobe. The septum is displaced upward, out of the normal situation.

DR BRAILEY Is there any x-ray evidence to indicate whether or not air is going into that part of the lobe?

DR WYMAN No x-ray evidence, except that there is atelectasis. Presumably there is peripheral disease, whether or not it is due to bronchial plugging, I cannot say.

DR BRAILEY This process is in the upper lobe?

DR WYMAN Yes, entirely in the upper lobe.

DR BRAILEY The problem presented by this patient is defined rather sharply in the history. He was an unstable, ill adjusted person, to be sure, but he had an organic disease process as well, which appeared to be confined to the chest—in fact, to the anterolateral division of the right main bronchus. The evidence given implies an obstructive lesion of the bronchus in question, with atelectasis and some degree of infection distal thereto. Such an obstruction might be produced by any one of three things: foreign body, an inflammatory process or neoplasm. Foreign body does not need to be seriously considered, I think. An adult who has inhaled a foreign body will surely be able to give a vivid account of the time, place and circumstances under which it occurred.

The question that gives this history a lively interest is whether the bronchial obstruction was inflammatory or neoplastic, or, more exactly, whether it was tuberculous or neoplastic, since the odds are overwhelming that if the stenosis was the result of inflammation, the inflammation was endobronchial tuberculosis. What scraps of evidence in favor of tuberculosis can we dig up? At thirty-nine years the patient was a relatively young man, and furthermore he offered the information that for ten years he had not considered himself really well. Perhaps he was trying to describe the unexplained fatigability and lassitude that are often early signs of tuberculosis. The x-ray picture is not typical of tuberculosis, but neither is it inconsistent.

Do you agree that it is not inconsistent with tuberculosis, Dr Wyman?

DR WYMAN I agree, it is not inconsistent with it.

DR BRAILEY But certainly if he had acid fast bacilli of any considerable duration, the disease was an unusually benign and smoldering affair. He had had no hemoptysis. He seems to have had little fever. Nothing is said of weight loss, and finally no acid-fast bacilli were seen in the sputum. We are not told whether this was a single routine examination or whether the sputum was concentrated. Nevertheless, acid-fast bacilli are apt to be found easily in the sputum of patients with endobronchial disease and, therefore, some importance must be attached to the statement that they were not found in this case even though the search may have been casual.

In weighing the evidence for neoplasm one should consider adenoma first. Ten per cent of all pulmonary tumors are adenomas of the bronchi, and the great majority occur in persons under forty years of age. They typically produce obstruction with drowned lung upstream from the dam. On the other hand, they are prone to bleed, and this man raised no blood. Still worse, they occur almost exclusively in main-stem bronchi and are readily seen by the bronchoscopist whereas the lesion in this case could not be seen.

The only other obstructive lesion we need to consider seriously is carcinoma of the bronchus. It is the commonest pulmonary tumor, although it is true that only 10 to 15 per cent of such carcinomas occur in men as young as this patient. It usually arises in main-stem bronchi, but 25 per cent develop sufficiently remote from the trachea not to be visible by bronchoscope. The presenting symptom is characteristically a harassing and persistent cough, followed by dyspnea and later other signs, such as pain, hemoptysis and weight loss. This patient had clubbing of the fingers. The physiology of clubbing is still poorly understood, but it is a fact that clubbing frequently occurs in persons with carcinoma of the bronchus whereas it is a rather rare sign in tuberculosis. Against cancer we have a negative cytologic smear, but I do not believe that we can allow ourselves much reassurance on that account.

Judgment is difficult as Hippocrates warned. I would like a much more careful search for tubercle bacilli, but I am going to assume that the patient did not have tuberculosis. Obviously he was a

rather neurotic person with a history of "nervous breakdowns," requiring forty cigarettes a day and capable of describing normal stools as tarry. I think his alleged ill health of ten years' duration was only evidence of maladjustment. I think it is better judgment to guess that he had a cancer of the bronchus of a few months' duration, which produced early obstruction and which should have been easily resectable.

DR WYMAN: Could this have been purely an inflammatory process such as a solitary lung abscess, Dr Brailey?

DR BRAILEY: I do not see why not. You did not say he had an abscess until just now. Furthermore, an abscess certainly could arise *de novo* with no obvious excuse. But the film suggests that the bronchus was plugged and that the abscess was secondary to plugging. I think the important thing is not whether the patient had an abscess but why the bronchus was stenosed.

DR WYMAN: From the x-ray point of view this could be a peripheral tumor or inflammation. The area of rarefaction could be an abscess cavity or cavitation in tumor. It is poorly seen on these films, however.

DR DONALD S. KING: As we watched this patient preoperatively we came to the conclusion that the process in the lung was due to a chronic nontuberculous infection rather than tuberculosis or infection secondary to a bronchial tumor. At one time he had had definite foul sputum, but this persisted for only a short time and in general the cough and sputum became less troublesome rather than more so. Besides this we had the evidence of a negative bronchoscopy and a negative examination of bronchial secretion for tumor cells. Nevertheless, the x-ray densities persisted, and we believed that exploratory operation was definitely indicated.

## CLINICAL DIAGNOSIS

Chronic nontuberculous pulmonary infection

## DR BRAILEY'S DIAGNOSIS

Carcinoma of bronchus

## ANATOMICAL DIAGNOSIS

*Lung abscess*

## PATHOLOGICAL DISCUSSION

DR BENJAMIN CASTLEMAN: The surgeon removed the right upper lobe. On cutting through the lobe it was found to be slightly smaller than normal and very heavy, with very little air anywhere in the lobe. On section, there was a collapsed cavity 7 cm in diameter, and the surrounding area was atelectatic. Microscopical examination showed no evidence of tumor but a chronic inflammatory process, the center of which showed acute inflammation with necrosis. Surrounding it was a great deal of necrosis with destruction of the alveolar walls. So I think we have to assume that this was a chronic lung abscess, etiology undetermined.

DR BRAILEY: It started out with upper respiratory infection?

DR CASTLEMAN: Yes.

DR KING: Because the patient was of a very nervous disposition we anticipated a stormy convalescence but were happily surprised to find that he had very little postoperative difficulty and could be discharged just a little less than two weeks after the lobectomy. He was still worried about all sorts of extrapulmonary symptoms, but I believe that the pulmonary condition has been cured.

# The New England Journal of Medicine

Formerly  
The Boston Medical and Surgical Journal  
Established 1828

Official Organ of  
THE MASSACHUSETTS MEDICAL SOCIETY  
and  
THE NEW HAMPSHIRE MEDICAL SOCIETY

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND  
PUBLISHED WEEKLY UNDER THE JURISDICTION OF THE  
COMMITTEE ON PUBLICATIONS

James P. O'Hare M.D. Richard M. Smith, M.D. *Chairman*  
Oliver Cope M.D. Conrad Wessellhoeft M.D.  
John Fallon M.D.

Joseph Garland M.D., Editor

ASSOCIATE EDITORS

Thomas H. Lanman M.D. Donald Munro M.D.

Henry Jackson Jr. M.D.

Clara D. Davies, EXECUTIVE EDITOR

Robert O. Leary, ASSISTANT EDITOR

EDITORIAL BOARD

C. Guy Lane M.D.	Maxwell Finland M.D.
Henry R. Viets M.D.	James M. Faulkner M.D.
Robert M. Green M.D.	Carroll B. Larson M.D.
Dwight O'Hara M.D.	Francis D. Moore M.D.
Fletcher H. Colby, M.D.	C. Stuart Welch M.D.
Robert L. Goodale M.D.	Vernon P. Williams M.D.
Chester M. Jones M.D.	Benjamin Castleman M.D.
Harvey R. Morrison M.D.	Hugh R. Leavell M.D.

SUBSCRIPTION TERMS \$7.00 per year in advance, postage paid for the United States (medical students \$4.00 per year) Canada \$8.00 per year (Boston funds) \$9.50 per year for all foreign countries belonging to the Postal Union

MATERIAL should be received not later than noon on Thursday three weeks before date of publication

THE JOURNAL does not hold itself responsible for statements made by any contributor

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts Telephone KE 6 2094

NEW ENGLAND ADVERTISING REPRESENTATIVE Edwin B. Tyler, 89 State Street, Boston, Massachusetts Telephone LA 3 5516

## POPULATION TRENDS

ENGLAND has become so alarmed over her trend toward an aging and declining population, that four years ago the Coalition Government appointed a Royal Commission to study the problem. For sixty years the birth rate had been falling, but also the country had known demoralizing unemployment, resulting in a paradoxical and disturbing state of affairs. Concerned as the kingdom was over its declining population it could not adequately care for what it had.

Immediately on appointment of the Commission, according to *The Lancet*\* the birth rate suddenly rose "impishly and awkwardly" to confuse the planners and becloud the issue. This rise was not sustained. The rate again started downward, per-

haps because the Government had given the family man a woefully inadequate relief in taxes to compensate for his increased expenses.

In general, reactions toward population trends are hardly consistent with the apparent facts. Politicians, with a nearly pathologic fervor, crave large populations, viewing them, apparently, almost in the light of standing armies despite the inevitable consequences, sooner or later, of unemployment, poverty and discontent. Yet even from a military standpoint large populations are not necessarily the important factor in a nation's greatness. Certainly in some of the countries of Asia, the most heavily populated in the world, numbers have proved to be no asset from any angle.

This much must be conceded. Declining population levels are frequently a sign of decadence. They mark the turning point of nations that have passed their peak in expansion, in strength and in character, and are substituting for a waning national ambition an attempt—that has always proved eventually vain—to consolidate their gains, rest on their laurels, withdraw behind their defenses and exist in comfort and security.

The aggressive behavior that results in wars between nations represents to many persons an intolerably nationalistic attitude, but the fact remains that when a species or a nation or a person is forward bound and headed toward some destined goal, aggressiveness, and in the instance of the first two, growth, are of the essence of their strength.

Population, however, while it tends to increase as a nation struggles into the sun, does not provide the best answer to the problem of prolonged survival. The spirit of a people is more important than its numbers. Population trends are important only as they indicate a nation's spirit of survival, or its loss. And without that spirit no economy, however well planned, can long be successful.

## CENTENNIAL OF THE MEDICAL SOCIETY OF THE STATE OF PENNSYLVANIA

ELSEWHERE in this issue of the *Journal* attention is called to the centennial celebration of the founding of the Medical Society of the State of Pennsylvania in Philadelphia from October 3 to 7

\*Leading Article "Population policy," *Lancet* 1 717 1948

An interesting scientific and social program has been arranged for the meeting

The organization of the society followed close on the heels of the first meeting of the American Medical Association in 1847. In December of that year representatives of the Chester County Medical Society, believing that physicians should organize on a state-wide basis, met in Lancaster, where the following resolution, proposed by Dr Wilmer Worthington, later president of the State Society, was adopted:

Whereas no State Medical Society exists in Pennsylvania and believing that such an institution would greatly contribute to the advancement of medical knowledge within its bounds,

Therefore *Resolved* that it is expedient to hold a convention at such time and place as may be hereafter agreed upon to effect such permanent organization as may be deemed best suited to accomplish the object in view.

The Lancaster County Medical Society concurred in this resolution and in April 1848 gathered the men who organized the Medical Society of the State of Pennsylvania.

The *Journal* extends heartiest congratulations to the Pennsylvania physicians and expresses the hope that the centennial celebration will be as successful and pleasant as the fiftieth anniversary in 1898 for which it had been announced that Lancaster County Medical Society was prepared to 'set out barrels and barrels of pretzels.'

REFERENCES

1 Editorial: Founding of State Medical Society. *Pennsylvania M J* 1:325 1898.  
2 Editorial: Next meeting of State Society and its scientific program. *Pennsylvania M J* 1:416 1898.

PUBLIC HEALTH AND THE DISEASES OF OLD AGE

ONE of the recent Saturday morning sessions of the Health Forum conducted by the Harvard School of Public Health was devoted to a discussion of public health and diseases of old age by Louis I. Dublin, chief statistician for the Metropolitan Life Insurance Company.\* In his address Dr Dublin pointed out the marked change that the mortality picture in this country has undergone since the turn of the century. The basic shift has been in the direction

of greatly increasing the importance of the diseases of later life. These changes he noted have been brought about by two major developments: the extraordinary success achieved by medical science and public-health administration in the control of infectious diseases and the progressive aging of the population. The indications are that these trends will continue.

Dr Dublin called attention to the striking change that the age structure of the population is undergoing. In 1900 only 4.1 per cent of the population of this country was sixty-five years or older; by 1940 the proportion increased to 6.8 per cent and it is estimated that by 1960 more than 9 per cent and by the turn of the century more than 15 per cent of the population will be in this old-age bracket. The actual numbers involved are even more impressive. In 1900 there were about 3,000,000 people in the United States who were sixty-five or older; in 1940 the number in this age group increased to nearly 9,000,000 and by 1960 their total is expected to reach 14,000,000 and by the end of the century 21,500,000.

Accompanying this change in age distribution of population there are parallel changes in the ranking of the leading causes of death. In 1900 the first ten causes of death were tuberculosis, pneumonia, diarrhea and enteritis, heart disease, nephritis, accidents and violence, cerebral hemorrhage, cancer, bronchitis and diphtheria, in that order. By 1940 diseases of the heart, cancer, accidents and violence, cerebral hemorrhage and nephritis were the five leading causes of death and pneumonia, tuberculosis, premature birth, diabetes and arteriosclerosis followed in that order. Thus of the ten principal causes of death at present only one is concentrated in early life; the others either show a heavy concentration in later life or have the highest death rates in the older age groups.

The data that Dr Dublin brought out indicate the need for a reorientation in the point of view and in the activities of social and welfare agencies, health officers and physicians to meet the changing needs of their communities. The public-health and medical professions, he believes, have largely solved the major problems of sanitation and communicable-disease control and should now be prepared to

\*Public health and diseases of old age (Summary). *Statist Bull Met-Life Ins Co* 9:1 1948.

wrestle with the more difficult problems of conserving life and health in the middle-aged and older people. The major concern should be with the cardiovascular-renal diseases, cancer and diabetes since the greatest amount of ill health is due to these conditions. There are a number of other causes of sickness and death among older people that he believes should merit greater attention, these include tuberculosis, pneumonia, mental diseases, nutritional diseases and accidents. Dr. Dublin suggests that the efforts of health departments, private physicians and organized medical groups and voluntary health and safety agencies should be co-ordinated at the local level. The person most suited to take the primary responsibility of co-ordinating these efforts is the health officer, who should be the logical leader in developing effective health service for his community.

## PR

PUBLIC relations and the practice of medicine have practically always been nearly synonymous, although their affinity had not been officially recognized until the term "public relations" was recently popularized. The invention of the term and the recognition of its importance have resulted from modern attempts at the orderly organization of all human activities where one group of persons has dealings with another.

Then it was discovered that the old personal relations of the physician with his public were suffering considerably from neglect on both sides and that attempts at repair must be made forthwith.

Certainly considerable elements of the public that have never known and consequently could scarcely appreciate the relations between the good family physician and his practice have found that they did not know how to obtain satisfactory medical advice. Too many physicians have been unconscious of or indifferent to the cordial and reciprocal relations that may and should exist between physician and patient. It is unfortunate but consistent with modern methods that repairs must be made on an assembly-line pattern.

As a result of this growing need in a world where each man looks askance at his neighbor the first

national medical public relations conference ever to be held will meet in St. Louis on November 27 to tackle six common objectives confronting the medical profession. The conference is under the sponsorship of the Secretary's office of the American Medical Association, its theme is "Shooting at Common Targets in Medical Public Relations," and qualified speakers will talk on such subjects as "The Public Speaks on Health," "What Public Relations Did for Us," and "Yes, the Profession needs PR."

The six major social issues that will be tackled are selling the need of public relations to state-medical society members, encouraging wider use of medical prepayment plans, setting up workable systems for handling night calls, the rebate problem, developing good will with labor, farm, industrial and co-op groups, and co-operating with health agencies.

If, out of the expected welter of slogans, catch phrases, maxims, speech making and general escape of steam in all directions can come the idea that man, and particularly the physician, is after all his brother's keeper, much good will come of the conference.

## MASSACHUSETTS MEDICAL SOCIETY

### DEATHS

APPEL — Bernard H. Appel, M.D., of Brighton, died on September 3. He was in his fiftieth year.

Dr. Appel received his degree from Tufts College Medical School in 1922. He was associate visiting physician at Beth Israel Hospital.

His widow, a son and a daughter survive.

DENNY — Francis P. Denny, M.D., of Brookline, died on September 6. He was in his eightieth year.

Dr. Denny received his degree from Harvard Medical School in 1895. He was chairman of the Advisory Council of Public Health and formerly health director in New London, New Hampshire, and was a member of the New England Pediatric Society and a fellow of the American Medical Association.

His widow survives.

MYERSON — Abraham Myerson, M.D., of Brookline, died on September 3. He was in his sixty-seventh year.

Dr. Myerson received his degree from Tufts College Medical School in 1908. He was professor emeritus of neurology at Tufts College Medical School and formerly clinical professor of psychiatry at Harvard Medical School. He was director of research at Boston State Hospital and was a member of the American Neurological Association, American Psychiatric Association, New England Society of Psychiatry and American Psychopathological Association and a fellow of the American Medical Association.

His widow, two sons and a daughter survive.

## RICHARD PEARSON STRONG (1872-1948)

Richard Pearson Strong was born at Fortress Monroe, Virginia, the son of Colonel Richard Pearson Strong. Throughout his life he exemplified the Army tradition of devotion to duty, whatever he undertook was carried through to the best of his ability. He was never discouraged by difficulties, and he never spared himself when his services were needed, the pre-eminent success of his medical career being due in large measure to these qualities. They were supplemented, however, by good basic training as a member of the first medical class to graduate from Johns Hopkins University School of Medicine and by postgraduate work in Berlin.

Strong's career began as a surgeon in the regular Army during the Spanish-American War. He organized medical research for the Army in the Philippine Islands, serving until 1902. Thereafter, until 1913, he directed the Biological Laboratory of the Bureau of Science in Manila. During this period, he personally conducted a series of important studies on dysentery, plague, cholera and other diseases that made him an international figure in the field of tropical medicine. When the terrible epidemic of pneumonic plague swept northern China in the winter of 1911, Strong was the American delegate to the International Plague Conference, which met in Peking. He and his associate, Teague, went into the stricken area to conduct experiments and to perform autopsies, working in unheated rooms during extremely cold weather, where they were exposed to infection of the most deadly character.

Strong was called to Harvard Medical School in 1913 to become its first professor of tropical medicine. He held this position until 1938, when he became professor emeritus.

From time to time, Strong led expeditions to tropical countries to gather data and to study tropical diseases in their natural habitat. Important among these expeditions were those to Peru in 1913, to the Amazon Basin in connection with

the Seventh Hamilton Rice Expedition in 1925, to Liberia and the Belgian Congo in 1926 and 1927, to Guatemala in 1931 and 1932 and again to the Belgian Congo in 1934.

So great was the demand for Strong's services that he was repeatedly granted leave of absence from his University duties. He combated the epidemic of typhus fever that raged in Serbia in 1915,

he demonstrated the mode of transmission of trench fever during World War I, he organized the Cannes Conference for the Red Cross in 1919 and assumed leadership of the medical section of the League of Red Cross Societies in Geneva in 1919 and 1920.

After retirement from his professorship at Harvard and at the request of his old friend Admiral Stitt, Strong largely rewrote Stitt's textbook on tropical diseases.

The United States had scarcely entered World War II when Strong was called upon to organize and conduct teaching in tropical medicine at the Army Medical School in Washington. Class

after class passed through his hands at intervals of six weeks until the war was over. The acclaim that he received for this teaching and the affectionate admiration that he inspired in the hearts of those who took the courses and in his associates as well testify to the excellence and the value of his contribution. This Washington assignment may be considered as the crowning achievement of his career.

Dr Strong received many honors from the United States Government, from medical institutions, and from other scientific bodies and universities in the United States, as well as from foreign governments. He died on July 4, 1948, after a protracted and painful illness. His courage and sweetness while in pain were an inspiration to those who were privileged to see him during this period. He will live long in the hearts of his many devoted friends and his influence will outlive them all.



## BOSTON MEDICAL LIBRARY

## IMPORTANT REFERENCE WORKS

The Library, aware of its responsibility to the medical profession of Massachusetts and northern New England, is particularly interested in procuring large or expensive reference works and especially the collected works of famous physicians. In this connection the following works have recently been acquired:

*Traité de médecine* Paris, 1948-1949 To be published in seventeen volumes. Eight volumes have been issued to date, covering the subjects of infectious diseases, avitaminoses, intoxications and anaphylaxis, respiratory diseases, diseases of the digestive tract, liver and pancreas and the endocrine glands.

Curry, Manfred *Bioklimatik Die Steuerung des gesunden und kranken Organismus durch die Atmosphäre* Two volumes Riederau, 1946. This is a monumental work on the relation of climate and weather to man in health and disease.

Gradwohl, R. B. H. *Clinical Laboratory Methods and Diagnosis* Fourth edition. Three volumes. St. Louis, 1948. This new edition has been greatly expanded. Volume III comprises the material on the subjects of parasitology and tropical medicine. The previous edition was issued in two volumes.

Fuchs, Adalbert *Die Erkrankungen des Augenhintergrundes* Wien, 1943. Illustrated with forty-four excellent color plates.

Freud, Sigmund *Gesammelte Schriften* Eleven volumes. Leipzig, 1925-1928. The collected works of this important pioneer in psychoanalysis.

Purkyne, Jan Evangelista *Sebrane spisy* Four volumes. Prague, 1919-1941. The collected works of a famous physiologist noted for his work on ophthalmoscopy. He made observations on the interior and background of the eye at least twenty-five years before Helmholtz.

## NOTE

The Library has recently received a handsome English grandfather's clock from the executors of Mrs. Mary Fifield King. It was presented to the Library in 1897 by Mrs. William B. C. Fifield after the death of Dr. Fifield but was to remain in the possession of Mrs. King as long as she desired. The clock was constructed by Henry Thornton, of London, a member of the Clock Makers Company, in 1699. The date of manufacture was about 1700. After cleaning it will be placed in or near the Fifield Room.

## MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

## CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

The October schedule for Consultation Clinics for Crippled Children in Massachusetts under the provisions of the Social Security Act follows:

CLINIC	DATE	CLINIC CONSULTANT
Lowell	October 1	Albert H. Brewster
Salem	October 4	Paul W. Hugenberger
Haverhill	October 6	William T. Green
Greenfield	October 11	Charles L. Sturdevant
Brockton	October 14	George W. Van Gorder
Worcester	October 15	John W. O'Meara
Gardner	October 19	Carter R. Rowe
Springfield	October 19	Garry deN. Hough, Jr.
Pittsfield	October 20	Frank A. Slowick
Fall River	October 25	David S. Gnee
Hyannis	October 28	Paul L. Norton

Physicians referring new patients to clinics should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

## MISCELLANY

## GRAFTON STATE HOSPITAL

Dr. Harlan L. Paine resigned his position as superintendent of the Grafton State Hospital on September 15, 1948, after completing 27 years' service on that date. He will assume the superintendency of the Channing Sanitarium, Inc., in Wellesley, Massachusetts.

## QUALIFICATIONS FOR SPECIALIST'S RATING IN PREVENTIVE MEDICINE

Applications from medical officers of the armed forces who want to be certified as specialists in preventive medicine may now be submitted to the Interim Board of Preventive Medicine, according to Department of the Army Circular No. 234, dated August 5, 1948. The circular also outlines the qualifications required of applicants and lists the items to be included in the applications. Written and oral examinations will be held during the fall of 1948 or the spring of 1949.

The circular also announces that the first group of officers to be certified will include those selected by the board as having "considerable experience and a long record of distinguished service in responsible preventive medicine or public health positions." For this first group, formal training and supervised experience requirements, as well as written examination, will be waived.

Examinations and certification will be administered by the Interim Board of Preventive Medicine, formed early this year by joint action of the Surgeons General of the Army, Navy, and United States Public Health Service in anticipation of the formation of an American Specialty Board in this field by the Advisory Board for Medical Specialties of the American Medical Association. The Interim Board was set up to serve only the three services.

Prerequisite qualifications include, among other things, membership in the American Medical Association, graduation from a medical school and internship in a hospital approved by the Council of Medical Education and Hospitals of the American Medical Association or by the Army or Navy, the degree of Master of Public Health or its equivalent, and both supervised experience and experience in a position of responsibility in the field of public health or preventive medicine.

## CORRESPONDENCE

## DRUGS IN HYPERTHYROIDISM

To the Editor An alarming statement subject to considerable unfavorable notoriety is made in an editorial in the August 5 issue of the *Journal* entitled "The Thyroid Nodule." This statement is quoted in its entirety "There is also the possibility that the drugs used in the treatment of hyperthyroidism may in some cases precipitate the development of carcinoma."

In view of the large number of patients who are receiving medical treatment of the thyroid gland, either definitively or preoperatively, this statement has widespread implications and deserves amplification and verification. If there is supportive evidence that certain drugs used in thyroid therapy are carcinogenic, they should be specifically mentioned. This type of aspersion may create unnecessary alarm for both patients and physicians and should be either adequately explained or withdrawn.

SEYMOUR B. LONDON, M.D.

ROSE E. LONDON, M.D.

Miami Beach 39, Florida

Note Payne, Crane and Price, in a study entitled "Thiouracil and Carcinoma of the Thyroid" (*Surgery* 22:496-501, 1947), reported a carcinoma of the thyroid gland developing in a patient receiving thiouracil in preparation for operation for hyperthyroidism. In unpublished data Bowler presents a similar case. Broders and Parkhill, in an article entitled "Diffuse and Adenomatous Goiter and Goiter Induced by Various Agents" (*Surgery* 16:633-646, 1944), describe the histology of thiouracil-induced goiters as characterized by cellular hyperplasia with marked mitotic activity, suggestive of carcinoma. In his study on "Tumours of the Thyroid Produced by 2-Acetyl-Amino-Fluorine and Allyl-Thiourea" (*Brit J Exper Path* 25:90-95, 1944), Bielchowsky produced thyroid carcinoma in animals by the use of allyl-thiourea in conjunction with the carcinogen 2-acetyl-amino-fluorine, but was unable to cause thyroid carcinoma by the use of the carcinogen alone. Purves and Griesbach produced thyroid tumors and some cancers in rats treated with thiourea (*Brit J Exper Path* 27:294-297, 1946). They stated "We believe that the production of these thyroid tumors is due, not to any direct carcinogenic action of the thiourea administered, but rather to the excessive and prolonged stimulation of the thyroid epithelium."

It is evident that thiourea derivatives result in extensive hyperplasia with mitoses in man as well as in experimental animals. In animals, adenomas arise as a result of the hyperplasias, as pointed out by Hellwig in a study entitled "Thyroid Adenoma in Experimental Animals" (*Am J Cancer* 23:550-555, 1935). The relation of adenomas to carcinoma development is rather widely accepted.—En

## BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

*Progress in Clinical Medicine*. By various authors. Edited by Raymond Daley, M.A., M.D. (Camb.), M.R.C.P., and Henry G. Miller, M.D. (Durh.), M.R.C.P., D.P.M. 8°, cloth 356 pp., with 22 illustrations and 15 plates. New York: Grune and Stratton, 1948. \$6.00.

Twelve specialists in their particular fields have collaborated in writing this report of progress in certain clinical subjects. The subjects discussed comprise the control of infections, venereal diseases, tropical medicine, gastrointestinal disorders including liver diseases, metabolic disorders, cardiovascular and renal diseases, blood diseases, diseases of the chest and nervous system, endocrine disorders, psychosomatic medicine and chronic rheumatism. Each subject is documented with a list of selected references. A good index

concludes the volume. The printing and type are good. The heavy, coated paper is unnecessary since all plates are inserts. The glare from the paper is distressing and fatiguing to the eyes. The book is recommended for all medical libraries as a reference source.

*Foundations of Neuropsychiatry*. By Stanley Cobb, M.D., Bullard Professor of Neuropathology, Harvard Medical School, and psychiatrist in chief, Massachusetts General Hospital. Fourth revised and enlarged edition of the work formerly known as *A Preface to Nervous Disease*. 8°, cloth, 260 pp. Baltimore: The Williams and Wilkins Company, 1948. \$2.50.

In this fourth edition of a popular standard manual, first published in 1936 and largely amplified in succeeding editions, the author has made corrections in all sections to keep the text up to date, and new references have been added where considered pertinent. The manual is written for students and practitioners with the object of giving the facts and correlations needed to understand the simpler workings of the central nervous system. The book is well published and is recommended for all medical libraries.

*A Synopsis of Anesthesia*. By J. Alfred Lee, M.R.C.S., L.R.C.P., M.M.S.A., D.A., consultant anesthetist to Southend General Hospital and Southend Municipal Hospital, Rockford, anesthetist to Tilbury Hospital, Runwell Hospital, East Ham Memorial Hospital and Essex County Council, assistant anesthetist to King George Hospital, Ilford. 12°, cloth, 254 pp., with 42 illustrations. Baltimore: The Williams and Wilkins Company, 1947. \$4.00.

This small manual, written for the student, the resident anesthetist and the general practitioner, is a summary of current teaching and practice, and is not intended to displace the large works on the subject. The text covers the whole field of anesthesia and is well arranged. A short first chapter is devoted to notes on history, including a chronology of important dates from 1771 to 1940. The text was printed in England and the sheets bound in the United States. The work reflects the best English practice. It should be in all anesthesia collections.

*The Aseptic Treatment of Wounds*. By Carl W. Walter, M.D., assistant professor of surgery, Harvard Medical School, and senior associate in surgery, Peter Bent Brigham Hospital. 4°, cloth, 372 pp., with 255 illustrations by Mildred B. Coddington, A.M., surgical artist, Peter Bent Brigham Hospital. New York: The Macmillan Company, 1948. \$9.00.

This monograph has been written primarily as a text for medical-school courses in surgical technic, but it should prove valuable to operating-room nurses and attendants, manufacturers and distributors of surgical apparatus and to technologists and craftsmen who have to do with such apparatus. The technic described is that elaborated at the Peter Bent Brigham Hospital at Boston during the past twelve years, and reflects the surgical philosophy of Harvey Cushing and Elliott C. Cutler. The author expresses the thought that because of the wide use of chemotherapy surgeons are becoming careless and not following a rigid standardized technic so essential to clean wound healing. Therefore, he has attempted to correlate the existing knowledge on the aseptic treatment of wounds for the general benefit of the operating surgeon and his assistants and technicians. The material is well organized and the text well written. The subjects of disinfection and sterilization in all their aspects are covered thoroughly. There are chapters on chemical and physical destruction of bacteria, air-borne contamination, operating-room technic, preparation of parenteral fluids, blood and plasma facilities, central-supply-room technic, hospital infection of wounds and the control of communicable disease. The illustrations carry a large part of the book and are excellent in their delineation of the points portrayed. The selected references are printed as footnotes to the text. A good index concludes the volume. The printing is well done with an excellent type, on good, light nonglare paper. The book is delightful to read and is a credit to the publisher. It is recommended for all medical-school and nursing-school libraries and to all persons interested in surgery.

*Taking the Cure The patient's approach to tuberculosis* By Robert G Lovell, M.D., University Hospital, University of Michigan, Ann Arbor 12<sup>o</sup>, cloth, 93 pp., with illustrations by Donald Gooch New York The Macmillan Company, 1948 \$2.00

This small book has been written for the new tuberculosis patient and contains much sensible practical information. There is a chapter on tuberculosis written for the layman who desires medical information about the disease. The book is well published and easy to read. It should be available to patients and their families.

## NOTICES

### ANNOUNCEMENT

Dr Richard N Abbott announces the opening of his office for the practice of pediatrics at 15 Winnemav Street, Natick.

### FBI

The Federal Bureau of Investigation announces that the fugitive from justice concerning whom a notice was published in the *Journal* of August 12, 1948, has been apprehended and is now in custody.

### SUFFOLK CENSORS' MEETING

The censors of the Suffolk District Medical Society will meet for the examination of candidates at the Boston Medical Library, 8 Fenway, Boston, on Thursday, December 2, at 4:00 p.m.

### HAMPDEN DISTRICT MEDICAL SOCIETY

The Program Committee of the Hampden District Medical Society has arranged for the following meetings in 1948-1949. On November 30, 1948, at 8:30 p.m., in the Academy of Medicine, Springfield, Dr Grantley W Taylor will speak on the subject "Carcinoma of the Breast." On January 25, 1949, at 8:30 p.m., in the Academy of Medicine, Springfield, Dr John Rock will speak on the subject "A Review of the Sterility Problem." And on April 26, 1949, at 6:00 p.m., in the Hotel Highland, Springfield (dinner meeting), Dr Douglas T Davidson will speak on the subject "Convulsive Disorders."

### NEW YORK ACADEMY OF MEDICINE

The Twenty-First Graduate Fortnight of the New York Academy of Medicine will be held October 4 through October 15, the subject being "Advances in Therapy." The program includes morning panel discussions, afternoon clinics, evening lectures, scientific exhibits and demonstrations.

A physician who is not a fellow of the Academy may obtain registration by sending his name and address, accompanied by a check for six dollars, to the New York Academy of Medicine, 2 East 103rd Street, New York 29, New York.

### AMERICAN BOARD OF OPHTHALMOLOGY

The American Board of Ophthalmology will hold practical examinations in San Francisco from March 21-24, in New York City from June 11-15, in St. Louis from October 15-19 and in Boston in December, 1949. A written qualifying test will be held in January, 1949. Applications for the 1950 written qualifying test are now being accepted.

Candidates for the certificate of the American Board of Ophthalmology are accepted for examination on the evidence of a Written Qualifying Test. These tests are held annually in various parts of the United States.

Registration is already closed for the next test to be given in January 1949.

Applications are now being accepted for the 1950 Written Test. They will be considered in order of receipt until the quota is filled.

A supplementary list of diplomates from January, 1948, to January, 1949, will be sent without charge to all purchasers of the Board's *Directory*. This supplementary material is arranged alphabetically and geographically. No biographical material is included.

### MEDICAL SOCIETY OF THE STATE OF PENNSYLVANIA

The centennial celebration of the Medical Society of the State of Pennsylvania will be held in Philadelphia from October 3 to 7. The meeting will consist of scientific sessions at the University of Pennsylvania, social gatherings at the Bellevue-Stratford Hotel and clinicopathological conferences.

Further information regarding the program may be obtained from Dr Walter F Donaldson, secretary-treasurer, Medical Society of the State of Pennsylvania, 8104 Jenkins Arcade, Pittsburgh 22, Pennsylvania.

### VAN METER PRIZE AWARD

The American Goutier Association again offers the Van Meter Prize Award of three hundred dollars and two honorable mentions for the best essays submitted concerning original work on problems related to the thyroid gland. Provided essays of sufficient merit are presented in competition, the award will be made at the annual meeting of the association, which will be held in Madison, Wisconsin, on May 26, 27 and 28, 1949.

The competing essays may cover either clinical or research investigations, should not exceed three thousand words in length and must be presented in English, and a typewritten double-spaced copy sent to the corresponding secretary, Dr T C Davison, 207 Doctors' Building, Atlanta 3, Georgia, not later than March 15, 1949. The committee, who will review the manuscripts, is composed of men well qualified to judge the merits of the competing essays.

A place will be reserved on the program of the annual meeting for presentation of the winning essay by the author if it is possible for him to attend. The essay will be published in the annual *Proceedings* of the association. This will not prevent its further publication, however, in any journal selected by the author.

### ARMY MEDICAL RESIDENT TRAINING PROGRAM

Applications for the Military Resident Training Program (in Army general hospitals) are currently being received in the Office of the Surgeon General, United States Army. Under this training program any physician who qualifies for and accepts a commission in the Regular Army Medical Corps will be given the opportunity of competing for an approved residency in the field of his choice.

Medical specialty training available for newly commissioned officers under this program is as follows: a limited number of senior residencies in thoracic surgery, orthopedics, pulmonary diseases, pathology, ophthalmology and physical medicine, a limited number of residencies in orthopedics, pathology and physical medicine, a limited number of assistant residencies in obstetrics, urology, thoracic surgery, dermatology and pediatrics, and a substantial number of assistant residencies in anesthesia, general surgery, orthopedics, internal medicine, psychiatry, pathology, ophthalmology, otolaryngology, radiology, physical medicine and clinical physician training. Some of the assistant residencies in urology, general surgery, internal medicine and radiology are available at the Gorgas Hospital, Canal Zone.

Officers who are not selected to enter residency training on January 1 or July 1, 1949, will, if qualified, be furnished a certificate indicating the date on which they will enter approved professional training. The program is designed to ensure that all qualified applicants will be given the opportunity of completing their requirements for certification by an American specialty board.

October 1, 1949, has been established as the deadline for receipt of applications from physicians who are interested in participating in this training program. Complete information and application blanks may be obtained from the Surgeon General, Department of the Army, Washington 25, D.C.

(Notices concluded on page xv)

OTICES (Concluded from page 492)

## SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING  
THURSDAY, SEPTEMBER 30

### FRIDAY OCTOBER 1

\*9-00 a.m.-12-00 m. Combined Medical and Surgical Staff Rounds  
Peter Bent Brigham Hospital  
\*12-00 m. X-Ray Conference Margaret Jewett Hall Mt. Auburn  
Hospital Cambridge

### TUESDAY OCTOBER 5

\*12-15-15 p.m. Clinicoroentgenological Conference Peter Bent  
Brigham Hospital  
\*1-30-2-30 p.m. Pediatric Rounds Burnham Memorial Hospital  
for Children Massachusetts General Hospital

### WEDNESDAY OCTOBER 6

\*11-00 a.m. 12-00 m. Medical Clinic Amphitheater Children's  
Hospital  
\*12-00 m. Clinicopathological Conference (Children's Hospital)  
Amphitheater Peter Bent Brigham Hospital  
\*2-00-3-00 p.m. Combined Clinic by the Medical Surgical and  
Orthopedic Services Amphitheater Children's Hospital

\*Open to the medical profession

SEPTEMBER 28 Norfolk District Medical Society Page 452 issue of  
September 16.

SEPTEMBER 29 Mississippi Valley Medical Editors Association  
Page 170 issue of January 29

OCTOBER 1 and 2. American Society of Anesthesiologists Inc Page 482,  
issue of September 2.

OCTOBER 1-MAY 20 Metropolitan State Hospital Page 416 issue of  
September 9

OCTOBER 3-7 Medical Society of the State of Pennsylvania Page 492

OCTOBER 4 South Boston Medical Society Page 452 issue of  
September 16

OCTOBER 4-15 New York Academy of Medicine Page 492

OCTOBER 6-9 American Board of Ophthalmology Page 170 issue of  
January 29

OCTOBER 9 Suffolk District Medical Society Page 452 issue of  
September 16.

OCTOBER 14 The Practical and Clinical Sides of the Management of  
the Rh Problem in Pregnancy Dr. William C. Moloney Pentucket  
Association of Physicians 8-30 p.m. Haverhill

OCTOBER 15 American Trudeau Society Page 416 issue of Septem-  
ber 9

OCTOBER 18-22. American College of Surgeons. Page 417 issue of  
September 9

OCTOBER 27 New England Obstetrical and Gynecological Society  
Annual Meeting Hotel Somerset, Boston

NOVEMBER 13 American Clinical and Climatological Association  
Page 582 issue of April 15

NOVEMBER 3 and 4. Annual Meeting of National Committee for Mental  
Hygiene Inc. Page 282 issue of August 12

NOVEMBER 3-5 Seventh New England Postgraduate Assembly Copley  
Place Hotel, Boston

NOVEMBER 4-6. American Society of Anesthesiologists Page 418  
issue of September 9

NOVEMBER 8-12 American Public Health Association Page 420 issue  
of March 18

NOVEMBER 10-13 Association of Military Surgeons of the United  
States Page 722 issue of May 15

NOVEMBER 20-23 American Academy of Pediatrics Annual Meeting  
Chalfonte-Haddon Hall Hotel Atlantic City New Jersey

NOVEMBER 30 Hampden District Medical Society Page 492

DECEMBER 2. Suffolk Censors Meeting Page 492

DECEMBER 7-9 Southern Surgical Association Annual Meeting  
Page 543 issue of April 8

DECEMBER 9 and 10 New York State Society of Anesthesiologists  
Page 34 issue of July 1

FEBRUARY 4 1949 American Board of Obstetrics and Gynecology Inc  
Page 244 issue of August 5

MARCH 28-APRIL 1 1949 American College of Physicians Page 158  
issue of July 22

MAY 16-19 1949 American Urological Association Baltimore Hotel  
Los Angeles

MAY 26-28 1949 American Gopher Association Hotel Lorraine  
Madison Wisconsin

NOVEMBER 11-17 1949 Third Inter American Congress of Radiology  
Page 158 issue of July 22.

## DISTRICT MEDICAL SOCIETIES

### HAMPDEN

NOVEMBER 30 8-30 p.m. Academy of Medicine, Springfield. Car-  
cinoma of the Breasts Dr. Grantley W. Taylor

### NORFOLK

SEPTEMBER 28 Specialty Night.

### SUFFOLK

OCTOBER 9 Fall Dinner

DECEMBER 2. Suffolk Censors Meeting

Advertisement



From where I sit  
by Joe Marsh

## Who Is This Man?

Now and then, in the pages of the  
*Clarion*, I run a biographical quiz,  
under the heading of "Who Is This  
Man?" For instance .

*"He was one of the earliest lovers  
in American history*

*"And yet he was too shy to court  
a woman outright .*

*"He came to the New World on  
the Mayflower .*

*"A cooper to repair the beer barrels  
accompanying the Pilgrims . . .*


*"Who is this man?"*

I thought that everybody was  
stumped But not Ma Hopkins, who  
returned the clipping to me with  
"John Alden" on it She recognized all  
the clues—including that reference to  
"beer" and "cooper"

*For Ma—who's read her history,  
knows that beer as the beverage of  
moderation, is as old in this land of  
ours as the never-ending American  
search for tolerance which brought the  
Pilgrims over to this country in the  
first place*

Joe Marsh

Copyright, 1948, United States Brewers Foundation



This baby's mother learned  
about Mead's Oleum Percomorphum from her physician, not from  
public advertising or displays

*"Servamus Fidem"*

## HOW much sun does the infant really get?

*Not very much* (1) When the baby is bundled to protect against weather or (2) when shaded to protect against glare or (3) when the sun does not shine for days at a time Mead's Oleum Percomorphum is a prophylactic against rickets available 365½ days in the year, in measurable potency and in controllable dosage *Use the sun, too*

Mead Johnson & Co., Evansville, Ind., U S A

# The New England Journal of Medicine

Copyright, 1948 by the Massachusetts Medical Society

Volume 239

SEPTEMBER 30, 1948

Number 14

## CHRONIC SUBDURAL HEMATOMA\*

### Expansion of Compressed Cerebral Hemisphere and Relief of Hypotension by Spinal Injection of Physiologic Saline Solution

ALBERT A. LALONDE, M.D., J. AND W. JAMES GARDNER, M.D. ‡

CLEVELAND, OHIO

AFTER evacuation of a subdural hematoma the compressed hemisphere may fail to expand spontaneously. This may be a grave prognostic sign. Trotter,<sup>1</sup> Coleman,<sup>2</sup> Coblenz<sup>3</sup> and Voris<sup>4</sup> have discussed this aspect of subdural hematoma.

We agree with Coleman and Coblenz that failure of the compressed hemisphere to expand is more likely than cerebral edema to cause serious symptoms. Coleman found that the compressed hemisphere may not expand for several days after evacuation of the clot. It has been shown that the hemisphere may still be in a compressed state at autopsy even though the hematoma has been adequately evacuated.<sup>5</sup>

We have found that in some patients with postoperative recurrence of symptoms lumbar puncture may reveal the pressure to be subnormal. Re-exposure of the operative field in these cases demonstrates that the brain has failed to expand. The cerebrospinal-fluid hypotension and the associated state of compression of the hemisphere before and sometimes after evacuation of the hematoma may produce symptoms and signs indistinguishable from those of increased intracranial pressure.

Laudig, Browder and Watson<sup>6</sup> studied 143 cases of subdural hematoma and found that some patients with large hematomas had low cerebrospinal-fluid pressures, as measured in the lumbar thecal sac. This low intracranial pressure was substantiated at operation in some cases. The authors were unable to explain the altered state of consciousness in the presence of the low intracranial pressure.

Why the hemisphere fails to expand or why the intracranial pressure remains subnormal in these cases is not known, nor is it known which of these conditions is cause and which is effect. We have found that both conditions respond favorably to

the intraspinal injection of physiologic saline solution. The presence or absence of the hematoma membrane does not affect the syndrome, removal of the membrane is not necessary to cure it.

It may be significant that our patients were all in the sixth and seventh decades of life and did not have increased intracranial pressure before operation.

The literature contains reports of the treatment of this condition by intravenous injection of half-strength physiologic saline solution and placing the head in the dependent position<sup>7</sup>, instillation of distilled water into the cranial subdural space and intravenous injection of distilled water and saline solution, and removal of the inner membrane of the hematoma from the cortex.<sup>8</sup> It occurred to one of us (W. J. G.) that intraspinal injection of saline solution during the operation would quickly re-expand the compressed hemisphere and restore it to a more normal anatomic and physiologic state, as well as effecting a more complete removal of the hematoma by obliterating the cranial subdural space. This procedure has since been employed in all cases in which there is failure of spontaneous re-expansion of the compressed hemisphere.

The presence of the inner hematoma membrane has not prevented expansion of the compressed hemisphere in any case in which saline solution was injected intraspinally, and the expansion was accomplished in every case without raising the spinal-fluid pressure above the equivalent of 150 mm. of water. We believe that postoperative intracranial hypotension is less likely to occur after this procedure. No patient treated by such technic has developed evidence of cerebral edema after operation, and there has been prompt improvement of symptoms in all cases. In some cases we believe it to have been responsible for saving the patient's life.

With one exception the brain was under direct observation as it was being re-expanded by this procedure after evacuation of a subdural hematoma. In the majority of cases the brain was expanded

\*From the Cleveland Clinic and the Frank E. Bunts Educational Institute.  
Presented at a meeting of the Society of Neurological Surgeons, Omaha, Nebraska, June 11, 1948.

‡Formerly staff assistant, Department of Neurosurgery, Cleveland Clinic.  
Head, Department of Neurosurgery, Cleveland Clinic; professor of neurosurgery, Frank E. Bunts Educational Institute.

until it was in contact with the inner surface of the dura. Expansion was accomplished by intraspinal injection of saline solution in 5 cases and by intraventricular injection in 2 cases. The volume of fluid introduced at a single injection varied from 50 to 220 cc. No attempt was made to remove the inner hematoma membrane. Drainage was employed in only 1 of the 7 cases—drainage is not necessary if re-expansion of the hemisphere is complete.

In addition to the 7 cases of subdural hematoma in which the compressed hemisphere failed to expand spontaneously, this procedure was employed in 2 cases of intracranial hypotension following operation for other conditions.

### CASE REPORTS

**CASE 1** A 50-year-old man had bumped his head on a low porch about 1 month before admission on November 12, 1944. On the day of admission he had suddenly developed weakness of the left arm and leg and had difficulty in speaking. Roentgenograms of the skull showed the pineal gland displaced to the left. The spinal-fluid pressure was equivalent to 48 mm of water, and the fluid was xanthochromic.

On the night of November 14 the patient became comatose and developed Cheyne-Stokes respiration and extreme rigidity of the left arm and leg. The head was turned to the left and there was severe opisthotonos. A trephine opening was made on the right side just anterior to the fissure of Rolando, and a large, liquid, subdural hematoma was evacuated. The brain could be seen through the trephine opening and was depressed about 1.5 cm from the inner surface of the dura. This undoubtedly did not represent the point of greatest compression of the brain. The subdural cavity was irrigated with physiologic saline solution, and no solid clot was evident. The brain pulsed feebly and did not expand in the slightest. To expand the brain the patient was turned on his side, and a spinal puncture performed. When 220 cc of saline solution had been injected, the brain had expanded until it was almost in contact with the inner surface of the dura. A rubber tissue drain was then introduced into the subdural space, and the wound closed with a single layer of buried, interrupted silk sutures. On returning to his room the patient was quite restless. The respirations were 52 per minute, deep and labored. The temperature mounted rapidly to 103.4°F and the pulse was 160 per minute. In spite of these signs he was regaining consciousness and responded when spoken to. During the next 12 hours he drank 4000 cc of fluid but remained thirsty. Twelve hours after operation he was lucid, and the left hemiplegia was rapidly improving. The drain was then removed. The patient made an uneventful recovery and was discharged on the 12th postoperative day. He was not seen again until 3 years later, when he reported that he had had no symptoms referable to his head.

**CASE 2** A 59-year-old man had had severe frontal headaches, nausea and vomiting, as well as mild confusion, for 6 weeks. The headache was always relieved immediately when he lay down. On March 8, 1946 neurologic examination was negative. The spinal-fluid pressure was too low to be recorded. The fluid contained a protein of 58 mg per 100 cc and 10 cells. Pneumoencephalography was performed on March 25. The spinal-fluid pressure was equivalent to only 260 mm of water with patient in the sitting position. The total volume of fluid recovered was 99 cc, and encephalograms revealed evidence of an expanding lesion on the left side. A left frontal craniotomy disclosed a subdural hematoma. The hematoma was evacuated but the brain showed no tendency to re-expand. The wound was closed without drainage. Six hours later the patient was still comatose and had developed Cheyne-Stokes respiration and a bilateral Babinski reflex. The spinal-fluid pressure again was too low to record. A needle was introduced through the scalp into the cranial subdural space to permit evacuation of its contents. Fifty cubic centimeters of 1 per cent saline solution was then injected into the lumbar subarachnoid space, raising the spinal-

fluid pressure to the equivalent of 120 mm of water and producing a flow of bloody fluid from the scalp needle. Immediately thereafter, the patient opened his eyes, answered to his name, and moved his limbs for the first time since operation. The Babinski reflex could no longer be elicited on the left. On the day after operation the symptoms and signs recurred, and a similar procedure was carried out. 130 cc of saline solution being injected with the same immediate and gratifying response. The foot of the bed was elevated. On the 3rd postoperative day the symptoms again recurred, and the spinal fluid pressure was again not recordable. A continuous intraspinal drip of physiologic saline solution containing 30,000 units of penicillin per liter was started and maintained at a pressure equivalent to 120 mm of water. The patient improved during the first 24 hours of this therapy but during the next 24 hours he developed fever and stupor and the procedure was discontinued. His condition continued to grow worse until he appeared moribund. Recalling the experiments of Weed<sup>9</sup> in which intracranial pressure in animals was raised by the subarachnoid injection of India ink, and in the hope of demonstrating a point of leakage of the cerebrospinal fluid in case the patient came to autopsy, we decided to use this procedure. Accordingly, on the 10th postoperative day 0.5 cc of sterile India ink was injected into the lumbar spinal canal. The spinal-fluid pressure at that time was too low to record. Twelve hours later the patient's condition was improved, the spinal-fluid pressure was equivalent to 250 mm of water, and the fluid contained 137 polymorphonuclear leukocytes. A specimen of this fluid was sterile on culture. On the 11th postoperative day the patient was well oriented and able to get out of bed. However, on the 13th postoperative day he again developed severe headache, and the spinal-fluid pressure was once more too low to record. He was given hypotonic saline solution intravenously, but the hypotension persisted. By the 17th day, however, without further intraspinal injections, he was free of headache and was discharged. He made a complete recovery, and no sequelae were demonstrable when he was seen 8 months after operation.

This case demonstrated how rapidly the neurologic signs and symptoms due to cerebrospinal fluid hypotension will respond to the raising of intraspinal pressure. However, we do not recommend the subarachnoid injection of India ink to accomplish this purpose. We believe that the failure to obtain sustained improvement by the intraspinal injection of saline solution in this case was caused by an unsatisfactory evacuation of the cranial subdural space through the scalp needle. The effect would have been lasting if the operative wound had been reopened during the injection to make certain that the cavity was obliterated.

**CASE 3** A 68-year-old man was admitted to the Cleveland Clinic on June 29, 1946. On March 11 he had fallen from a desk on which he was standing and had struck the back of his head on the floor. He was unconscious for about 30 minutes. During the next 24 hours he was comfortable and alert, but then became restless, incoherent and finally stuporous. He was treated by lumbar punctures, with temporary improvement.

Neurologic examination revealed a right hemiparesis, right homonymous hemianopsia and aphasia. The spinal fluid pressure was equivalent to 180 mm of water, and the fluid was clear and colorless. Roentgenograms of the skull showed a linear fracture on the left side with the pineal gland dislocated to the right.

On July 3 a left parietal craniotomy was performed. The exposed portion of the dura with the attached outer dural hematoma membrane was excised, and a large, liquid, subdural hematoma was evacuated. The brain was depressed 2.5 cm below the inner surface of the dura and showed no tendency to expand spontaneously. A spinal puncture was performed, and 130 cc of saline solution injected. The brain expanded until it was in contact with the dura. The bone was then replaced, and the wound closed without drainage.

On the 1st postoperative day the patient was no longer aphasic but was somewhat drowsy. A Babinski reflex was present on the right, and there was a slight weakness of the right side of the face. On the 2nd postoperative day he developed jargon aphasia and a bilateral Babinski reflex, but no demonstrable hemianopsia. The spinal-fluid pressure was equivalent to 170 mm of water, and the fluid was bloody. No fluid could be aspirated through the trephine opening in the skull. On the 5th postoperative day he was no longer aphasic, and neurologic examination was negative. He was discharged on the 10th postoperative day in excellent condition and was in good health when last seen 2 months after operation.

**CASE 4** A 64-year-old man was thrown from a horse in June, 1946, and was unconscious for 25 minutes. Two months later he suddenly developed severe headache and a left hemiparesis. Neurologic examination on September 24 revealed a left hemiparesis with a Babinski reflex. There was no papilledema, and the spinal-fluid pressure was equivalent to 170 mm of water. This fluid was clear and colorless. A pneumoencephalogram was made on September 28. All the fluid was removed, measuring 104 cc. The films showed no ventricular filling. On September 30 a right temporal trephine opening was made, and a large, coffee-colored, liquid, subdural hematoma was evacuated. As the brain did not expand, the patient was turned on his side, and 100 cc. of physiologic saline solution was injected into the lumbar canal. The needle then became dislodged, and the injection was discontinued, although this quantity was not sufficient to bring the brain into contact with the dura. The wound was closed without drainage. The patient awakened promptly after returning to his room and exhibited improvement of the hemiparesis. On the 5th postoperative day there was no demonstrable weakness of the extremities, and he was discharged the next day. He remained well until 19 days after operation, when he had a left jacksonian convulsion. A similar attack occurred 3 days later, with loss of consciousness and paresis of the left arm. He was readmitted to the hospital on October 25, and an encephalogram was made the next day. All the fluid was removed, measuring 119 cc. The initial pressure was normal. There was again no air in the ventricles, but the callosal sulcus was tilted, indicating an expanding lesion on the right. On October 28 bilateral trephine openings were made in the frontal and parietal regions. Only a small amount of chocolate-colored fluid was present on the right side. About 20 cc. of thick, coffee-colored fluid was evacuated through the left parietal trephine opening, and about 60 cc. of clear yellow subdural fluid was evacuated through the left frontal trephine opening. The incisions were closed without drainage, since the brain expanded spontaneously. The weakness of the left arm improved gradually, and the patient was discharged on the 5th postoperative day. Follow-up examination on January 23, 1948, revealed a slight weakness of the left hand grasp. The remainder of the neurologic examination was normal. He stated that he had had no headaches and had been doing his usual farm work since hospital discharge.

It may be significant that in this case, in which reoperation was necessary, the intraspinal injection of physiologic saline solution was discontinued before the hemisphere was restored to its normal shape.

**CASE 5** A 60-year-old man had been well until November 14, 1946, when he fainted while walking down the street, striking his head on the sidewalk. He was unconscious for about 5 minutes. During the next 2 weeks he complained of headache and failing memory and weakness of the left arm and leg. During January 1947, he developed a definite change in personality, and his headaches became severe. On January 22 he developed aphasia and stupor. Neurologic examination on March 1 revealed amimia on the right, ataxic gait and a Babinski reflex on the left. There was marked loss of memory. The spinal-fluid pressure was equivalent to 160 mm of water, and the fluid was faintly xanthochromic.

On March 4 with the patient in the supine position, trephine openings were made in front of each parietal emi-

nence. There was no subdural hematoma on the right, but on the left side a large quantity of coffee-colored subdural fluid was evacuated. The brain showed no tendency to expand. To avoid turning the patient on his side for a spinal injection it was decided to inject the saline solution into the right lateral ventricle, and 67 cc. of solution was introduced. This expanded the left hemisphere until it was in contact with the inner surface of the dura. The wound was closed without drainage. The patient awakened soon after returning to his room, and no aphasia or Babinski reflex could be elicited. There was no recurrence of symptoms, and he was discharged on the 5th postoperative day. Follow-up examination on February 21, 1948, revealed no neurologic deficit.

Ventricular injection of physiologic saline solution in these cases is a more simple procedure than spinal injection if the patient is operated upon in the supine position, but it may aggravate an existing incisural hernia. On the other hand, intraspinal injection of saline solution may reduce an incisural hernia.

**CASE 6** A 52-year-old man was struck by an automobile on February 15, 1947. He was unconscious for a few minutes but had no other complaints until April 13, when he developed increasingly severe suboccipital and frontal headache. On April 11 his left arm and leg became weak, and he was confused. Neurologic examination 2 days later revealed a left hemiparesis. There was no papilledema. At pneumoencephalography the initial spinal-fluid pressure was normal and 74 cc. of fluid was recovered. The ventricles were markedly displaced toward the left. A right parietal trephine was performed, with evacuation of a large, liquid, coffee-colored, subdural hematoma. The brain was depressed 2.5 cm below the dura. A left parietal trephine revealed a small subdural clot. One hundred cubic centimeters of physiologic saline solution was injected into the lumbar canal, but this quantity was not sufficient to effect a complete re-expansion of the right hemisphere. The wound was closed without drainage. The patient awakened soon after returning to his room, and the hemiparesis was much improved. On the 2nd postoperative day nausea and vomiting developed. The spinal-fluid pressure was equivalent to 210 mm of water. This fluid contained 6 white cells per cubic millimeter and a protein of 41 mg per 100 cc.\* On the 5th postoperative day neurologic examination was negative, and he was discharged. Follow-up examination on May 20 revealed no neurologic deficit.

**CASE 7** A 66-year-old woman was first seen at the Cleveland Clinic on May 12, 1947, because of paralysis of the left arm and leg. Three weeks previously she had slipped and fallen to the sidewalk, striking her head. She had not lost consciousness. One week later she awakened with weakness of her left arm and leg, which gradually progressed to complete paralysis. Neurologic examination revealed a left homonymous hemianopsia, paralysis of left lateral gaze, dilatation of the left pupil, a central type of facial weakness on the left and paralysis of the left arm and leg. The spinal-fluid pressure was equivalent to 160 mm of water. The fluid was clear and faintly xanthochromic. The next day bilateral trephine openings were made in the temporal regions. There was no abnormality on the left, but on the right side a large liquid subdural hematoma was evacuated. The brain failed to re-expand spontaneously. A cannula was introduced into the left lateral ventricle and 135 cc of physiologic saline solution was injected. This caused the right hemisphere to expand until it was in contact with the dura. The wounds were closed without drainage. There was pro-

\*Bedford<sup>18</sup> has reported the appearance of polymorphonuclear leukocytes in the cerebrospinal fluid in 9 out of 15 dogs by the introduction of isotonic sodium chloride into the cisterna magna, while no leukocytes appeared after the injection of distilled water or Ringer's solution (Dale's formula). We have had a similar experience after the intraspinal injection of 1 per cent saline solution in the treatment of cerebrospinal fluid hypotension from various causes although this meningeal reaction occurred very seldom. We believed that this reaction was probably due to an impurity in the saline solution since it does not invariably occur and plan to investigate this problem further. No symptoms of meningitis occurred in any of the cases of subdural hematoma in this paper.

gressive improvement in the strength of the left arm and leg from the 1st postoperative day, and the patient was discharged on the 7th postoperative day. Examination 1 month after operation revealed no neurologic deficit. When last seen on February 18, 1948, she had no complaints, and neurologic examination was negative.

This procedure was employed in the following cases of intracranial hypotension after operations for conditions other than subdural hematoma.

A 42-year-old man had a right frontal craniotomy on May 12, 1947, with removal of a pituitary adenoma. He awakened the evening of his operation and was in good condition. On the 1st postoperative day headache developed. The spinal-fluid pressure was equivalent to 210 mm of water, and the fluid was bloody. On the 2nd postoperative day he had a generalized convulsion and became somnolent. He was taken to the operating room, and the wound was reopened. When the section of bone was removed an extradural clot about 3 cm in thickness was disclosed. This clot was removed, and the dura opened, disclosing no intradural clot. The brain was moderately compressed below the inner surface of the dura, which was loosely closed, and the bone disk was replaced. On the next day the patient was more alert but complained of severe headache. The spinal-fluid pressure was equivalent to 165 mm of water. Five cubic centimeters of bloody fluid was removed, and the spinal-fluid pressure was equivalent to 110 mm of water. This relieved his headache, but on re-elevation of the head of the bed, the headache recurred and was relieved immediately when his head was lowered. On the 4th postoperative day he exhibited somnolence and complained of severe headache. During the next 48 hours the stupor deepened, and a bilateral Babinski reflex appeared. On the 6th postoperative day, with the patient in coma, the wound was reopened. The brain was found to be depressed to the same extent as at the time of closure of the previous exploration. There was no clot. The dura was closed, and a cannula was introduced into the anterior horn of the right ventricle. Forty cubic centimeters of physiologic saline solution was injected with some expansion of the dura, but when the bone was replaced the dura was still found to be depressed 1.5 cm from the inner table. The patient was then turned on his side, and a spinal puncture performed. After 150 cc of physiologic saline solution had been injected into the spinal canal the dura was in contact with the inner table. The spinal-fluid pressure at this point was just measurable. The wound was then closed without drainage. The patient awakened 2 hours after returning to his room, and his condition steadily improved. Forty-eight hours later he was normally alert and had no headache. He was discharged in good condition 9 days after the last operation.

This case shows that failure of the compressed hemisphere to expand is not peculiar to the subdural hematoma but may occur in acute extradural hematoma as well. The restoration of the shape of the brain to normal in this case appeared to be a life-saving measure.

A 57-year-old man had a right parietal craniotomy on November 4, 1947, with removal of a parasagittal meningioma. On the 1st postoperative day there was marked paresis of the left arm but less paresis of the left leg than had been present before operation. He was alert and talking. On the 2nd postoperative day he developed auricular fibrillation. The spinal-fluid pressure was equivalent to 110 mm of water. He then developed paralysis of the left arm and leg and became somnolent. A roentgenogram of the skull at that time showed the pineal gland to be in the midline. Thrombosis of the sagittal sinus was suspected, and heparin and dicumarol were started. On the 4th postoperative day he was more alert, and there was some movement of the left arm. On the 5th postoperative day a mild clonic convulsion occurred in the left side of the face and left arm. The spinal-fluid pressure was equivalent to 45 mm of water. On the 6th postoperative day he was comatose and could not be aroused. The spinal-fluid pressure was equivalent to 35 mm of water. Eighty cubic centimeters of physiologic saline solution was injected into the lumbar canal. When the spinal-fluid pressure had reached the equivalent of 120 mm of water the pa-

tient awakened and began to talk, and when the figure had reached 200 he was quite lucid. This improvement was not maintained, however, and the next day the spinal fluid pressure was too low to be recorded. Twenty cubic centimeters of physiologic saline solution injected into the lumbar canal raised the spinal-fluid pressure to the equivalent of 150 mm of water, and he again awakened and talked quite intelligently. Twelve hours later he was again stuporous, and the spinal-fluid pressure could not be recorded. Sixty cubic centimeters of physiologic saline solution was injected into the lumbar canal, raising the spinal-fluid pressure to the equivalent of 120 mm of water, with the same immediate gratifying result. Anticoagulant therapy was discontinued on the 7th postoperative day. Two days later the stupor had recurred, the foot of the bed was elevated, and 1000 cc of 0.5 physiologic saline solution given intravenously. There was some improvement, but it was not maintained. On the 10th postoperative day a continuous drip of saline solution into the lumbar canal was started. This was regulated to maintain the spinal-fluid pressure at the equivalent of 150 mm of water, and he showed immediate improvement. Later he was again given 1000 cc of 0.5 physiologic saline solution intravenously. The intraspinal drip was continued for 15 hours, and a total of 650 cc introduced. He was much brighter than he had been on any day since operation. The left hemiplegia persisted. There was no recurrence of stupor and his general condition was excellent at the time of his discharge on the 15th postoperative day.

This patient again demonstrated how rapidly the neurologic signs and symptoms due to cerebrospinal fluid hypotension will respond to the raising of the intraspinal pressure.

#### SUMMARY

Failure of the compressed hemisphere to expand after evacuation of a subdural hematoma is associated with cerebrospinal-fluid hypotension and may be a grave prognostic sign.

The compressed hemisphere may be expanded mechanically at the time of operation by the injection of physiologic saline solution into the spinal subarachnoid space or into the lateral ventricle.

Expansion of the compressed hemisphere decreases or abolishes the subdural dead space, restores the brain to a more normal anatomic and physiologic state, and obviates the need for drainage of the subdural space.

No ill effects have occurred from this procedure. Improvement has been immediate and dramatic.

This series of cases indicates that failure of expansion of the compressed hemisphere is more common in elderly patients who do not have increased intracranial pressure before operation.

The signs of intracranial hypotension may simulate those of intracranial hypertension.

#### REFERENCES

1. Trotter W. Chronic subdural haemorrhage of traumatic origin and its relation to pachymeningitis haemorrhagica interna. *Brit J Surg* 2:271-291 1914.
2. Coleman C. C. Chronic subdural hematoma: diagnosis and treatment. *Am J Surg* 28:341-363 1935.
3. Cohlentz R. G. Chronic subdural hematoma: diagnosis and treatment. *Surgery* 4:194-210 1938.
4. Voris H. C. Diagnosis and treatment of subdural hematoma. *Surgery* 10:447-456 1941.
5. White J. C. Case records of Massachusetts General Hospital (Case 24122). *New Eng J Med* 218:531-533 1938.
6. Ludwig G. H., Browder J. and Watson R. A. Subdural hematomas: study of 143 cases encountered during five-year period. *Ann Surg* 113:170-191 1941.
7. Oldberg E. Subdural hematoma. *M Clin. North America* 29:61-72 1945.
8. Elsberg C. Discussion of White's.
9. Weed L. H. Experimental production of internal hydrocephalus. *Contrib Embryol* 9:425-446 1920.
10. Bedford T. H. B. Effect of introduction of isotonic sodium chloride solution into cisterna magna of dog on cell content of cerebrospinal fluid. *J Physiol* 104:299-304 1946.

## STREPTOMYCIN IN THE TREATMENT OF BACTERIAL ENDOCARDITIS\*

## Report of Two Cases

NORMAN L. CRESSY, M.D.,† WILLIAM J. LAHEY, M.D.,‡ AND PAUL KUNKEL, M.D.§

NEW HAVEN, CONNECTICUT

**E**XPERIENCE with streptomycin in the treatment of bacterial endocarditis is as yet limited. Hunter<sup>1</sup> discussed 18 cases and suggested that streptomycin is the drug of choice in endocarditis caused by gram-negative bacilli and penicillin-resistant, gram-positive cocci, and in infections that fail to respond to maximal penicillin treatment.

The case reports that follow present features of bacteriologic and therapeutic interest. The causative organism in the first case was a gram-negative, anaerobic, non-spore forming bacillus (*bacteroides*), and in the second, a highly resistant alpha-hemolytic streptococcus.

**CASE 1** J. P., a 46-year-old man, entered the hospital in November, 1946, with a 2-month history of fever, night sweats, chills and intermittent pain along the inner aspect of the upper part of the left thigh. He had increasing weakness and fatigability and had lost 25 pounds. There was no history of antecedent trauma, infection or rheumatic fever.

Physical examination disclosed a pale and hyperpneic patient who appeared acutely ill. Herpes labialis was present, and the pharynx was moderately injected. The lungs were clear, and the heart was normal. There was spasm of the adductor muscles of the left thigh and marked tenderness at the attachment of these muscles at the pelvic level. There was no swelling, heat or redness, and no tenderness along the course of the venous channels.

The temperature was 103°F, the pulse 110, and the respiratory rate 25. The blood pressure was 115/75.

Examination of the blood revealed a red-cell count of 4,000,000, with a hemoglobin of 11.5 gm., and a white-cell count of 15,200, with 75 per cent neutrophils. The hematocrit was 36, and the corrected sedimentation rate was 108 mm. in 1 hour. The serologic test for syphilis was negative, and agglutinations for the organisms of typhoid and paratyphoid fever and for brucella and proteus OX19 were negative. A blood culture was sterile.

An electrocardiogram and an x-ray film of the chest were within normal limits. X-ray examinations revealed only slight roughening of the posterior, proximal, periosteal surfaces of both femurs but no definite evidence of osteomyelitis.

The patient continued to have a maximum temperature of 103°F. A diagnosis of osteomyelitis of the left femur was considered initially, and on the 7th hospital day exploratory aspiration was attempted. No pus was obtained. Despite the absence of a specific diagnosis penicillin was then instituted in dosage of 130,000 units intramuscularly every 3 hours. No improvement was noted, and the drug was discontinued on the 20th hospital day. On the 26th hospital day a flame-shaped hemorrhage was noted beneath the nail of the right index finger. Repeated blood cultures had shown no growth. On the 32nd hospital day the patient complained of double vision. Examination revealed the presence

of paralysis of the left superior rectus ocular muscle. The spinal fluid was normal. The diplopia persisted throughout the patient's hospital course.

On the 35th hospital day a Grade II apical systolic murmur was detected. On the same day a petechial lesion was noted on the left heel. Aspiration and culture yielded an anaerobic, gram-negative coccobacillus identified as *bacteroides*, species undetermined. On the 39th hospital day a blood culture incubated in thioglycollate medium yielded an organism similar to that isolated from the petechia. The organism at no time grew out in numbers sufficient for the determination of its sensitivity to penicillin and streptomycin. On the 43rd hospital day the spleen was palpable. On the following day a faint diastolic murmur was heard along the left sternal border.

On the 45th hospital day the blood culture was still positive, and streptomycin was instituted in a dosage of 1 gm. every 6 hours intramuscularly. Seventeen subsequent blood cultures were sterile. Despite the disappearance of bacteremia the temperature curve remained elevated, and on the 51st hospital day penicillin was again started in dosage of 10,000,000 units intravenously per day. Severe, generalized urticaria promptly appeared, and after 5 days penicillin was discontinued. On the 56th hospital day sulfadiazine in an initial dosage of 4 gm. and a subsequent dosage of 1 gm. every 4 hours was begun. On the 57th hospital day the patient complained of a "sticking" pain in the left upper quadrant, with radiation to the left shoulder. This was interpreted as an episode of splenic infarction.

The patient's clinical status continued essentially unchanged, and on the 62nd hospital day streptomycin was discontinued. In 2 days the patient was afebrile. On the 68th hospital day the temperature spiked to 102°F. Examination revealed signs of thrombophlebitis in the left leg. The patient was put on anticoagulant therapy with heparin and dicoumarol. Sulfadiazine was discontinued. Two days later bilateral femoral-vein ligation was performed. A large thrombus was removed from the left side but unfortunately was discarded before cultures could be taken. Two days postoperatively the temperature returned to normal. On the 74th hospital day there were symptoms and radiologic signs of pulmonary infarction, which promptly cleared.

The patient's course, thereafter, was essentially uneventful. The aortic diastolic murmur increased, however, and there was some widening of the pulse pressure. Tachycardia persisted for several weeks. The sedimentation rate slowly returned to normal. During the last hospital month the spleen was no longer palpable. Frequent electrocardiograms had been taken throughout the hospital course. Serial tracings from the 91st to the 116th hospital day showed changes in the ST segments and T waves suggestive of myocardial damage, although the patient was asymptomatic. The diplopia persisted and was not correctable by lenses. The patient was discharged on the 116th hospital day. Final x-ray films of the chest with a barium swallow showed no abnormalities in the configuration of the heart.

Three months later the patient was feeling well and had regained his former weight of 198 pounds. The blood pressure was 130/55. There was no change in the character of the aortic diastolic murmur. There was no anemia and the white-cell count and sedimentation rate were normal. An electrocardiogram and an x-ray film of the chest were within normal limits. Surgery directed toward the correction of the diplopia was successfully accomplished.

The pertinent features of the patient's hospital course are presented in Figure 1.

Reports of septicemias due to gram-negative, anaerobic, nonspore forming bacilli (*bacteroides*) are few, and reports of endocarditis are corre-

\*From the Veterans Administration Hospital, Newington, Connecticut, and the Department of Medicine, Yale University School of Medicine.

†Published with the permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the authors.

‡Clinical instructor in medicine, Yale University School of Medicine, assistant chief of medicine, Veterans Administration Hospital, Newington, Connecticut.

§Clinical instructor in medicine, Yale University School of Medicine, ca biologist, Veterans Administration Hospital, Newington, Connecticut.

¶Assistant clinical professor of medicine, Yale University School of Medicine, chief of medicine, Veterans Administration Hospital, Newington, Connecticut.

spondingly rare. The organisms are natural inhabitants of mucous membranes from which sites they may invade the tissues, blood or body cavities.<sup>2,3</sup> The most frequent severe bacteroides infections are septicemias arising from throat infection or following operation on the colon, and meningitides arising from chronic otitis media.<sup>4</sup> The genus is not well defined, and accurate identification is often unsatisfactory. Lewis and Rettger<sup>5</sup> state, "Differences in methods, inconsistent nomenclature, and inherent differences in the organisms

In the past these infections have usually been fatal, although a few patients have apparently recovered after administration of sulfonamides.<sup>10,11</sup> Foley,<sup>12</sup> in a recent study, found the genus bacteroides highly resistant to streptomycin *in vitro*, as well as to sulfadiazine and sulfathiazole. The role of streptomycin in this patient's recovery can only be inferred in view of the overlapping administration of penicillin and sulfadiazine. It is, however, noteworthy that the last positive blood culture was obtained on the day streptomycin was instituted

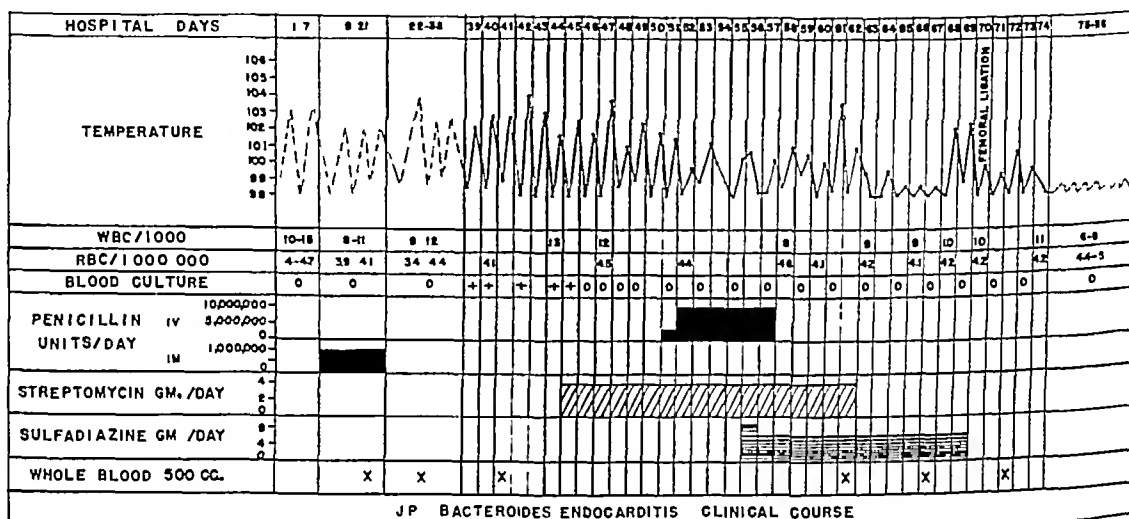


FIGURE 1 Clinical Course in Case 1

themselves have contributed to provide a complex and confusing picture." It is possible that the organism isolated from some cases of endocarditis and reported as an "unidentified gram-negative bacillus" would be classified as bacteroides by some laboratories. Smith and Ropes<sup>4</sup> believe that bacteroides infections are much more common than is appreciated clinically. The organisms are readily missed in routine bacteriologic study, since they are anaerobic, grow slowly and often require special medium. Bacteroides was first isolated from a petechia in this case and grew poorly and only in thioglycollate medium. This is of importance, since it has been shown that thioglycollate inhibits the bactericidal effect of streptomycin *in vitro*.<sup>6,7</sup> Hence, there are limitations to any sensitivity tests carried out in this medium.

In retrospect the presenting symptom of pain in the left upper thigh in this case is logically attributable to atypical thrombophlebitis. Reid et al.,<sup>8</sup> in analyzing 6 cases of septicemia due to bacteroides, found that thrombophlebitis was a constant feature. Appelbaum and Gelfand<sup>9</sup> report a case with an unidentified gram-negative bacillus, and it is significant that a prominent feature of the patient's presenting illness was thrombophlebitis.

Furthermore, negative cultures were obtained before the intravenous use of penicillin and sulfadiazine. It may be that the combination of drugs produced a therapeutic effect.

The prompt subsidence of fever after cessation of streptomycin suggests that the drug was exerting a toxic effect during the latter part of its administration. No vestibular, renal or dermatologic abnormalities were noted.

The serial electrocardiographic changes noted after the patient was clinically well are of interest. Seabury,<sup>13</sup> in an analysis of 165 cases of bacterial endocarditis, found that 25 per cent showed myocardial infarction at autopsy.

CASE 2. E. S., a 75-year-old man, was admitted to the urologic service of the hospital on February 16, 1947, with the chief complaint of trouble in passing urine. Two and a half weeks before entry he had been admitted to another hospital and placed on constant urinary drainage.

Physical examination revealed a well developed and fairly well nourished man in no acute distress. The chest was clear and there was a Grade II, blowing systolic murmur at the apex of the heart. The peripheral arteries were markedly sclerotic. The prostate was greatly enlarged and tender. An indwelling catheter was present.

The temperature was 99.8°F, the pulse 110, and the respiratory rate 22. The blood pressure was 170/70. Examination of the blood revealed a red-cell count of 4,150,000, with a hemoglobin of 13.5 gm, and a white cell

count of 15,650, with 85 per cent neutrophils. The specific gravity of the urine was 1.010, and there were 5 to 6 white blood cells per high-power field in the sediment. The blood urea nitrogen was 20 mg per 100 cc., and the total blood protein was normal. An x-ray film of the chest, an electrocardiogram and an intravenous pyelogram were within normal limits.

Sulfadiazine, in a dosage of 0.5 gm., was given four times daily. Cystoscopy was performed on the 6th hospital day. Culture of the urine yielded an alpha-hemolytic streptococcus and *Pseudomonas aeruginosa*. On the 9th hospital day the

mycin therapy. This organism grew in 500 but was inhibited by 50 units of streptomycin per cubic centimeter. On this day the patient's condition abruptly deteriorated, and he presented the picture of collapse, with a marked fall in blood pressure and clouding of consciousness. Since the bacteremia had returned and since it was not known what role streptomycin might be playing in the patient's sudden failure, the drug was discontinued.

Terminally, bronchopneumonia and oliguria developed. The blood urea nitrogen rose to a height of 37 mg per 100 cc., and the urinary sediment showed hyaline and granular

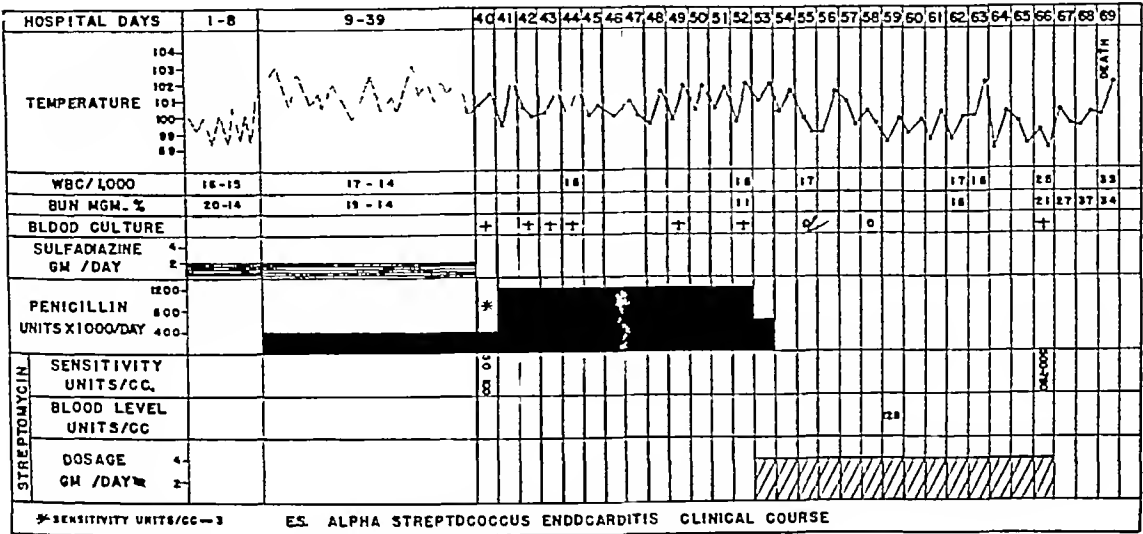


FIGURE 2 Clinical Course in Case 2

temperature rose to 103°F, and penicillin was started in a dosage of 50,000 units intramuscularly every 3 hours. On the 10th hospital day a suprapubic cystostomy and bilateral vasectomy were performed. Pathological examination of the specimen showed chronic inflammation. On the 5th postoperative day there was evidence of epididymitis. This subsided during the next hospital week, but the patient continued to run a temperature ranging from 100 to 102°F. Urine cultures were persistently positive.

The course continued essentially the same until the 40th hospital day, when, despite the continued administration of 400,000 units of penicillin daily, culture of the blood yielded an alpha-hemolytic streptococcus. On the same day a diastolic murmur was detected along the left sternal border. The spleen was not palpable, there were no petechiae and there was no anemia. Penicillin dosage was increased to 1,200,000 units daily. Subsequent sensitivity tests determined that the organism isolated from the blood grew in 2 but was inhibited by 3 units of penicillin per cubic centimeter. The blood cultures continued positive. Sensitivity tests to streptomycin indicated that the organism grew in 50 but was inhibited by 100 units of streptomycin per cubic centimeter. In view of the lack of response to the increased dosage of penicillin, it was discontinued on the 52nd hospital day, and treatment with streptomycin was instituted, 0.5 gm being given every 3 hours intramuscularly. The urine was alkalized.

Initially there was evidence of a favorable response. Blood cultures taken on the 2nd and 5th days of streptomycin therapy were negative. The temperature declined from a high of 102°F on the day streptomycin was started to near normal on the 7th day. On that day the blood streptomycin level was 128 units per cubic centimeter.

On the 11th day of streptomycin therapy the temperature again rose to 102°F. Culture of the blood again yielded an alpha-hemolytic streptococcus on the 14th day of strepto-

casts. Death occurred on the 69th hospital day. The clinical data are summarized in Figure 2.

Autopsy revealed bacterial endocarditis superimposed on calcareous aortic stenosis. Culture of the vegetations yielded an alpha-hemolytic streptococcus. The kidneys showed only mild arteriosclerotic changes.

This case emphasizes several important considerations in the management of bacterial infections. Penicillin is considered to be the drug of choice in the management of infections with a gram-positive coccus. In this case however, the presence of an alpha-hemolytic streptococcus in the blood was first demonstrated while the patient was receiving penicillin in an amount ordinarily sufficient for the control of this organism. Its relatively low sensitivity to penicillin—3 units per cubic centimeter—was subsequently confirmed. (In 12 cases of bacterial endocarditis, Goerner, Geiger and Blake<sup>14</sup> found the sensitivity of the alpha-hemolytic streptococcus to be in the range of 0.02 to 0.05 units per cubic centimeter.) Further studies in this case revealed that the resistance of the organism to streptomycin was also relatively high. Despite this the drug was given empirically. The temporary disappearance of bacteremia and the general clinical improvement early in the course of streptomycin therapy seem to justify this course

The ultimate failure of therapy was largely caused by the rapid, tenfold increase in the resistance of the organism to streptomycin.

In such resistant infections, in which studies in vitro show relative resistance of the organism to both streptomycin and penicillin, the use of both drugs together might be effective as suggested by Hunter.<sup>1</sup> Laboratory controls in the management of such cases are important.

The blood streptomycin level of 128 units per cubic centimeter observed in this case was unusually high and may have been related to decreased excretion. It perhaps explains the initial response of the patient to therapy. Such levels might be accompanied by a higher incidence of toxic effects. Hirshfeld,<sup>16</sup> however, has reported a level of 171 units per cubic centimeter in 1 case without toxic manifestations. An unusual type of fatty infiltration in the livers and kidneys of animals given large doses of streptomycin has been described by several investigators.<sup>16</sup> Similar changes have been reported in man in at least 1 case.<sup>17</sup> Fat stains of tissue sections in the fatal case reported above revealed no evidence of kidney or liver damage attributable to streptomycin.

#### SUMMARY

Two cases of bacterial endocarditis in which streptomycin was employed are presented, and certain important features are discussed.

In a case in which the patient recovered, the organism was an anaerobic, gram-negative, non-spore-forming bacillus (bacteroides).

In a fatal case, the etiologic agent was an alpha hemolytic streptococcus, which was highly resistant to both penicillin and streptomycin.

#### REFERENCES

1. Hunter T. H. Use of streptomycin in treatment of bacterial endocarditis. *Am J Med* 2:436-442 1947.
2. Olitsky, P. K. Studies on bacteriology of epidemic influenza. *Mishcine* 9:387-411 1930.
3. Eggerth A. H. and Gagnon B. H. Bacteroides of human feces. *J Bact* 25:389-413, 1933.
4. Smith W. E. and Ropes M. W. Bacteroides infections: a survey based on review of literature and study of 20 cases. *New Eng J Med* 232:31-37 1945.
5. Lewis K. H. and Rettger, L. F. Non sporulating anaerobic bacteria of intestinal tract. *J Bact* 40:287-307 1940.
6. Donovick, R. and Rake G. Influence of certain substances on activity of streptomycin modifications in test medium. *Proc. Soc. Exper Biol & Med* 61:224-227 1946.
7. Bondi A. Jr. Dietz, C. C. and Spaulding E. H. Interference with antibacterial action of streptomycin by reducing agents. *Science* 103:339-401 1946.
8. Reid, J. D. Snider G. E., Toone E. C. and Howe J. S. Anaerobic septicemia: report of six cases with clinical, bacteriologic and pathologic studies. *Am J Med Sc* 209:296-306 1945.
9. Appelbaum, E. and Gelfand M. Case of bacteremia due to unidentified gram-negative pasteurilla-like bacillus with recovery following streptomycin therapy. *Ann Int Med* 26:780-783 1947.
10. Brown A. E., Williams H. L. and Herrell W. E. Bacteroides septicemia: report of case with recovery. *J A M A* 116:401-404 1941.
11. Waring J. J., Ryan J. G., Thompson, R. and Spencer F. R. Bacteroides septicemia: report of case with recovery. *Laryngoscope* 53:717-723 1943.
12. Foley G. E. In vitro resistance of genus Bacteroides to streptomycin. *Science* 106:423 1947.
13. Seahury, J. H. Subacute bacterial endocarditis: experiences during past decade. *Arch Int Med* 79:1-21 1947.
14. Goerner J. R., Geiger A. J. and Blake F. G. Treatment of subacute bacterial endocarditis with penicillin: report of cases treated with out anticoagulant agents. *Ann Int Med* 23:491-519, 1945.
15. Hirshfeld J. W. Human pharmacology of streptomycin: absorption and excretion in man. In *Conference on Streptomycin*, 91 pp. Merck and Co. Inc. Rahway, New Jersey, June 20 1945. Pp. 11-14.
16. Molitor, H. et al. Some toxicological and pharmacological properties of streptomycin. *J Pharmacol. & Exper Therap* 86:151-173 1946.
17. Madigan D. G., Swift P. N. and Brownlee G. Clinical and pharmacological effect of streptomycin. *Lancet* 1:911 1947.

## CARCINOMA OF THE RECTUM

FREDERICK S HOPKINS, M D,\* AND ROBERT C TATE, M D†

SPRINGFIELD, MASSACHUSETTS

THIS report is based on the cases of carcinoma of the rectum that have been seen in the Cancer Section of the Westfield State Sanatorium since it opened in the fall of 1937. Of the 165 patients seen before 1943 and so available for a five-year study 112 had surgical treatment at Westfield. The latter group constitutes the principal basis for this statistical study.

The incidence was much greater in the male sex, there being 81 men and 31 women.

The average age was sixty-seven years, the sixth and seventh decades furnishing most of the cases, although both the third and ninth decades were represented, with 2 cases each.

The principal symptoms in order of frequency were blood in the stool, change in bowel habit, diarrhea, constipation, tenesmus and pain.

The duration of symptoms was less than three months in only 28 cases whereas in 7 it was over two years.

An extremely important feature of the physical examination is requesting the patient to strain while the physician is doing a digital rectal examination. With this procedure the tumor was felt in 92 cases or 82 per cent. The lesion was within 10 cm. of the anus in 90 cases.

Sigmoidoscopy with biopsy of the lesion was done routinely. Cystoscopy was done in most of the cases and revealed bladder invasion in 6. Barium enemas were usually done to assist in the identification of multiple lesions. Routine chest films revealed 3 cases of unsuspected lung metastases. About a third of the patients had a significant anemia, and slightly less had sufficient hypoproteinemia to require special preoperative preparation.

There were 5 patients who had clinical evidence of inguinal-lymph-node metastases. These were all cases of adenocarcinoma starting in the rectum but involving the anal canal. Only 2 of these had biopsies of the inguinal lymph nodes, and these showed metastatic carcinoma.

In 15 cases or 13 per cent, there was another primary cancer. Five of these involved the colon.

The study and preparation of the patient for operation required approximately a week. During the period covered by this survey cathartics and enemas were used routinely. Since then these have been replaced by sulfasuxadine usually given in the dose of 2 gm. every four hours for five days.

One hundred and twelve patients had operations done by 18 members of the visiting and resident staff. In only 50 of these cases was there any possibility of cure, the others having definite evidence of incurability such as metastases to the liver. Of the latter group 46 were simple colostomies, and 15 were palliative resections. The one-stage abdominoperineal resection of Miles is now done in nearly all cases. We still believe that there is occasionally an indication for the Lockhart-Mummery procedure in the patient with a tumor low in the rectum who is a very poor risk. This consists in a sigmoid-loop colostomy followed within two weeks by a posterior resection of the rectum and lower sigmoid.

All patients undergoing abdominoperineal resections received transfusions during operation. The average number of transfusions in such cases was two and a half.

In most of the Miles operations the end of the sigmoid was brought out through the left rectus incision as the permanent colostomy, and the lateral gutter was closed. During this period catgut sutures were usually used. There were 17 cases of hernia around the stoma, though none of these were incapacitating. With the use of a transverse incision and cotton sutures we have had no hernias.

The average time in the hospital after operation was thirty-five days. Since 1942 it has been twenty-eight days, and many patients go home in three weeks.

The time required for the healing of the posterior wound varied greatly. Five were healed in one month, and yet 15 required over three months.

Urinary-tract complications were frequent. All patients were placed on constant bladder drainage through a urethral catheter. The average time until the patient could void with negligible residual urine was nineteen days. Five patients had some permanent difficulty in urinary control.

The five-year results are as follows. Of the 35 patients who had the Miles operation with hope of cure 7 were postoperative fatalities, 13 are well, 9 died without any evidence of recurrence, 2 died with possible recurrence though there was no evidence of it on recent examination, 2 are living with recurrence, and 2 died with definite recurrence. One patient with a two-stage resection by the Daniel F. Jones technic, 1 with a Hochenegg sphincter-saving operation and 1 with a local removal of a malignant polyp are alive and well after five years. Nine Lockhart-Mummery operations were done in cases in which the liver was not involved. One

\*Director, Cancer Section, Westfield State Sanatorium, visiting surgeon.  
Springfield Hospital.

†Formerly assistant superintendent, Westfield State Sanatorium.

The ultimate failure of therapy was largely caused by the rapid, tenfold increase in the resistance of the organism to streptomycin.

In such resistant infections, in which studies in vitro show relative resistance of the organism to both streptomycin and penicillin, the use of both drugs together might be effective as suggested by Hunter.<sup>1</sup> Laboratory controls in the management of such cases are important.

The blood streptomycin level of 128 units per cubic centimeter observed in this case was unusually high and may have been related to decreased excretion. It perhaps explains the initial response of the patient to therapy. Such levels might be accompanied by a higher incidence of toxic effects. Hirshfeld,<sup>15</sup> however, has reported a level of 171 units per cubic centimeter in 1 case without toxic manifestations. An unusual type of fatty infiltration in the livers and kidneys of animals given large doses of streptomycin has been described by several investigators.<sup>16</sup> Similar changes have been reported in man in at least 1 case.<sup>17</sup> Fat stains of tissue sections in the fatal case reported above revealed no evidence of kidney or liver damage attributable to streptomycin.

#### SUMMARY

Two cases of bacterial endocarditis in which streptomycin was employed are presented, and certain important features are discussed.

In a case in which the patient recovered, the organism was an anaerobic, gram-negative, non-spore forming bacillus (bacteroides).

In a fatal case, the etiologic agent was an alpha hemolytic streptococcus, which was highly resistant to both penicillin and streptomycin.

#### REFERENCES

- 1 Hunter T H. Use of streptomycin in treatment of bacterial endocarditis. *Am J Med* 2:436-442 1947.
- 2 Olitsky P K. Studies on bacteriology of epidemic influenza. *Met. cine* 9:387-411 1930.
- 3 Eggerth A H and Gagnon, B H. Bacteroides of human feces. *J Bact* 25:389-413, 1933.
- 4 Smith W E. and Ropes M W. Bacteroides infections: analysis based on review of literature and study of 20 cases. *Am. Ex. J Med* 232:31-37, 1945.
- 5 Lewis K. H. and Rettger L. F. Non sporulating anaerobic bacteria of intestinal tract. *J Bact* 40:287-307 1940.
- 6 Donovick, R. and Rake G. Influence of certain substances on activity of streptomycin: modifications in test medium. *Proc. S. C. Exper Biol & Med* 61:224-227 1946.
- 7 Bondi, A. Jr. Dietz, C. C. and Spaulding E. H. Interference with antibacterial action of streptomycin by reducing agents. *Science* 103:339-401 1946.
- 8 Reid J D. Snider G E. Toone E. C. and Howe, J. S. Anaerobic septicemia: report of six cases with clinical, bacteriologic and pathologic studies. *Am J M Sc* 209:296-306 1945.
- 9 Appelbaum, E., and Gelfand M. Case of bacteremia due to unidentified gram negative pasteurilla like bacillus with recovery following streptomycin therapy. *Ann Int. Med* 26:780-783 1947.
- 10 Brown A. E. Williams H. L. and Herrell W. E. Bacteroides septicemia: report of case with recovery. *J A M A* 116:402-404, 1941.
- 11 Waring J J. Ryan J G. Thompson R. and Spencer F R. Bacteroides septicemia: report of case with recovery. *Laryngoscope* 53:717-723 1943.
- 12 Foley G E. In vitro resistance of genus Bacteroides to streptomycin. *Science* 106:423 1947.
- 13 Seabury, J. H. Subacute bacterial endocarditis: experiences during past decade. *Arch Int. Med* 79:1-21 1947.
- 14 Goerner J R., Geiger A. J. and Blake F G. Treatment of subacute bacterial endocarditis with penicillin: report of cases treated with out anticoagulant agents. *Ann Int. Med* 23:491-519 1945.
- 15 Hirshfeld, J W. Human pharmacology of streptomycin: absorption and excretion in man. In *Conference on Streptomycin*, 97 pp. Merck and Co. Inc. Rahway, New Jersey, June 20 1945. Pp. 11-14.
- 16 Molitor, H. et al. Some toxicological and pharmacological properties of streptomycin. *J Pharmacol & Exper Therap* 86:151-173 1946.
- 17 Madigan D G. Swift, P N. and Brownlee G. Clinical and pharmacological effect of streptomycin. *Lancet* 1:911 1947.

## MEDICAL PROGRESS

### VIRAL HEPATITIS\*

SYDNEY S. GELLIS, M.D.,† AND CHARLES A. JANEWAY, M.D.‡

BOSTON

**R**ECENT articles concerning infections of the liver by viral agents<sup>1,2</sup> have reviewed with great detail present-day concepts of such infections. The purpose of the present report is to summarize briefly the studies published during 1947 and the early part of 1948 on infectious hepatitis and homologous serum hepatitis.

Owing to the fact that no laboratory animals have been found to be susceptible to hepatitis virus, human volunteers still form the only source of experimental tests designed to furnish additional information regarding the etiologic agent or agents. As a result, modern knowledge of the virus of hepatitis is based on extremely limited studies, some of which have served to cloud rather than elucidate controversial issues concerning the nature, mode of spread, contagiousness, incubation period, immunologic relations and control of the viral agent. Perhaps the most controversial problem is the relation between the agent of infectious hepatitis and homologous serum jaundice.<sup>3</sup> Despite experimental work carried out during the past few years, which appears to establish the agents as separate though closely related entities, workers in this field continue to endeavor to prove that the agents are one and the same, differing in their behavior by virtue of different modes of entry into the body. It seems reasonable to expect that the clarification of this particular problem can come not from field studies or theoretical considerations but from further experimental work with volunteers. Despite the similarities of the two types of viral hepatitis, infectious hepatitis and homologous serum hepatitis are considered separately for purposes of review.

#### INFECTIOUS HEPATITIS

##### *Clinical Studies*

Relatively little regarding clinical findings has been added to the literature on hepatitis during the past year. Several articles have appeared reviewing the clinical course of the disease.<sup>4-6</sup> Goodman<sup>7</sup> points out the need of recognizing that infectious hepatitis is a generalized disease, with liver involvement as the most striking manifestation. In his series splenomegaly occurred in 48 per

cent of the patients, although lymphadenopathy, which has been stressed by Barker,<sup>5</sup> was not present. In Goodman's series, the white-cell count varied from 2450 to 9000, with a normal differential count in the initial stages and a subsequent absolute increase in lymphocytes and mononuclear cells, which frequently showed vacuolization. He concludes that infectious hepatitis is a disease of the reticuloendothelial system, and that the liver changes that were so striking in soldiers of World War II were exaggerated owing to the poor state of nutrition of the men at the time of their infection.

Kunkel and Hoagland<sup>8</sup> have added to the clinical findings of infectious hepatitis the occurrence of spider angiomas in patients with this disease—a finding that, though previously observed, had been little emphasized. They found that approximately 30 per cent of the patients developed spider angiomas during the acute stage of the disease and that the incidence was much higher among patients with chronic hepatitis. The authors believe that the angiomas serve as a useful physical sign for following the transition from acute to chronic infectious hepatitis. Furthermore, their appearance in patients who have never developed frank jaundice may be of considerable help in the diagnosis of infectious hepatitis. It is also of interest that angiomas persist for a long time after a short, apparently mild attack of hepatitis.

Headache, which frequently occurs in patients early in the course of infectious hepatitis, was reported by Zimmerman et al.<sup>9</sup> to be present in 70 per cent of their cases, and the authors comment on the localization of the pain, which in most of the patients was orbital or frontal. In their series, itching of the skin occurred in 20 per cent of the patients, an unusually high figure in hepatitis.

Röntgenographic and gastroscopic studies of the stomach and duodenum of human volunteers with experimentally induced infectious hepatitis<sup>10</sup> have confirmed earlier reports of the presence of gastritis and duodenitis in infectious hepatitis. Inflammation of the gastrointestinal tract apparently occurs early in the disease and may last into convalescence.

##### *Infectious Hepatitis in Children*

Although this disease has always been considered to be milder in children than in adults, relatively few studies employing modern laboratory methods

\*From the Children's Hospital and the Department of Pediatrics, Harvard Medical School.

†Associate in Pediatrics, Harvard Medical School; chief Medical Out-patient Department, Children's Hospital.

‡Professor of Pediatrics, Harvard Medical School; physician-in-chief, Children's Hospital.

of these patients is living with recurrence, 1 died with cancer, and 2 died with questionable recurrence of cancer. The other 5 died without evidence of recurrence. All the patients on whom palliative operations were done are dead.

These results are not so good as many that have recently been reported. The high operative mortality of the earlier years can be attributed to lack of experience. The use of chemotherapy and a better understanding of fluid balance have also assisted in improving the results. In the past six years the mortality for the radical resections without liver metastases has been 6.6 per cent, and in three of the years there were no postoperative deaths in this group.

In the 10 cases without obvious liver metastases in which there were recurrences or suspected recur-

peritoneal reflection. The patients with extraperitoneal rectal carcinomas had a 74.4 per cent five year survival without lymph-node metastases, whereas those with involved nodes showed 37.5 per cent alive after five years. The corresponding figures for the intraperitoneal rectal and sigmoid lesions were 90 per cent and 51.4 per cent.

Twenty patients had x-ray treatment after a colostomy. Twelve of these are considered to have obtained definite relief and improvement. One survived over four years, and 1 over five years after the onset of symptoms.

SUMMARY AND CONCLUSIONS

The 112 cases of cancer of the rectum receiving surgical treatment at the Westfield State Sanatorium more than five years ago have been reviewed.

TABLE 1 Patients Surviving Operation without Known Liver Metastases

TYPE OF OPERATION	LYMPH NODE INVOLVEMENT	NO. OF CASES	FIVE YEAR CURES	FIVE-YEAR SURVIVALS WITH NO RECURRENCE	DEATH IN FIVE YEARS WITH NO RECURRENCE	DEATH WITH RECURRENCE	DEATH, RECURRENCE DOUBTFUL
Miles	No	25	13	1	7	1	1
Miles	Yes	5	1	0	2	1	1
Hochenegg sphincter saving resection	No	1	1	0	0	0	0
Jones	No	1	1	0	0	0	0
Lockhart-Mummery	No	7	0	1	4	1	0
Lockhart-Mummery	Yes	2	0	0	1	1	0
Lynch posterior resection	Yes	1	0	0	0	0	1

rences, 8 patients had local extension beyond the bowel, and 2 had vascular invasion in addition to an anaplastic type of lesion microscopically.

The results according to metastases in the regional nodes are shown in Table 1. Of the 32 patients without positive evidence of lymph node involvement 15 are well over five years later. Eliminating the 11 patients who died without any evidence of cancer gives 71.4 per cent apparent cures. For the Miles procedure alone our figure is 81.2 per cent. Of the 8 patients with involved lymph nodes only 1 was apparently cured. Eliminating the 3 patients who died without recurrence gives a 20 per cent five-year cure. These figures are somewhat similar to most of those recently reported. Colcock<sup>1</sup> reports from the Lahey Clinic 60 per cent five-year survivals in which the lymph nodes were not involved and 30.2 per cent in which they showed metastases. Rankin's<sup>2</sup> comparable figures are 43.8 per cent without lymph-node involvement and 27.3 per cent with metastases. In a very thorough study of involved lymph nodes Gilchrist and David<sup>3</sup> found their results better when the lesion was above the

It is realized that this series is small and that many of the rates are based on too few cases to be statistically significant. The operative mortality has steadily decreased with increasing experience, the most rapid drop occurring in 1942 with the introduction of chemotherapy and a better understanding of body chemistry. The Miles abdominoperineal operation is the procedure of choice for most cancers of the rectum. It apparently cured 81.2 per cent of our patients without obvious metastases who did not die of other causes. Those who survive lead normal lives and are not significantly hampered by a colostomy. Many more patients could be placed in this relatively fortunate group if every physician would make an adequate rectal examination whenever a patient reports a change in bowel habits or rectal bleeding.

REFERENCES

1. Colcock B. P. Prognosis in carcinoma of colon and rectum. 10-year follow up of 337 patients. *Surg. Gynec. & Obst.* 85:8-13, 1947.
2. Rankin F. W. and Johnson C. C. Surgical treatment of cancer of rectum and rectosigmoid. *J. A. M. A.* 136:371-375, 1948.
3. Gilchrist R. K. and David V. C. Prognosis in carcinoma of bowel. *Surg. Gynec. & Obst.* 86:359-371, 1948.

## MEDICAL PROGRESS

## VIRAL HEPATITIS\*

SYDNEY S GELLIS, M D,<sup>†</sup> AND CHARLES A JANEWAY, M D<sup>‡</sup>

BOSTON

RECENT articles concerning infections of the liver by viral agents<sup>1,2</sup> have reviewed with great detail present-day concepts of such infections. The purpose of the present report is to summarize briefly the studies published during 1947 and the early part of 1948 on infectious hepatitis and homologous serum hepatitis.

Owing to the fact that no laboratory animals have been found to be susceptible to hepatitis virus, human volunteers still form the only source of experimental tests designed to furnish additional information regarding the etiologic agent or agents. As a result, modern knowledge of the virus of hepatitis is based on extremely limited studies, some of which have served to cloud rather than elucidate controversial issues concerning the nature, mode of spread, contagiousness, incubation period, immunologic relations and control of the viral agent. Perhaps the most controversial problem is the relation between the agent of infectious hepatitis and homologous serum jaundice.<sup>3</sup> Despite experimental work carried out during the past few years, which appears to establish the agents as separate though closely related entities, workers in this field continue to endeavor to prove that the agents are one and the same, differing in their behavior by virtue of different modes of entry into the body. It seems reasonable to expect that the clarification of this particular problem can come not from field studies or theoretical considerations but from further experimental work with volunteers. Despite the similarities of the two types of viral hepatitis, infectious hepatitis and homologous serum hepatitis are considered separately for purposes of review.

## INFECTIOUS HEPATITIS

*Clinical Studies*

Relatively little regarding clinical findings has been added to the literature on hepatitis during the past year. Several articles have appeared reviewing the clinical course of the disease.<sup>4-6</sup> Goodman<sup>7</sup> points out the need of recognizing that infectious hepatitis is a generalized disease, with liver involvement as the most striking manifestation. In his series splenomegaly occurred in 48 per

cent of the patients, although lymphadenopathy, which has been stressed by Barker,<sup>5</sup> was not present. In Goodman's series, the white-cell count varied from 2450 to 9000, with a normal differential count in the initial stages and a subsequent absolute increase in lymphocytes and mononuclear cells, which frequently showed vacuolization. He concludes that infectious hepatitis is a disease of the reticuloendothelial system, and that the liver changes that were so striking in soldiers of World War II were exaggerated owing to the poor state of nutrition of the men at the time of their infection.

Kunkel and Hoagland<sup>8</sup> have added to the clinical findings of infectious hepatitis the occurrence of spider angiomas in patients with this disease — a finding that, though previously observed, had been little emphasized. They found that approximately 30 per cent of the patients developed spider angiomas during the acute stage of the disease and that the incidence was much higher among patients with chronic hepatitis. The authors believe that the angiomas serve as a useful physical sign for following the transition from acute to chronic infectious hepatitis. Furthermore, their appearance in patients who have never developed frank jaundice may be of considerable help in the diagnosis of infectious hepatitis. It is also of interest that angiomas persist for a long time after a short, apparently mild attack of hepatitis.

Headache, which frequently occurs in patients early in the course of infectious hepatitis, was reported by Zimmerman et al.<sup>9</sup> to be present in 70 per cent of their cases, and the authors comment on the localization of the pain, which in most of the patients was orbital or frontal. In their series, itching of the skin occurred in 20 per cent of the patients, an unusually high figure in hepatitis.

Roentgenographic and gastroscopic studies of the stomach and duodenum of human volunteers with experimentally induced infectious hepatitis<sup>10</sup> have confirmed earlier reports of the presence of gastritis and duodenitis in infectious hepatitis. Inflammation of the gastrointestinal tract apparently occurs early in the disease and may last into convalescence.

*Infectious Hepatitis in Children*

Although this disease has always been considered to be milder in children than in adults, relatively few studies employing modern laboratory methods

\*From the Children's Hospital and the Department of Pediatrics, Harvard Medical School.

<sup>†</sup>Associate in Pediatrics, Harvard Medical School; chief, Medical Outpatient Department, Children's Hospital.

<sup>‡</sup>Professor of Pediatrics, Harvard Medical School; physician-in-chief, Children's Hospital.

in children have appeared in the literature. In the two institutional outbreaks reported by Horstmann and his co-workers,<sup>11</sup> studies comparable to those made in Army and civilian outbreaks involving adults reveal that the disease in children is indeed a mild one: the icteric stage averaged 98 days, whereas in military personnel the average period of icterus was 27 days, and no patient revealed evidence of protracted convalescence or prolonged jaundice. The authors point out that differences in epidemics can be due to variations in virus strains, however, inasmuch as previous observations are similar to those of the present study, it appears reasonable to conclude that the disease is milder in children. Randolph and DeVito,<sup>12</sup> in a review of 32 children with infectious hepatitis seen at the Children's Hospital, Washington, D. C., found that all but 3 had fever with their infection and that the highest temperature occurred during the first two days of the preicteric stage, which averaged 7 days. In their series there were three times as many female as male patients. Webb et al.<sup>13</sup> have observed in children with acute infectious hepatitis a higher incidence of hepatitis without jaundice than with jaundice. The great difference in incidence of hepatitis without jaundice in various outbreaks reported is interesting; it suggests either variations in the strains of virus or different criteria for the diagnosis of the syndrome. Furthermore, the similarities between infectious hepatitis with or without jaundice and infectious mononucleosis suggest that other diseases give rise to the clinical picture of viral hepatitis. For this reason the diagnosis of infectious hepatitis should be made by exclusion.<sup>14</sup> Abrams<sup>15</sup> has reported a patient with infectious mononucleosis whose jaundice persisted for eleven weeks. This author emphasizes the need of repeated heterophil-antibody tests in patients with apparent infectious hepatitis before the diagnosis of infectious mononucleosis is excluded. Sufficient testing for heterophil antibodies appears to have been performed to date so that the test when positive may be used to distinguish between infectious hepatitis and infectious mononucleosis. McNicholl<sup>16</sup> has reported 2 patients with hepatitis possibly related to mumps. One developed jaundice and liver enlargement within a week of the onset of mumps while the parotid swelling was still present. The second patient was an adult whose jaundice and liver enlargement occurred five weeks after the onset of the parotitis. Although it is possible that the liver involvement in these patients was due to infectious hepatitis, numerous infections may give rise to inflammation of the liver with a clinical picture similar to that of acute infectious hepatitis.

### *Chronic Infectious Hepatitis*

At present the relatively new concept of a chronic stage of infectious hepatitis has been widely accepted. There can be no valid argument against

this concept when applied to patients who, recovering from their acute illness, continue to have large, tender livers, anorexia, nausea, right-upper-quadrant pain and laboratory tests indicative of persistent liver disturbance. However, the diagnosis of chronic hepatitis in patients clinically recovered from their disease, but whose laboratory tests continue positive, is still a matter of controversy and will continue so until improved tests or greater understanding of present-day tests have been achieved. The diagnosis on the basis of the persistence of a single type of positive test is open to question, but the minimal amount of liver dysfunction, as measured by modern laboratory tests, required to warrant the diagnosis has not yet been established. There is still no single test to determine liver dysfunction in infectious hepatitis comparable to the sedimentation rate in the determination of persistent rheumatic activity. Thus, until chronic hepatitis is more clearly defined, the reported incidence of this stage of the disease will vary considerably.

Klatskin and Rappaport,<sup>17</sup> in a study of 217 patients considered fully recovered from acute infectious hepatitis, found that half had residua consisting of fat intolerance, liver pains, hepatomegaly or impaired liver function for periods ranging up to twenty-seven years. The only factor they could correlate with the occurrence of residua was the intensity of jaundice during the acute attack; they found no relation between lack of bed rest and persistence of symptoms and signs. Since no liver biopsies were done on these patients, the authors were unable to relate the findings to structural changes. Kunkel, Labby and Hoagland<sup>18</sup> studied 350 men with acute infectious hepatitis and found that 60 (17 per cent) showed an abnormal convalescence, of these, 47 suffered a simple relapse with recovery, 2 a relapse with transition to chronic hepatitis, 4 chronic hepatitis and 7 persistent hyperbilirubinemia. Eight patients (23 per cent) did not recover completely after more than a year. The authors point out that these were older men and suggest that more conservative care is needed for patients over thirty years of age than for those in the younger age groups.

The relation between chronic hepatitis and cirrhosis of the liver continues to be a highly controversial one.<sup>19</sup> On theoretical grounds alone, infectious hepatitis appears to be a likely explanation for many cases of cirrhosis of the liver, in view of the fact that it may occur without visible jaundice and therefore not be diagnosed. Klatskin and Rappaport<sup>17</sup> found no symptoms of portal cirrhosis in their series but state that nodular cirrhosis may follow infectious hepatitis. Howard and Watson<sup>20</sup> have collected 6 cases of cholangiolitic (Hanot) cirrhosis and 15 of portal (Laennec) cirrhosis in which there was an antecedent history indicative of infectious hepatitis. These authors believe that in a certain small per-

centage of cases hepatitis becomes chronic or recurrent and may ultimately lead to cirrhosis. On the other hand, when patients with cirrhosis are studied, it is their opinion that antecedent hepatitis plays a significant etiologic role. Flood and James<sup>21</sup> studied 37 patients with viral hepatitis persisting for over two months after the onset of symptoms. Biopsies were performed on 15, in 12 of whom the biopsy showed evidence of periportal inflammation at intervals varying from two to twenty-five months after onset. The authors concluded from their series that there was little to suggest cirrhosis, and that complete recovery is to be expected after prolonged hepatitis. However, 1 patient in the series with homologous serum hepatitis, whose symptoms never completely disappeared, and whose death occurred three years after the onset of symptoms, revealed marked cirrhosis of the liver at post-mortem examination. It is stated that this case, which "may have been a sequel of acute hepatitis, should be interpreted with caution because of the rarity of frank cirrhosis following acute hepatitis." If this case is included, one might also draw the conclusion that cirrhosis after acute hepatitis is not such a rare condition. Fearnley<sup>22</sup> reported a patient who developed clinical signs of portal cirrhosis of the liver with ascites four years after an attack of infectious hepatitis. At post-mortem examination, however, the liver showed subacute necrosis with a multiple nodular hyperplasia. Spellberg<sup>23</sup> described 2 cases of portal cirrhosis following acute hepatitis, probably of the homologous serum type. Sherlock<sup>24</sup> reported 9 patients with cirrhosis developing after infectious hepatitis and concluded that infectious hepatitis appears to be an important etiologic factor in classic portal cirrhosis.

Kelsall, Stewart and Witts,<sup>25</sup> in reviewing their cases of subacute and chronic hepatitis, came to the conclusion that in hepatitis as in nephritis every gradation of chronicity exists and that various types of cirrhosis may develop in the course of the hepatitis, whether it is due to a virus, a chemical poison or an unknown etiologic agent. They reported that in the Oxford area cirrhosis is considerably more common in women than in men and that alcohol no longer ranks as an important etiologic factor. In his follow-up examination of 400 Navy men with acute infectious hepatitis who had been studied from the onset of the disease Kunkel<sup>1</sup> found none who had developed ascites or other evidence of severe cirrhosis. However, he studied 5 other young service men<sup>26</sup> in whom liver biopsy or post-mortem examination revealed large masses of regenerated liver cells without a lobular pattern, surrounded by dense areas of fibrous tissue. He believed that the picture was different from that in the usual portal cirrhosis and appeared similar to the post-necrotic type of cirrhosis described by Mallory. As further evidence of the difference between post-hepatic cirrhosis and portal cirrhosis

Kunkel states that the former is rarely amenable to the usual dietary forms of treatment that are valuable in portal cirrhosis. In another series of 82 patients with acute infectious hepatitis, studied in Army hospitals<sup>27</sup> 4 were considered to have gone on to early cirrhosis. This diagnosis was not confirmed by biopsy. McHardy et al.<sup>28</sup> reported the cases of 16 patients with initially severe infectious hepatitis in whom, on the average of three years from the subsidence of jaundice, peritoneoscopy and biopsy revealed significant cirrhotic changes. The authors believed that "there is a definite relationship of prolonged severe infectious hepatitis to a 'chronic latent hepatitis' and to actual cirrhosis, despite some opposing opinions."

The solution to the problem of the relation of cirrhosis to viral hepatitis appears to lie in the long-term studies of military personnel involved in epidemics of this disease being conducted by the Veterans Administration. The investigation of histories of patients with fully established cirrhosis is of questionable value inasmuch as their original illness is of uncertain etiology.

Little is known at present of the presence of virus in the patient with chronic hepatitis. Numerous blood banks refuse as donors volunteers with a past history of jaundice, others accept as donors volunteers who have had no history of jaundice during the preceding six months or a year. There is no scientific basis for either choice since little is known regarding the maximum period during which the patient with infectious hepatitis or homologous serum jaundice may act as a carrier of hepatitis virus. If such knowledge were available, the fact that either type of disease may occur without visible jaundice makes the task of refusing as donors volunteers with a past history of hepatitis a formidable one indeed. During the past year one study was conducted to determine the presence of virus in patients with chronic hepatitis.<sup>29</sup> Feces, serum and liver-biopsy material collected from patients with chronic hepatitis three to twelve months after the onset of their disease were administered orally to volunteers. Several of the men developed mild to moderate illness after ingestion of the feces and liver preparations, no illness resulted from the ingestion of serum. Although the illnesses were frequently suggestive of hepatitis, the absence of confirmatory laboratory findings makes definite conclusions regarding the persistence of the virus in the materials studied impossible, and further studies will be necessary.

#### *Mode of Transmission*

Although several modes of spread of the virus of infectious hepatitis have been suggested, there has been no proof favoring any one method of transmission with the exception of spread through contaminated drinking water. Numerous outbreaks reported in the literature do not, however, appear

to be explained by the ingestion of contaminated water, and contact and respiratory spread still seem likely. Trussell<sup>30</sup> has recently reported an outbreak in military personnel that he regards as suggesting transmission of the virus by flies or by food handlers, utensils, dishwater and food. Anderson,<sup>31</sup> in reviewing infectious hepatitis in Iceland, where the disease has been four times greater in rural than in urban areas, attributed the difference to the poor disposal of excreta in the rural areas. He believes that in Iceland the infection is spread by dust-borne dried excreta. Harrison<sup>32</sup> has reported an outbreak that appeared to originate from a polluted well but offers no direct proof of this method of spread of the disease.

### *Virus Strains*

The reports from Denmark during the past year of a malignant form of hepatitis<sup>33, 34</sup> again raise the possibility that there are various strains of infectious hepatitis virus. The outbreaks in Denmark have involved primarily women past the menopause, with a mortality of 50 to 61 per cent. The duration of the illness was four to nine months, a period much longer than that of infectious hepatitis seen in other parts of the world. In addition, evidence of portal obstruction in the form of ascites and edema was striking in these patients, and there was widespread destruction of liver cells, with replacement by fibrous tissue in the chronic cases. Infectious hepatitis as observed in this country and Europe occurs primarily in children and young adults, hence its relation to the malignant hepatitis seen in Denmark is obscure. Whether or not malignant hepatitis is due to a virus remains to be determined, as does its relation to infectious hepatitis.

Stokes and Miller<sup>35</sup> have reported an outbreak of severe infectious hepatitis in Burma with a mortality of 20 per cent, and raise the question whether the higher mortality is due to an increase in virulence of the virus. The importance of the state of nutrition of people involved in an outbreak as a determining factor in the severity of the disease still remains to be determined, though these authors believe the higher mortality cannot be explained on a nutritional basis, but is due to increased virulence of the virus.

### *Infectious Hepatitis in Pregnancy*

Martin and Ferguson<sup>36</sup> have reported 4 cases of infectious hepatitis in pregnant women, 2 of whom had prolonged periods of jaundice. According to these writers hepatitis has been infrequent during pregnancy. There were no deaths in the mothers, and the 2 deaths in the offspring could not be attributed to the maternal disease. The authors believe that interruption of pregnancy should be considered if the patient's disease is severe and suggest the prophylactic use of gamma globulin in pregnant women exposed to the disease.

Zondek and Bromberg<sup>37</sup> have recently recorded 29 cases of infectious hepatitis occurring during pregnancy. Five women died of acute liver atrophy, and 2 developed chronic hepatitis. These writers found that premature deliveries were frequent in the women with severe hepatitis but that no effect on the fetus could be demonstrated. All the severe and fatal cases occurred during the latter part of the second half of pregnancy in women with poor nutrition. In contrast to Martin and Ferguson, Zondek and Bromberg believe that the clinical course of the disease is aggravated after spontaneous abortion, and therefore argue against the artificial interruption of pregnancy. Decrease in blood urea and a positive estrone clearance test indicated severity of the disease more successfully than other tests of liver function. The authors were unable to determine a correlation between intensity of jaundice and severity of the clinical course.

### *Treatment*

To date, no therapy has clearly affected the course of acute infectious hepatitis other than bed rest and a high-protein diet. Kunkel<sup>1</sup> has emphasized the value of a high-protein, normal fat and normal-carbohydrate diet in the treatment of infectious hepatitis; he believes that the low-fat diet is very unpalatable and hence causes a fall in caloric intake. Jones and Volwiler<sup>38</sup> similarly maintain that a rigid restriction of fat is unwise in the treatment of hepatitis and point out that "when protein intake is maintained at a high level, there is as yet no real evidence that a moderately high fat intake will harm the liver or enhance toxic injury."

No definite value can be attributed at present to the use of methionine, choline chloride, liver extract or vitamins in the therapy of infectious hepatitis.<sup>39</sup> Hanger et al. believe that normal human serum albumin administered to patients with severely damaged livers and ascites and edema is beneficial.

There appears to be almost universal acceptance at present of the importance of bed rest in acute infectious hepatitis.<sup>39</sup> Klatskin and Rappaport,<sup>40</sup> as stated above, failed to find any correlation between lack of bed rest and persistence of signs and symptoms of chronic hepatitis, but the experience of most investigators has shown a definite relation between the early return of patients to full activity and the recurrence or persistence of signs and symptoms of hepatitis. Infectious hepatitis is a disease comparable to rheumatic fever; the patient should continue bed rest not only until the signs and symptoms of the disease have disappeared but also until most of the laboratory tests for liver dysfunction have returned to normal. Such tests must be weighed with caution; the persistence of an abnormal bromsulfalein retention is of much greater significance than a positive thymol-flocculation test.

Since the latter may persist for a long time after this disease and its exact significance is as yet unknown, it appears unwise to insist on bed rest until this test reaches normal. As in rheumatic fever the return of a patient to full activity should be graduated and should be accompanied by clinical and laboratory investigation for evidence of recurrence of liver dysfunction.

### Prevention

Although gamma globulin is of great value in the prevention of infectious hepatitis, its practical use is limited to outbreaks of the disease in institutions and camps and in the rare family such as the one described by Kunkel and Hoagland,<sup>8</sup> in which several members developed the disease. Since infectious hepatitis during childhood is mild the use of gamma globulin to prevent the disease in normal healthy children might well be open to question. There can be no disagreement, however, concerning its use in pregnant women or in adults and children with various types of chronic disease. Even in this group its value is limited owing to the fact that exposure to hepatitis without jaundice may occur and not be recognized.

In view of the several possible methods of spread of the virus, real control of infectious hepatitis will be achieved only when a vaccine becomes available. Until that time methods for the prevention of spread of the disease must be sought. Neefe and his associates,<sup>40</sup> who in the past have stressed contaminated drinking water as the means of spread of the virus agent, have extended their studies of the action of chlorine on the virus of infectious hepatitis. They have found that a thirty-minute residual total chlorine concentration of one part per million was effective in inactivating the virus in water that had been coagulated, settled and filtered but was ineffective when employed in previously untreated water. They have not yet determined the minimal effective dose of chlorine in coagulated, settled and filtered water, as a result the efficacy of modern municipal methods of water treatment against this virus is still unknown.

### HOMOLOGOUS SERUM HEPATITIS

The majority of the work on homologous serum hepatitis reported during the past year and a half comprises studies on the incidence of jaundice after transfusion with pooled plasma. The Committee on Blood and Blood Derivatives of the Advisory Board on Health Services of the American National Red Cross has emphasized the potential risk to patients in the administration of pooled plasma, recommending instead the use of whole blood or normal human serum albumin. During the past year Brightman and Korns,<sup>41</sup> in a follow-up study of patients transfused with pooled plasma, have

reported a 4.5 per cent incidence of homologous serum jaundice. Rosenthal<sup>42</sup> found that 4.08 per cent of the patients in his study developed jaundice after transfusion with plasma or plasma and whole blood. No patient receiving whole blood alone developed homologous serum hepatitis. Scheinberg, Kinney and Janeway,<sup>43</sup> in investigating jaundice following plasma and blood transfusions at the Peter Bent Brigham Hospital, estimated that 1 case of jaundice occurred in every 86 transfusions.

All such studies to date reveal that the use of pooled plasma provides a real danger and should be avoided whenever possible. No investigation has yet been made regarding the incidence of hepatitis without jaundice after transfusion with whole blood or blood products, and it is extremely likely that the true incidence of homologous serum hepatitis is higher than present studies indicate.

### "Syringe" Jaundice

The transmission of hepatitis virus by means of improperly sterilized syringes and needles is now well established. During the past year several additional reports of jaundice transmitted by syringe were published.<sup>44-45</sup> Truelove and Hogben<sup>46</sup> found that approximately 50 per cent of syphilitic patients started on arsenical treatment in certain British military venereal-disease centers developed jaundice, when syringes were sterilized by boiling, the incidence of jaundice fell to about 5 per cent. Turner<sup>47</sup> reported a series of cases of what appeared to be homologous serum jaundice after penicillin injections in which syringes were not sterilized between patients but sterile needles were employed. Capps, Sborov and Scheiffley<sup>48</sup> described an outbreak of hepatitis apparently due to transmission of virus by syringes. One hundred and ten men received an intramuscular injection of tetanus toxoid, the material was administered from 10-cc syringes containing ten doses each, and needles were changed between patients. The authors estimated that at least 20 per cent of the men developed acute infectious hepatitis. The incubation period varied from 21 to 38 days in 21 men and was 15 and 16 days respectively in 2 others. Because of the short incubation period, the authors concluded that they were dealing with the epidemic virus of infectious hepatitis. The possibility that this was a spontaneous outbreak of infectious hepatitis and not disease transmitted by syringe cannot be excluded. Ninety-one per cent of the cases had no jaundice, the laboratory findings on which the diagnosis of hepatitis without jaundice were based were frequently borderline, and the diagnosis in a number of these men is therefore open to question.

Chalmers<sup>49</sup> presented an interesting study of jaundice in patients with malaria induced by blood

inoculation. He found that of 450 patients treated with malaria 36 developed jaundice and that only half of these had their jaundice during the attack of malaria. He speculates on the possibility that these delayed cases of jaundice are due to homologous serum hepatitis.

### *Clinical and Pathological Studies*

Several clinical and pathological reviews of homologous serum hepatitis have been published during the past year<sup>49-53</sup> but little has been added to the literature previously reported. Klatzkin and Rappaport<sup>54</sup> describe the cases of 2 patients who, during convalescence from homologous serum hepatitis, developed bilateral gynecomastia. In 1 case the enlargement developed seven weeks after onset of the disease when jaundice had largely subsided, and in the other fourteen weeks after onset. Gynecomastia is not a rare finding in cirrhosis of the liver and is thought to be due to the resultant hyperestrinemia. The authors believe that though both patients had unusually severe and protracted jaundice, there was no evidence of the development of cirrhosis.

### *Epidemiologic Studies*

Gauld<sup>55</sup> has reported an interesting study of homologous serum jaundice and infectious hepatitis in Army personnel in the Mediterranean Theater of Operations. He found that men who had had an attack of homologous serum jaundice (from yellow-fever vaccine) had less immunity to infectious hepatitis than men with no previous jaundice. In addition, soldiers who had contracted infectious hepatitis appeared to develop an immunity to subsequent development of infectious hepatitis. These studies are in accord with human experiments in the past, which indicate that there is no cross-immunity between homologous serum hepatitis and infectious hepatitis.

McKinlay and Truelove,<sup>56</sup> in similar studies conducted among Canadian and New Zealand troops stationed in Italy, found that in these men the incidence of homologous (post-arsphenamine) serum jaundice, unlike infectious hepatitis, was uninfluenced by age and had no striking seasonal variation. They also determined that previous attacks of infectious hepatitis conferred no immunity to homologous serum jaundice and concluded that the two diseases were caused by different viral agents.

Aycock and Oren<sup>57</sup> have published an interesting study of infectious hepatitis and homologous serum hepatitis. They argue that the virus of homologous serum hepatitis has a long incubation period because it enters the body with serum that may contain antibodies and thus prolong the incubation period, whereas in infectious hepatitis the virus

(from feces or nasal secretions) enters free of such antibodies, resulting in a short incubation period. They believe that analogous studies in poliomyelitis and influenza suggest that the two viruses of infectious hepatitis and homologous serum hepatitis are not different entities and that infectious hepatitis serves as the "virus reservoir" for homologous serum hepatitis. Although the results of experimental studies in volunteers with these viruses are not in accord with the views of Aycock and Oren, it must be re-emphasized that the work with volunteers has of necessity been limited, requiring further confirmation before definite conclusions regarding the relation of the viral agents can be reached.

### *Homologous Serum Hepatitis in Infancy*

During 1947 the first cases of homologous serum hepatitis in infants were reported. Three infants developed the disease after plasma transfusions,<sup>41, 43</sup> and a fourth after blood transfusion.<sup>58</sup> Two infants died with necrosis of the liver. Karelitz<sup>59</sup> has reported 6 infants who developed homologous serum hepatitis, 5 after plasma transfusion and 1 after whole-blood transfusion. Four patients in his series died of acute liver necrosis. Although the danger of homologous serum hepatitis after whole-blood transfusion is far less than that of hepatitis after pooled-plasma transfusion, the occurrence of this disease in 2 infants with erythroblastosis fetalis treated with replacement transfusion emphasizes the increasing risk with multiple transfusions.

Scott and Tovey<sup>61</sup> reported a case of homologous serum hepatitis in a young mother who received two bottles of plasma and one of blood at the time of delivery. Although she developed jaundice seventy-nine days later, 2 infants whom she had been nursing (her own and that of a neighbor) did not develop the disease. It is of interest to speculate on the possibility that the virus of homologous serum hepatitis passes into the breast milk. However, if virus were present in breast milk, it is unlikely that disease would result in nursing infants since experimental work with human volunteers appears to show that the virus of homologous serum hepatitis is ineffective when administered orally.

### *Prevention of Homologous Serum Jaundice*

Because of the value of gamma globulin in the prevention of infectious hepatitis, investigations of its use in the prophylaxis of homologous serum hepatitis naturally followed. Although initial studies indicated that gamma globulin was effective as a method of prevention, two reports published in 1947 failed to confirm the earlier findings.<sup>41, 62</sup> Duncan et al.<sup>62</sup> believed that the discrepancy in the findings might be explained by the fact that two injections of globulin thirty days apart were given

in the earlier studies whereas in those reported during the past year only a single injection was administered. In view of the long incubation period of homologous serum jaundice it appeared possible that the passive immunity conferred by a single injection was of too brief duration. The use of gamma globulin in prophylaxis, though of practical value in military personnel, would be difficult to employ in the civilian population.

Much interest and hope is centered about the use of ultraviolet irradiation as a means of inactivating the virus of homologous serum hepatitis in blood and blood products since the report by Oliphant in 1944 indicating that such irradiation appeared of value. Although MacCallum failed to substantiate Oliphant's findings, the method appeared promising and worthy of further investigation. Wolf and his co-workers<sup>62</sup> have reported the administration of irradiated plasma to 21 persons without untoward reaction. They tentatively concluded that the irradiation of plasma appeared to be a safe procedure that will free plasma from the presence of active virus of homologous serum jaundice. These writers offer no evidence that the virus is inactivated, and studies investigating the incidence of homologous serum jaundice in patients receiving irradiated plasma will be awaited with much interest.\* Gellis et al.<sup>64</sup> have reported the use of heat in an attempt to ensure the inactivation of hepatitis virus in normal human serum albumin solution. Bird, Enders and Boyd<sup>65</sup> have shown that certain viruses (Theiler's mouse-encephalomyelitis virus, vaccinia virus, tobacco-mosaic virus and tobacco-necrosis virus) added to pooled plasma survived fractionation and were found in all fractions prepared from the plasma. It therefore appears possible that the hepatitis virus might similarly survive fractionation and appear in the albumin. Albumin solutions to which the virus was added, heated to 60°C for ten hours, failed to give rise to homologous serum hepatitis when injected into volunteers, whereas the injection of unheated mixture of albumin and virus resulted in hepatitis though without clinical jaundice. These writers did not determine the minimum degree of heating required to inactivate the virus. All albumin solutions are now heated at 60°C for ten hours as a routine procedure, on the basis of these limited studies albumin solution appears to be free of active hepatitis virus. This method can be applied to albumin owing to the fact that albumin solutions can be stabilized to withstand heating, but is not applicable to serum, plasma or whole blood.

\*Blanchard and his co-workers in a personal communication reported the successful inactivation of the virus of homologous serum hepatitis by ultraviolet irradiation of plasma. Their experiments were conducted on volunteers inoculated with plasma known to contain the viral agent.

## REFERENCES

1. Hanger F M., et al. Hepatitis. *Am J Med* 4 285-301 1948
2. Young L. E. Current concepts of jaundice with particular reference to hepatitis. *New Eng J Med* 237 225-231 and 261-268 1947
3. Havens W. P., Jr. Etiology of infectious hepatitis. *J A M A* 134 653-655 1947
4. Capp R. B., Sborov A. M., and Barker M. H. Diagnosis of infectious hepatitis. *J A M A* 134 595-597 1947
5. Barker M. H. Infectious hepatitis. *Texas State J Med* 42 521-526 1947
6. Deutsch E., and MacMahon H. E. Epidemic hepatitis. *Gastroenterology* 8 311-331 1947
7. Goodman J. I. Pathogenesis of acute infectious hepatitis. *Am J Digest Dis* 14 26-29 1947
8. Kunkel H. G., and Hoagland C. L. Observations on family epidemic of infectious hepatitis. *New Eng J Med* 236 891-897 1947
9. Zimmerman H. J., Lowry C. F., Ueyama K., and Reiser R. Infectious hepatitis: clinical and laboratory features. *Am J Med Sci* 213 395-409 1947
10. Havens W. P., Jr., Kushlan S. D., and Green M. R. Experimentally induced infectious hepatitis: roentgenographic and gastroscopic observations. *Arch Int Med* 79 457-464 1947
11. Horstmann D. M., Havens W. P., Jr., and Deutsch, J. Infectious hepatitis in childhood: report of two institutional outbreaks and comparison of disease in adults and children. *J Pediatr* 30 381-387 1947
12. Randolph M., and DeVito A. Infectious hepatitis. *Clin Proc Child Hosp* 3 244-247 1947
13. Webb C. H., Wolfe S. G., Lucas R. T., and Anderson C. E., Jr. Acute hepatitis in children: clinical features and laboratory tests. *South M J* 40 340-409 1947
14. DeMarsh Q. B., and Alt, H. L. Hepatitis without jaundice in infectious mononucleosis. *Arch Int Med* 80 257-264 1947
15. Abrams H. L. Infectious mononucleosis with intense jaundice of long duration. *New Eng J Med* 238 295-297 1948
16. McNicholl, B. Infectious hepatitis following mumps. *Lancet* 1 195 1947
17. Klauskin G., and Rappaport E. M. Late residuals in presumably cured acute infectious hepatitis. *Ann Int Med* 26 1-26 1947
18. Kunkel H. G., Labby D. H., and Hoagland C. L. Chronic liver disease following infectious hepatitis. I. Abnormal convalescence from initial attack. *Ann Int Med* 27 202-219 1947
19. Kimball S., Chapple W. H. C., and Sames S. Jaundice in relation to cirrhosis of liver. *J A M A* 134 662-666 1947
20. Howard R., and Watson C. I. Antecedent jaundice in cirrhosis of liver. *Arch Int Med* 80 1-10 1947
21. Flood C. A., and James E. M. Clinical and pathological findings in prolonged hepatitis. *Gastroenterology* 8 172-184 1947
22. Fearnley G. R. Ascites following infectious hepatitis. *Lancet* 1 1 7-139 1947
23. Spellberg M. A. Sequelae of acute hepatitis. *Am Practitioner* 2 311-320 1948
24. Sherlock S. Abstract, discussion on infectious hepatitis. *Bull New York Acad Med* 24 201 1948
25. Kelsall A. R., Stewart A., and Witty L. J. Subacute and chronic hepatitis. *Lancet* 2 195 198 1947
26. Kunkel H. G. Infectious hepatitis: clinical aspects. *Bull New York Acad Med* 24 199 1948
27. Marion D. F. Delayed convalescence following acute hepatitis: clinical and laboratory evaluation. *Gastroenterology* 8 717-723 1947
28. McHardy C., Browne D. C., and Edwards E. Peritoneoscopic and biopsy evaluation of hepatic disease. *Gastroenterology* 9 632-685 1947
29. Neefe J. R., Stokes J. Jr., Garber R. S., and Gellis S. S. Studies on relationship of hepatic virus to persistent symptoms, disability and hepatic disturbance (chronic hepatitis syndrome) following acute infectious hepatitis. *J Clin. Investigation* 26 29-8 1947
30. Trussell R. E. Epidemiologic aspects of outbreak of infectious hepatitis. *Am J Hyg* 45 42 1947
31. Anderson L. S. Infective jaundice in Iceland. *Lancet* 1 778-781 1947
32. Harrison F. F. Infectious hepatitis: report of outbreak apparently water borne. *Arch Int Med* 79 622-625 1947
33. Alstead G. Studies on malignant hepatitis. *Am J Med Sci* 213 257-267 1947
34. Jersild, M. Infectious hepatitis with subacute atrophy of liver epidemic in women after menopause. *New Eng J Med* 237 8-11 1947
35. Stokes J. F., and Miller A. A. Outbreak of severe infectious hepatitis in Burma. *Quart J Med* 16 211-236 1947
36. Martin R., and Ferguson F. C., Jr. Infectious hepatitis associated with pregnancy: report of four cases. *New Eng J Med* 237 114-117 1947
37. Zondek, B., and Bromberg Y. M. Infectious hepatitis in pregnancy. *J Mt Sinai Hosp* 14 222-24 1947
38. Jones C. M., and Volwiler W. Therapeutic considerations in subacute and chronic hepatitis. *M Clin North America* 31 1059-1076 1947
39. Capps R. B., and Barker M. H. Management of infectious hepatitis. *Ann Int Med* 26 40-416 1947
40. Neefe J. R., Baty J. B., Reinhold J. G., and Stokes J. Jr. Inactivation of virus of infectious hepatitis in drinking water. *Am J Pub Health* 37 65-72 1947
41. Brightman I. J., and Korn R. F. Homologous serum jaundice in recipient of pooled plasma. *J A M A* 135 268-272 1947
42. Rosenthal L. T. Homologous serum hepatitis in civilian hospital. *Gastroenterology* 9 25-1 1947
43. Scheinberg I. H., Kinney T. D., and Janeway C. A. Homologous serum jaundice: problem in operation of blood banks. *J A M A* 134 841-848 1947
44. Laird S. M. Syndrome transmitted hepatitis. *Glas Med J* 28 199-219 1947

inoculation. He found that of 450 patients treated with malaria 36 developed jaundice and that only half of these had their jaundice during the attack of malaria. He speculates on the possibility that these delayed cases of jaundice are due to homologous serum hepatitis.

### *Clinical and Pathological Studies*

Several clinical and pathological reviews of homologous serum hepatitis have been published during the past year<sup>49-53</sup> but little has been added to the literature previously reported. Klatskin and Rappaport<sup>54</sup> describe the cases of 2 patients who, during convalescence from homologous serum hepatitis, developed bilateral gynecomastia. In 1 case the enlargement developed seven weeks after onset of the disease when jaundice had largely subsided, and in the other fourteen weeks after onset. Gynecomastia is not a rare finding in cirrhosis of the liver and is thought to be due to the resultant hyperestrinemia. The authors believe that though both patients had unusually severe and protracted jaundice, there was no evidence of the development of cirrhosis.

### *Epidemiologic Studies*

Gauld<sup>55</sup> has reported an interesting study of homologous serum jaundice and infectious hepatitis in Army personnel in the Mediterranean Theater of Operations. He found that men who had had an attack of homologous serum jaundice (from yellow-fever vaccine) had less immunity to infectious hepatitis than men with no previous jaundice. In addition, soldiers who had contracted infectious hepatitis appeared to develop an immunity to subsequent development of infectious hepatitis. These studies are in accord with human experiments in the past, which indicate that there is no cross-immunity between homologous serum hepatitis and infectious hepatitis.

McKinlay and Truelove,<sup>56</sup> in similar studies conducted among Canadian and New Zealand troops stationed in Italy, found that in these men the incidence of homologous (post-arsphenamine) serum jaundice, unlike infectious hepatitis, was uninfluenced by age and had no striking seasonal variation. They also determined that previous attacks of infectious hepatitis conferred no immunity to homologous serum jaundice and concluded that the two diseases were caused by different viral agents.

Aycock and Oren<sup>57</sup> have published an interesting study of infectious hepatitis and homologous serum hepatitis. They argue that the virus of homologous serum hepatitis has a long incubation period because it enters the body with serum that may contain antibodies and thus prolong the incubation period, whereas in infectious hepatitis the virus

(from feces or nasal secretions) enters free of such antibodies, resulting in a short incubation period. They believe that analogous studies in poliomyelitis and influenza suggest that the two viruses of infectious hepatitis and homologous serum hepatitis are not different entities and that infectious hepatitis serves as the "virus reservoir" for homologous serum hepatitis. Although the results of experimental studies in volunteers with these viruses are not in accord with the views of Aycock and Oren, it must be re-emphasized that the work with volunteers has of necessity been limited, requiring further confirmation before definite conclusions regarding the relation of the viral agents can be reached.

### *Homologous Serum Hepatitis in Infancy*

During 1947 the first cases of homologous serum hepatitis in infants were reported. Three infants developed the disease after plasma transfusions,<sup>49, 58</sup> and a fourth after blood transfusion.<sup>59</sup> Two infants died with necrosis of the liver. Karelitz<sup>60</sup> has reported 6 infants who developed homologous serum hepatitis, 5 after plasma transfusion and 1 after whole-blood transfusion. Four patients in his series died of acute liver necrosis. Although the danger of homologous serum hepatitis after whole-blood transfusion is far less than that of hepatitis after pooled-plasma transfusion, the occurrence of this disease in 2 infants with erythroblastosis fetalis treated with replacement transfusion emphasizes the increasing risk with multiple transfusions.

Scott and Tovey<sup>61</sup> reported a case of homologous serum hepatitis in a young mother who received two bottles of plasma and one of blood at the time of delivery. Although she developed jaundice seventy-nine days later, 2 infants whom she had been nursing (her own and that of a neighbor) did not develop the disease. It is of interest to speculate on the possibility that the virus of homologous serum hepatitis passes into the breast milk. However, if virus were present in breast milk, it is unlikely that disease would result in nursing infants since experimental work with human volunteers appears to show that the virus of homologous serum hepatitis is ineffective when administered orally.

### *Prevention of Homologous Serum Jaundice*

Because of the value of gamma globulin in the prevention of infectious hepatitis, investigations of its use in the prophylaxis of homologous serum hepatitis naturally followed. Although initial studies indicated that gamma globulin was effective as a method of prevention, two reports published in 1947 failed to confirm the earlier findings.<sup>49, 62</sup> Duncan et al.<sup>62</sup> believed that the discrepancy in the findings might be explained by the fact that two injections of globulin thirty days apart were given

FINANCIAL STATEMENT  
RECEIPTS

January 1, 1947 — balance forward	\$450 10
Belknap County	410 00
Carroll County	140 00
Cheshire County	310 00
Cos County	256 00
Grafton County	799 00
Hillsborough County	1450 00
Merrimack County	610 00
Rockingham County	620 00
Sullivan County	210 00
Strafford County	410 00
Dues collected at annual meeting	26 00
Members not in county society	18 00
Donation to National Physicians Committee	417 00
(Belknap County \$156 Cos County \$22 Hillsborough County \$92 Strafford County \$41 Merrimack County \$50 Rockingham County \$56)	
Benevolence Fund	120 00
(Hillsborough County \$20 Rockingham County 1946 \$40 Rockingham County 1947 \$35, Merrimack County \$25)	
Net receipts 1947 meeting	1000 83
Refund Cancer Committee	4 44
Check No 1414 stopped payment for Benevolence Fund (Merrimack County)	20 00
(New check made out in 1947 to Trustees)	
	<u>\$7361 37</u>

## EXPENDITURES

<i>New England Journal of Medicine</i>	
Journals	\$556 47
Transactions	1633 94
2 subscriptions	3 00
Carlton R. Metcalf (salary)	700 00
Printing	215 92
Envelopes stamps and stationery	37 70
Hairstone cuts	26 75
Clerical work	344 00
Telephone and telegraph calls	39 45
Retaining fee (Mr Sulloway)	100 00
Guest speakers (fees)	287 76
Cancer committee	60 00
Council of the New England State Medical Societies	100 00
Benevolence Fund	140 00
Merrimack County (1946)	\$10 00
Merrimack County (1947)	25 00
Hillsborough County	20 00
Rockingham County (1946)	40 00
Rockingham County (1947)	35 00
National Physicians Committee	417 00
Belknap County	156 00
Cos County	22 00
Rockingham County	56 00
Strafford County	41 00
Hillsborough County	92 00
Merrimack County	50 00
Madeline A. May (stenographer at annual meeting)	396 32
Committee lunches	9 30
Hotel Wentworth	667 60
Deering G Smith (expenses as delegate to American Medical Association)	153 10
Auditor: trustees books	10 00
Service charges at bank	45
Refund on dues	18 00
Projector and lantern service at annual meeting	217 00
Hodges Badge Company	56 79
	<u>\$6150 55</u>
Balance January 1 1948	1170 82
	<u>\$7361 37</u>

Since my report a year ago three former presidents of the Society have died Charles H Dolloff, Concord, Samuel T Ladd, Portsmouth, and Richard W Robinson, Laconia. At the time of his death Dr Ladd was a trustee.

In accordance with instructions from the House of Delegates the following measures have been carried out \$60 was given to the Cancer Committee, and \$100 was contributed for membership in the Council of the New England State Medical Societies. If we continue our membership in the Council the annual fee of \$100 will be due again this year. I have asked Dr Tuttle, who is reporting on the Council, to take this question up in his report.

The House of Delegates a year ago expressed disapproval of a barbiturate bill, which was submitted to the State Senate. Under this bill doctors could prescribe and dispense barbiturates only with the approval of the State Board of Pharmacy. This bill will presumably come up again next year, and unless it is materially changed in form it is my understanding that the members wish the Society to oppose it.

The Veterans Administration was notified that the Society approves the fee schedule and agreement for hometown care of veterans with service-connected dis-

abilities. This schedule and agreement must be renewed annually. It meets with the approval of the delegates. I shall sign and submit to the Veterans Administration the necessary papers each year until further notice.

Two new committees were added to our roster the Committee on Rural Health and the Committee on Industrial Health.

For the first time since the war we are giving gold medals to the men who have been members for fifty consecutive years. The Indiana Medical Society, instead of a medal, gives a button, which may be worn in the lapel. I have a sample button here this evening.

The round-table conferences have been increased to two-hour periods on the morning of each day.

The committee that arranged this annual meeting decided, for reasons described in a circular, to omit exhibits, the Committee also wished to have members of the Society present brief papers at the afternoon sessions. For this reason at these sessions we are having only four out-of-State speakers. The Committee sent postal cards to all members asking them if they would like to take part in the program this year. It was impossible to find a place on the program for all the members who replied in the affirmative. These postal cards have been kept, however, and will probably be used in the future if this type of program meets with approval.

The Women's Auxiliary has asked us to help it financially for its part in this meeting. Before the war it was our custom to give the Auxiliary \$100 annually. During the war this donation was not given. The House of Delegates thought we could not afford it because so many members were not paying dues. Now that the finances are in much better shape I recommend that the Auxiliary be given \$100 this year and annually until further notice.

Our attorney has asked for an increase in his retaining fee. Mr Sulloway investigates all cases in which suit is threatened against a doctor, he gives free consultation to any member of the Society who needs legal help on a medical problem, he covers all medical legislation that is submitted every other year in the Senate and the House of Representatives, he is a guide, philosopher and friend at all the meetings of the Advisory Committee on Jurisprudence, he settles all cases that in the opinion of this Advisory Committee should be settled, and he conducts the trials in cases that go to Court. It is interesting to note that since Mr Sulloway was appointed counsel some twelve years ago he has not lost a suit that, on recommendation of the Advisory Committee on Jurisprudence, has gone to trial. I recommend that Mr Sulloway's retaining fee be increased to \$200 annually until further notice.

The Connecticut State Medical Society has recently given medical students the privileges of the Society without charge. You may wish to make this friendly gesture in New Hampshire. Presumably, all it would mean would be that students of the Dartmouth Medical School could attend a meeting of a county society or of the State Society if they wished to do so.

An essay contest authorized last year has recently been completed. This contest was open to all students in high schools and junior high schools throughout the State. We received 105 essays. These were screened and the seven essays that seemed to be the best were submitted to the three judges. Most Reverend Matthew F Brady, Bishop of Manchester, Dr Edgar Fuller, Commissioner of Education, and President John A Hunter.

The first prize of \$100 was awarded unanimously by the judges to Miss Irene Moore, of Rochester. Two second prizes of \$50 each were awarded to Miss Violette Nadeau, of Cascade, and Mr Aristotle Bonras, of Newmarket. In addition, county prizes of \$10 each were awarded. The total outlay came approximately to the \$300 that was allotted by the House of Delegates for this contest, and we received from the contest a great deal of favorable comment from the newspapers throughout the State.

A weekly radio broadcast called "Doctors' Orders" has been on the air for the past few years in all the New England States except Vermont and New Hampshire. We have received overtures from the Yankee Network to put this program on in New Hampshire beginning next fall. A sponsor who must be approved by the Society is furnished by the network. A member of the Society

- 45 Capps, R. B. Sborov V and Scheiffley, C S. Syringe transmitted epidemic of infectious hepatitis *J A M A* 136 819-824 1948
- 46 Truelove S C and Hogben, L. A. Documentary study of jaundice associated with syphilis treatment and blood transfusion *Brit J Social Med* 1 18-32, 1947
- 47 Turner R. Hepatitis after penicillin injections *Lancet* 1 103, 1946
- 48 Chalmers T C Jr. Occurrence of jaundice in therapeutic and natural malaria *J Clin Investigation* 26 1055-1059 1947
- 49 Berk J E. Hepatitis following transfusion *Gastroenterology* 8 296-310 1947
- 50 Ginsberg, H S. Homologous serum hepatitis following transfusion *Arch Int Med* 79 555-569, 1947
- 51 Schiff, L. Homologous serum hepatitis clinical implications *New Orleans M & S J* 99 611-616 1947
- 52 Neefe J R. Infectious (epidemic) hepatitis and homologous serum hepatitis *Pennsylvania M J* 50 1323-1327 1947
- 53 Guy E. G., and Lisansky E. T. Clinical and pathologic manifestations of infectious hepatitis *Bull School of Med, Univ Maryland* 32 1, 1947
- 54 Klatskin G., and Rappaport E. M. Gynecomastia due to infectious hepatitis of homologous serum type *Am J M Sc* 214 121-127, 1947
- 55 Gauld R L. Field studies relating to immunity in infectious hepatitis and homologous serum jaundice *Am J Pub Health* 37 400-406, 1947
- 56 McKinlay, P L., and Truelove S C. Epidemiology of infectious hepatitis among Allied troops in Italy *Brit J Social Med* 133-50 1947
- 57 Aycock W L. and Oren, W F. Prolonged incubation period as epidemiological principle infectious hepatitis and homologous serum jaundice *Am J M Sc* 214 483-492 1947
- 58 Apley J and Wallis, H R. E. Homologous serum jaundice in infancy *Brit M J* 1 197, 1948
- 59 Bruyn H B. Homologous serum hepatitis following transfusion in infant. *J Pediat* 31 60-69 1947
- 60 Karelitz, S. Discussion on infectious hepatitis (Abstr) *Bull New York Acad Med* 24 201 1948
- 61 Scott, K B. and Tovey G H. Homologous serum jaundice. *Brit M J* 1 196 1948
- 62 Duncan, G G. et al. Evaluation of immune serum globulin as prophylactic agent against homologous serum hepatitis *Am J M Sc* 213 53-57 1947
- 63 Wolf A M. Mason J. Fitzpatrick W J. Schwartz, S O., and Lennson S O. Ultraviolet irradiation of human plasma to control homologous serum jaundice *J A M A* 135 476 1947
- 64 Gellis S. S., et al. Chemical clinical and immunological studies on products of human plasma fractionation. XXXVI. Inactivation of virus of homologous serum hepatitis in solutions of normal human serum albumin by means of heat. *J Clin Investigation* 27 239-244, 1948
- 65 Bird K. T. Enders J F. and Boyd W C. Unpublished data.

## NEW HAMPSHIRE MEDICAL SOCIETY

### PROCEEDINGS OF THE ONE-HUNDRED AND FIFTY-SEVENTH ANNIVERSARY

House of Delegates, June 1, 2 and 3, 1948

THE House of Delegates convened at Wentworth Hotel, Newcastle, on June 1, 1948, at 7 30 p m., with Speaker Donald G McIvor, presiding

The following members answered the roll call

The President, *ex-officio*  
 The Vice-President, *ex-officio*  
 The Secretary-Treasurer, *ex-officio*  
 Nathan Brody, Laconia  
 Reginald F DeWitt, Plymouth  
 W J Paul Dye, Wolfeboro  
 Francis J C Dube, Center Ossipee  
 Walter H Lacey, Keene, alternate  
 Albert C Johnston, Keene  
 Marjorie A Parsons, Colebrook  
 Francis M Appleton, Gorham  
 Leslie K Sycamore, Hanover  
 Leslie E McKinlay, North Haverhill  
 Everett C Campbell, Woodsville  
 Reginald K House, Hanover  
 Joseph N Friborg, Manchester  
 Robert E Biron, Manchester  
 Norman W Crisp, Nashua  
 Claire G Cayward, New Ipswich  
 Daniel J Sullivan, Nashua  
 Andrew L MacMillan, Concord  
 Francis Brown, Henniker  
 L Whittaker, Portsmouth, alternate  
 Donald W Leonard, Exeter  
 Fred Fernald, Exeter  
 A E Barecomb, Rochester, alternate  
 Edna Walck, Dover  
 B Read Lewin, Claremont  
 George C Wilkins, Manchester  
 David W Parker, Manchester  
 Deering G Smith, Nashua

Leslie K Sycamore (chairman), Joseph N Friborg and Fred Fernald To the Committee on Memorials and Communications, he appointed Drs Brown, Cayward and Moriarty To the Committee on Nominations, he appointed Drs Dye, Parsons, House, Crisp and Whittaker

On motion duly made and seconded, it was voted to omit the reading of the previous minutes, because of the publication of the proceedings

On motion duly made and seconded, it was voted to dispense with the reading of the reports of the councilors, since they will be published in the *Transactions*

The secretary-treasurer, Dr Carleton R Metcalf, presented his report as follows

The total membership on December 31, 1946 was 557, that on December 31, 1947, was as follows

PAID	
Belknap County	37
Carroll County	15
Cheshire County	32
Cooks County	26
Grafton County	75
Hillsborough County	165
Merrimack County	78
Rockingham County	58
Strafford County	41
Sullivan County	21
Not in County Society	2
	— 550

#### UNPAID

Life members	23
Members in service and delinquents	18
	— 41
	591

The Speaker declared a quorum present, and appointed the Credentials Committee as follows Drs Johnston, MacMillan and House To the Committee on Officers' Reports, he appointed Drs

annual meeting from the exhibitors, and that there was to be no such income this year. The Committee wondered what that was going to do to the balance on hand of \$1170.

The Secretary replied that the balance of more than \$1100 had been increased to about \$4000, so that there would probably be \$1500 or more on December 31 without exhibitors.

The Secretary then recommended that the House of Delegates consider the Earl Warren matter. He had thought of sending the information to the New Hampshire delegates to the Republican National Convention in Philadelphia that the president of the California Medical Society had stated that Governor Warren favors, or has announced that he favors, socialized medicine on a national level and wants to put it in the platform of the Republican Party.

Dr Sycamore observed that a recommendation would be brought in on the next morning.

The report of the Council of the New England State Medical Societies was then presented by Dr Ralph W Tuttle.

The Council has now finished its third year of service to the component state medical societies in bringing the different societies closer together in their relations, and at the same time presenting a program of education and information.

The October meeting was highlighted by guest speakers on the antivivisection situation in New England, a subject of vital importance to New England medicine if we wish to retain our place in medical research. There was also presented a discussion on the medical approaches in the treatment of alcoholism.

At our next meeting a public-relations conference was conducted with a sizable attendance from throughout New England. The main speakers were top men from the radio and press. The doctors were more or less put on the pan because of their aloofness and indifference to the public in general and to the press and radio in particular. Much publicity accrued to the Council from the meeting, as evidenced by news clippings from papers throughout the area.

A closer alliance with the New England States Dental Officers' Conference was effected by having members of that organization as our guests at the meeting in March at Boston, and with the president of the Council, Dr Arthur H. Ruggles, their guest speaker on the subject of medical-dental relations, at their annual session at Hartford in April.

At our annual meeting in April it was brought to our attention that the American Public Health Association was holding a meeting in November, and that the New England Health Institute was to be held in Amherst, Massachusetts, from June 16 to 18, under the auspices of the Massachusetts State Department of Health. It was generally agreed that an effort should be made to have the Council actively connected with the health institute another year, if it is possible for such a relation to be effected.

The general appeal and effect on public relations of the radio program "Doctor's Orders" were discussed.

There was a discussion on medical organization for a national emergency. We already have such a committee in New Hampshire, and the other states are contemplating such committees.

There is a bill before Congress providing that physicians up to forty-five years of age could be inducted. The many telegrams from the state medical societies threatened to defeat the plan. But the armed service group are quite adamant. The Navy is not particularly concerned because most of its doctors are subject to recall. The armed

service group feels that it would have an immature group if only physicians under twenty-six were drafted.

There was considerable inquiry directed to hospitals in New England regarding general practitioners, and what standing they should have on the services of general hospitals.

In an effort to determine the privileges and restrictions regarding practice in the hospitals in New England by general practitioners, an inquiry was sent to fifty hospitals in the region. Replies were received from twenty-seven, including at least one from each of the New England states. Some of the large hospitals evaded the question. The tendency is toward concentration in specialties for staff privileges, with the specific criterion qualification by one of the various boards or colleges. Very few give the general practitioner much opportunity to render care for the majority of his patients.

This suggestion appears worthy of the consideration that the Council establish a committee of its own, or for it to make a complete study of the situation in the New England area to rationalize in this region what might be done in the best interests of the public and the medical profession, to give the general practitioner hospital privileges.

It is my opinion that the Council of the New England State Medical Societies is doing a worthwhile job in the interests of medical practice and general welfare, and I suggest to the House of Delegates that the usual sum of \$100 be appropriated to continue the work of the Council.

This motion was duly seconded and was carried. President John A. Hunter then spoke as follows:

Your president wishes to take this opportunity to give a brief account of his stewardship for the year 1947-1948, which, although nothing spectacular was accomplished, seems on the whole to have been a busy one.

In the beginning, Dr Metcalf was ill for some time, and later went away to convalesce, and you can well realize what this meant to an incoming officer, since our efficient secretary knows the ropes so well and handles the maze of details connected with this organization. However, with Mrs. Oulette's assistance and good counsel from ex-president Ralph Tuttle, we got the ball rolling.

The Scientific Committee held two lengthy meetings at the Eagle Hotel and Dr. Metcalf's office, planning the program for our annual meeting, and the majority concluded that we would eliminate the exhibits this year, the reasons for this decision having been mailed to each member with his program, and we trust that the experiment will work out satisfactorily.

Five counties invited the President to attend one or both of their meetings, and three such visitations were made, illness and weather conditions preventing attendance at the other two. Members of two of these societies brought their wives to the banquet, and afterward the ladies had a meeting of the auxiliary. It seemed to work out very bappily, with fine attendance.

In March I was appointed director of the Blue Cross and Blue Shield, and many long hours were spent at Concord revising the fee list, in an effort to get the organization out of the red. I never realized before the amount of work the officials and directors put into this organization, and in passing I ought to mention Drs. Harwood, of Burlington, Vermont, and Johnson, of St. Johnsbury, Vermont, who drove so far in miserable weather and stayed with us late into the night on more than one occasion, working out the new program.

I attended the March meeting of the New England Medical Council held at the Copley Plaza in Boston on March 7, which was a most interesting meeting. Public relations was one of the main subjects discussed by the editors of a large and a small newspaper. In the discussion that followed, it was pointed out that often the paper did not get the information correct, exploited a doctor's name and so forth, but the editors and some members present felt it was time for the doctors to come out of their citadel.

I attended an informal meeting at the Eagle Hotel in February, called by Secretary Metcalf, to hear Edward F.

takes part in the broadcast each week. There is no expense to the Society. I have referred this matter to the Committee on Communications and Memorials and have asked them to report and make a recommendation at this meeting.

Last February I received a telephone call from Chicago from Mr. Stegen, an associate director of the National Physicians Committee. Mr. Stegen, who said that he was coming to New Hampshire, wanted to know if I would invite a small group of members from the Society to confer with him about legislation and the part therein played by the National Physicians Committee. This meeting with Mr. Stegen, with 15 or 20 members of the Society in attendance, was held at the Eagle Hotel in Concord on the evening of February 19.

The National Physicians Committee wants us to form an informal group to co-operate more closely with it. We have, of course, been doing this to a certain extent for several years through some of our county societies.

The members of the Society who met in Concord on February 19 approved the formation of a State committee on the following basis:

Such a group in New Hampshire would be informal. It would not join the National Physicians Committee. It would receive their literature and could get advice on legislation if it wished such advice. The State group would not be bound by any opinions, plans or activities of the National Physicians Committee, and would be free to criticize or advise this Committee if the Committee seemed to be off the track.

I recommend that you approve the appointment of an informal committee without placing the Committee officially on the list of standing committees. If your approval is forthcoming several members have agreed to serve.

Before the war we used to send delegates to the annual meetings of the other state medical societies in New England. Some of the delegates from New Hampshire enjoyed these trips, occasionally, delegates felt that they were not very warmly received in other states. This procedure was omitted during the war because of the difficulties of travel. Do you wish again to send delegates or shall we let the procedure remain in status quo?

The *New England Journal of Medicine* has found it necessary to increase the subscription rate for our members who wish to receive all the fifty-two issues of the *Journal* each year. The Society pays the *Journal* \$1.00 a year for each member, and for this the member receives twelve copies annually. Hereafter any member who wishes to receive fifty-two copies annually must send, individually, \$3.00 to the *Journal*, in addition to the \$1.00 that is sent by the Society.

On April 5 and 6 Dr. Daniel J. Sullivan, chairman of the Committee on National Emergency Medical Service, attended a meeting in Chicago, which considered the medical needs in the event of another national emergency. This meeting was sponsored by the American Medical Association, and several top officials from the federal Government were present.

There seem to be three hotels in New Hampshire that can accommodate a convention as large as ours where many who attend wish to stay overnight. These hotels are the Hotel Wentworth in Newcastle, the Mount Washington Hotel, in Bretton Woods, and the Mountain View House, in Whitefield.

On motion duly made and seconded, it was voted that the report of the Secretary-Treasurer be referred to the Committee on Officers' Reports.

Dr. Sycamore, for the Committee on Officers' Reports, recommended that the House of Delegates stand in silent tribute to the memory of Charles H. Dolloff, Samuel T. Ladd and Richard W. Robinson.

This motion was duly seconded and was carried.

Dr. Sycamore then recommended that the Committee on Public Relations be instructed to oppose any barbiturate bill that might be introduced into

the New Hampshire General Court, similar to the bill that the House of Delegates disapproved at its 1947 session.

This motion was duly seconded and was carried.

Dr. Sycamore also recommended that the Secretary be instructed to renew the agreement between the New Hampshire Medical Society and the Veterans Administration regarding hometown care of veterans, renewal to be made each year until further notice.

This motion was duly seconded and was carried.

Dr. Sycamore then stated that it did not appear too clear just what the functions of the Women's Auxiliary were, if it is to be of aid and assistance to the Society, it should stand on its own feet and pay its own way.

Dr. Metcalf stated that the money was used largely for a party that was held each year. The Auxiliary also contributed to the Benevolence Fund by giving parties and engaging in other home activities.

Dr. Leonard then remarked that the ladies paid \$1.00 a year, of which fifty cents went to the national organization.

Dr. Dye moved that the Women's Auxiliary be given \$100.

This motion was duly seconded and was carried.

Dr. Sycamore then moved that the retainer fee for Attorney Frank J. Sulloway be increased to \$200.

This motion was duly seconded and was carried.

Dr. Sycamore recommended that the House of Delegates approve the appointment of an informal committee to co-operate with the National Physicians Committee.

This motion was duly seconded and was carried.

The secretary read the names of this committee, as follows: Drs. Miller and Smart, of Belknap County; W. J. Paul Dye, of Carroll; Johnston and Almqvist, of Cheshire; Marjorie Parsons, of Coos; Campbell, Sycamore and House, of Grafton; Smith and Powers, of Hillsborough; Graves, Blood, Brown and Metcalf, of Merrimack; Leonard, of Rockingham; Hunter and Walch, of Strafford; and Lewin, of Sullivan.

The Speaker then asked if the House of Delegates approved this committee. There was a unanimous answer in favor of approval.

Dr. Sycamore then moved that no official delegates be appointed to attend the meetings of the medical societies of the other New England states. After some discussion, the motion was duly seconded and was carried.

Dr. Sycamore recommended that the next annual meeting be held at either the Mount Washington Hotel or the Mountain View House. After some discussion consideration of the matter was postponed until the last day of the meeting.

Dr. Sycamore then remarked that last year there had been an item of \$1000 net received from the

This motion was duly seconded and was carried. The report of the Committee on Medical Economics was then presented by the chairman, Dr Leslie K. Sycamore.

The Committee reports with deep regret the loss by death of one of its members. Dr Richard W. Robinson has been a member of the Committee for many years, and always took a keen and active interest in the problems with which the Committee was concerned. His consideration of any question was characterized by a penetrating insight into its implications, coupled with an uncompromising loyalty to the highest ideals of his profession and a sympathetic concern for the best interests of the patient. The members of the Committee experienced a keen sense of personal loss in the passing of a friend. The Committee is the poorer for the lack of his wise and kindly counsel, and the New Hampshire Medical Society has lost one of its ablest and best-loved leaders.

#### *Welfare Fee Schedule*

At the last session of the House of Delegates, the Committee was instructed to investigate the possibility of obtaining increased fees for services to welfare patients. Accordingly, an interview was arranged with Mr Elmer Andrews, commissioner of public welfare, who stated that any change would be impossible during the current biennium, because no funds were available in the appropriation for meeting any increase. He suggested that representation should be made at the budget hearing to be held in the fall by the Board of Public Welfare. The Committee plans to take this action.

#### *New Hampshire—Vermont Physician Service*

Several significant developments have occurred during the year regarding the Blue Shield program. Enrollment has steadily increased and has reached 170,000 for the Surgical Division and 85,000 for the Medical Division; gross income has reached a rate of \$1,500,000 per year. This places us high on the list of nonprofit medical-society plans.

On the other side of the picture, however, there has been over the past fifteen months a steadily rising utilization of service, from 220 to 275 cases per 1000 participants with some indication at present that this trend is leveling off. From the medical viewpoint, this may be considered an indication that the Service is better achieving its aim of making medical care more widely available. From the actuarial viewpoint, however, this increased utilization has exceeded the anticipated load and has resulted in a serious operating deficit in the Surgical Division amounting in the first three months of 1948 to the sum of \$60,000, or 23 per cent of income. The Board of Directors has deemed it necessary, therefore, to make a substantial increase in the premium rates to meet the deficit and to provide a reasonable surplus for reserves. Utilization in the Medical Division has also increased, but has not exceeded a satisfactory loss ratio.

Obviously, there must be a point beyond which any increase in premiums will result in a decrease in enrollment, and will result also in putting Blue Shield in an unfavorable position from competition from commercial insurance companies. Where that point lies, we are not at present in a position to predict. The situation does raise the question whether any of the increase in utilization is unnecessary in the sense that procedures employed are not essential in diagnosis or treatment. This admittedly is a very difficult line to draw, especially in the face of pressure from the patient, who wants to "get his money's worth" from his insurance. If any overuse does exist, each physician can assist in discouraging it by pointing out to the patient that each item of service enters into the cost to the subscriber.

Another area in which the individual physician can be of help to the Service is in the more accurate definition for the Claims Department of the pre-existing conditions that come under the exclusion clause in the contract and in an explanation to the patient that such exclusions are necessary to prevent overloading the service with chronic conditions, and to prevent a subscriber from joining for

a brief period for the sole purpose of obtaining treatment for a known condition.

Particularly in view of the increase in premium rates, it behooves us as members of the New Hampshire Medical Society to remind ourselves of the conditions under which the New Hampshire Physician Service was constituted under the aegis of the Society. To avoid the complications of a service contract with an income limit for the subscriber, it was decided to get up the program on an indemnity basis, but at the same time to protect the low-income subscriber by mutually agreeing that in this subscriber group the fee charged should approximate the benefit listed in the schedule. The low-income group comprises roughly individual incomes up to \$2500 per year, and family incomes up to \$3500 per year. For such subscribers, therefore, the fee in the average case should not exceed the benefit allowed.

In the national field, an important development has been the appointment of Dr Paul R. Hawley, formerly of the Veterans Administration, as chief executive officer of the Blue Shield and Blue Cross National Organizations. A joint session of the Blue Shield and Blue Cross representatives was held this spring to discuss plans for the formation of a National Blue Cross-Blue Shield Association to co-ordinate the activities of the various local plans. Final action has not been taken on this proposal.

The American Medical Association has taken the incomprehensible action of cancelling its Blue Cross coverage for its employees and placing its insurance with a commercial carrier. Your committee considers this action a betrayal of the nonprofit plans set up under medical-society sponsorship, and therefore recommends the adoption of the following resolution.

Whereas, the American Medical Association has urged its component Medical Societies to establish nonprofit Medical insurance programs as the doctor's answer to the problem of distribution of medical care, and

Whereas, the American Medical Association has cancelled its Blue Cross coverage of its employees in favor of a commercial carrier, and

Whereas, this action represents a betrayal of the principle of nonprofit voluntary sickness insurance, which is the foundation of the medical-care plans sponsored by the component societies, therefore be it

*Resolved* that the New Hampshire Medical Society strongly disapproves of the action of the American Medical Association in cancelling its Blue Cross coverage and urges that the contract with Blue Cross be renewed.

The Committee is firmly convinced that the Blue Shield program is performing a valuable service both for the patient and for the physician, and therefore continues to merit the full support of the members of the New Hampshire Medical Society.

Dr Sycamore moved that the Committee on Medical Economics be instructed to continue its negotiations with the State Board of Public Welfare regarding the welfare fee schedule.

The motion was duly seconded, and was carried, with one dissenting vote.

Dr Sycamore then moved that the House of Delegates recommend to the members of the New Hampshire Medical Society that their full support be given to the New Hampshire-Vermont Physician Service.

This motion was duly seconded and was carried.

Dr Sycamore further moved that the proposed resolution regarding the American Medical Association and Blue Cross be adopted, and that the Secretary be instructed to forward a copy to the Secretary of the American Medical Association.

Dr Sullivan asked why the American Medical Association had changed the procedure.

Stagen, of the National Physicians Committee, who presented legislative problems concerning medicine as we wish it practiced today, and hoped that a group from New Hampshire would be willing to lend their assistance, by communicating with their legislators, should national-emergency legislation arise. A letter from the Secretary to county secretaries explains our attitude in this matter.

A communication from Howard B. Sprague, M.D., was received asking for support for the New England Heart Association. I replied that no action, if any could be taken until after the House of Delegates had met on June 1. I trust that you gentlemen will make some decision so that the Secretary can give Dr. Sprague an answer.

In October I attended a get-together at Greenfield, New Hampshire, of many people in different walks of life who were interested in the Crotched Mountain project for rehabilitation of the crippled children of New Hampshire, and subsequently was present at the banquet in Manchester Armory when the drive was officially launched, Governor Thomas Dewey being the main speaker.

In conclusion I wish to thank everyone who helped make the year a success, and trust we will have an interesting scientific program the next two days, and a wealth of good fellowship.

Dr. Francis Brown then presented the report of the Committee on Memorials and Communications, as follows:

A communication from Mr. Frank Jones, of Providence, Rhode Island, suggests that the Society approve the radio program "Doctor's Orders" as a public-service program entitled to participation by local doctors. "Doctor's Orders" consists of weekly interviews with local physicians, presented from scripts prepared by the broadcasting companies subject to revision by the man presenting the material. Sample interviews included in the correspondence contain no particularly controversial matter. However it is not stated what the approval of the Society would be taken to mean in the way of responsibility. Because of one incidental reference to Society officers who must line up the speakers, the Committee assumes that the Society would be expected to undertake this function. The question of financial sponsorship is not involved in our approval. During the 1947-1948 season the program is said to have been approved by all the New England state medical societies except ours.

While realizing that public relations are becoming a more and more important function of medical societies, the Committee nevertheless submits the following considerations:

That it is questionable whether any New Hampshire radio station carries a sufficiently wide appeal throughout the State to make the proposal of much value as advertising for the Society.

That if our approval involves the responsibilities for providing the speakers, probably the entire load would be carried by members in Manchester, both for speaking and for finding the speakers. It is doubtful if any other city has enough physicians to make the program feasible.

That if any county society wishes to undertake such a responsibility, the approval of the Society would be superfluous.

We therefore recommend that approval of "Doctor's Orders" by the New Hampshire Medical Society be withheld.

After considerable discussion Dr. Brody moved that the broadcasting setup be approved and that the supervision of this medical broadcasting for the Society be by Dr. Brown, chairman of the Committee on Communications and Memorials.

Dr. Dye suggested the amendment that Dr. Brown be appointed on that Committee of Public Relations, so that he could supervise the program from there and consult with other members of the Committee from time to time, the other members

of the Committee being the President, the Vice President and Secretary-Treasurer.

Dr. Brody accepted the amendment to the motion.

The motion was carried.

The Report of Committee on the Control of Cancer was then presented.

On April 28, 1948, the third annual Cancer Conference Day, conducted by the Committee, was held at the Carpenter Hotel in Manchester. This meeting appeared to be a very successful one from the viewpoint of attendance, interest and the quality of the talks. The subjects presented by the three guest speakers from Boston and the five New Hampshire men were all on various aspects of cancer diagnosis or treatment, and the talks were well discussed by the audience. A luncheon was given at noon. All the expenses of the meeting were assumed as usual by the New Hampshire Division of the Field Army of the American Cancer Society. We only regret that more members of the New Hampshire Medical Society did not attend this meeting.

The Field Army has continued its excellent work in lay education, transportation of patients to clinics, making of surgical dressings for indigent patients and keeping together its large and enthusiastic membership. It has also continued its work in high-school cancer education.

During the year, as usual, three letters on pertinent cancer subjects have been mailed to each member of the Society. One on "Carcinoma of the Colon" gave suggestive symptoms, particularly the early symptoms, and advice regarding what should be done, including x-ray and protoscopic examinations in suspected cases. The usual warning of the importance of early rather than late examination was stressed. The second letter discussed the increasing lay criticism of the medical profession for its apparent inability to recognize cancer or the possibility of cancer early enough for the patient to be cured. These criticisms have appeared in medical journals as well as in lay magazines, and some criticisms were unjust and some were deserved. This letter admitted the inadequate examinations of some doctors but urged more careful examinations and suggested methods for carrying out such a program. It also stated that the patient who fears cancer should be examined as carefully as one fearing heart disease, stomach ulcer or gall-bladder disease. The third letter discussed cancer of the larynx in its two anatomic locations and stressed the importance of the early symptoms of persistent hoarseness and dysphagia. Any patient with such symptoms should be examined by a laryngologist as early as possible, and if cancer is found, the patient should have immediate treatment, either operation or x-ray therapy.

The functions of the cancer clinics have continued as usual, although the ones at Littleton and Nashua have been discontinued on account of lack of patients. There has been an increase in the number of patients entering the clinics during the past year, and the expenses of the Cancer Commission in caring for needy patients with cancer have increased quite considerably because of the increase in hospital rates. The American Cancer Society in its April issue of *Cancer News*, devoted the entire issue to the subject of cancer clinics, and honored the State by describing it as a model for other states, partly because we are the only state in the union having one clinic for every 50,000 people. A very full description of the functions of the Cancer Commission and the cancer clinics was given in the text, and it was accompanied by a group of photographs taken in one of the New Hampshire clinics. The Committee has expended \$52.31 of the \$60.00 appropriation, and requests the sum of \$60.00 for the next year's expenses.

GEORGE C. WILKINS, Chairman  
GEORGE F. DWIGELL  
RALPH E. MILLER  
WALTER H. LACEY  
ALBERT OPPENHEIMER

Dr. Sycamore moved that the sum of \$60 be appropriated for the expenses of the Committee on the Control of Cancer for the current year.

This motion was duly seconded and was carried. The report of the Committee on Medical Economics was then presented by the chairman, Dr Leslie K. Sycamore.

The Committee reports with deep regret the loss by death of one of its members Dr Richard W. Robinson has been a member of the Committee for many years, and always took a keen and active interest in the problems with which the Committee was concerned. His consideration of any question was characterized by a penetrating insight into its implications, coupled with an uncompromising loyalty to the highest ideals of his profession and a sympathetic concern for the best interests of the patient. The members of the Committee experienced a keen sense of personal loss in the passing of a friend, the Committee is the poorer for the lack of his wise and kindly counsel, and the New Hampshire Medical Society has lost one of its ablest and best-loved leaders.

#### *Welfare Fee Schedule*

At the last session of the House of Delegates, the Committee was instructed to investigate the possibility of obtaining increased fees for services to welfare patients. Accordingly, an interview was arranged with Mr Elmer Andrews, commissioner of public welfare, who stated that any change would be impossible during the current biennium, because no funds were available in the appropriation for meeting any increase. He suggested that representation should be made at the budget hearing to be held in the fall by the Board of Public Welfare. The Committee plans to take this action.

#### *New Hampshire — Vermont Physician Service*

Several significant developments have occurred during the year regarding the Blue Shield program. Enrollment has steadily increased and has reached 170,000 for the Surgical Division and 85,000 for the Medical Division, gross income has reached a rate of \$1,500,000 per year. This places us high on the list of nonprofit medical-society plans.

On the other side of the picture, however, there has been over the past fifteen months a steadily rising utilization of service, from 220 to 275 cases per 1000 participants with some indication at present that this trend is leveling off. From the medical viewpoint, this may be considered an indication that the Service is better achieving its aim of making medical care more widely available. From the actuarial viewpoint, however, this increased utilization has exceeded the anticipated load and has resulted in a serious operating deficit in the Surgical Division, amounting in the first three months of 1948 to the sum of \$60,000, or 25 per cent of income. The Board of Directors has deemed it necessary, therefore, to make a substantial increase in the premium rates to meet the deficit and to provide a reasonable surplus for reserves. Utilization in the Medical Division has also increased, but has not exceeded a satisfactory loss ratio.

Obviously, there must be a point beyond which any increase in premiums will result in a decrease in enrollment, and will result also in putting Blue Shield in an unfavorable position from competition from commercial insurance companies. Where that point lies, we are not at present in a position to predict. The situation does raise the question whether any of the increase in utilization is unnecessary in the sense that procedures employed are not essential in diagnosis or treatment. This admittedly is a very difficult line to draw, especially in the face of pressure from the patient, who wants to "get his money's worth" from his insurance. If any overuse does exist, each physician can assist in discouraging it by pointing out to the patient that each item of service enters into the cost to the subscriber.

Another area in which the individual physician can be of help to the Service is in the more accurate definition for the Claims Department of the pre-existing conditions that come under the exclusion clause in the contract, and in an explanation to the patient that such exclusions are necessary to prevent overloading the service with chronic conditions, and to prevent a subscriber from joining for

a brief period for the sole purpose of obtaining treatment for a known condition.

Particularly in view of the increase in premium rates, it behooves us as members of the New Hampshire Medical Society to remind ourselves of the conditions under which the New Hampshire Physician Service was constituted under the aegis of the Society. To avoid the complications of a service contract with an income limit for the subscriber, it was decided to get up the program on an indemnity basis, but at the same time to protect the low-income subscriber by mutually agreeing that in this subscriber group the fee charged should approximate the benefit listed in the schedule. The low-income group comprises roughly individual incomes up to \$2500 per year, and family incomes up to \$5500 per year. For such subscribers, therefore, the fee in the average case should not exceed the benefit allowed.

In the national field, an important development has been the appointment of Dr Paul R. Hawley, formerly of the Veterans Administration, as chief executive officer of the Blue Shield and Blue Cross National Organizations. A joint session of the Blue Shield and Blue Cross representatives was held this spring to discuss plans for the formation of a National Blue Cross-Blue Shield Association to co-ordinate the activities of the various local plans. Final action has not been taken on this proposal.

The American Medical Association has taken the incomprehensible action of cancelling its Blue Cross coverage for its employees and placing its insurance with a commercial carrier. Your committee considers this action a betrayal of the nonprofit plans set up under medical-society sponsorship, and therefore recommends the adoption of the following resolution.

Whereas, the American Medical Association has urged its component Medical Societies to establish nonprofit Medical insurance programs as the doctor's answer to the problem of distribution of medical care, and

Whereas, the American Medical Association has cancelled its Blue Cross coverage of its employees in favor of a commercial carrier, and

Whereas, this action represents a betrayal of the principle of nonprofit voluntary sickness insurance, which is the foundation of the medical-care plans sponsored by the component societies, therefore be it

*Resolved* that the New Hampshire Medical Society strongly disapproves of the action of the American Medical Association in cancelling its Blue Cross coverage and urges that the contract with Blue Cross be renewed.

The Committee is firmly convinced that the Blue Shield program is performing a valuable service both for the patient and for the physician and therefore continues to merit the full support of the members of the New Hampshire Medical Society.

Dr Sycamore moved that the Committee on Medical Economics be instructed to continue its negotiations with the State Board of Public Welfare regarding the welfare fee schedule.

The motion was duly seconded, and was carried with one dissenting vote.

Dr Sycamore then moved that the House of Delegates recommend to the members of the New Hampshire Medical Society that their full support be given to the New Hampshire-Vermont Physician Service.

This motion was duly seconded and was carried.

Dr Sycamore further moved that the proposed resolution regarding the American Medical Association and Blue Cross be adopted and that the Secretary be instructed to forward a copy to the Secretary of the American Medical Association.

Dr Sullivan asked why the American Medical Association had changed the procedure.

Dr Sycamore replied that a commercial company had offered to give the American Medical Association a guaranteed premium rate for the year, and the Blue Cross could not. The commercial company was offering indemnity contracts, and, of course, could guarantee the rates. Blue Cross was offering service contracts, and its costs might go up as hospital costs went up. The point at issue was that the American Medical Association had been fostering these nonprofit plans and had been requesting the local state and county societies to set them up and that, in taking the action discussed, had allied itself with the competitors of Blue Cross, in effect, it is saying that the commercial plans are more desirable.

Dr Friberg seconded Dr Sycamore's motion.

The Speaker then asked all those in favor of the motion to signify assent by saying "aye."

There was a chorus of "ayes" and some dissenting votes, but the motion was carried.

The report of the Committee on Mental Hygiene was then presented, as follows:

The New Hampshire Mental Hygiene and Child Guidance Clinics have been partly reorganized, and a full program is looked for in 1949. This program includes not only the diagnostic traveling activities but also the establishment of a program of psychiatric and psychologic care in a residential setting for children who need it—that is, for children who are emotionally disturbed, suffering from neuroses and with behavior and character disorders.

Since July, 1947, two psychologists, a psychiatric social worker and a senior clerk-stenographer have been added to the Mental Hygiene Clinic Staff, making a total personnel of nine.

Two new monthly clinics have been established, one in Portsmouth at the General Hospital, being sponsored by the Portsmouth Visiting Nursing Association and the Portsmouth Hospital. The second is in Keene at the headquarters of the Department of Public Welfare. These are in addition to the regular clinics held monthly in Concord, Manchester, Nashua, Laconia and Rochester, and also the three clinics of two days' duration held in Berlin, with plans to hold several clinics in the northern part of the State this summer.

The educational program in mental hygiene has been doubled this year. The director, Dr Anna Philbrook, has given thirty-seven talks to groups of nurses and teachers, parent-teachers groups and mothers' clubs and at present is teaching a course in mental hygiene to the Winnepesaukee Teachers Association. The course is attended by fifty-eight teachers, and consists of two-hour lectures given each week on Monday.

The Clinic psychologists are writing a mental-hygiene column for the newspaper, called "Know Yourself."

More treatment has been done by the individual members of the Clinic staff, particularly play therapy with children who are emotionally disturbed. Finger painting and play therapy carried out with the doll house and doll family have proved to be very useful this year, and more has been done than ever before.

Through the Veterans Administration, clinics for veterans with emotional disturbances are being conducted regularly by Dr Everett F. Lombard as director, who formerly was a member of the New Hampshire State Hospital Staff and a volunteer worker in the Mental Hygiene Clinic.

With the opening of the Children's Center in Concord and the addition of another psychiatrist to the Mental Hygiene Clinic Staff, there is a definite plan that should provide adequate service to the State.

The State Hospital is now planning also to open mental clinics in Manchester, Nashua, Dover, Rochester and Portsmouth, to which patients out on convalescent leave

may come to review their condition and progress. These clinics will be held monthly and will be attended by one of the physicians of the staff at the Hospital, a social worker, a psychologist and one clerical worker. It is hoped that the reopening of these clinics will give indigent adult patients suffering from emotional disturbances, neuroses or borderline mental illnesses an opportunity to attend the clinics for advice and outpatient treatment.

The State Department of Health, in co-operation with the State Hospital and the State Mental Hygiene Clinics, has recently opened a clinic for diagnosis and treatment of indigent patients with convulsive seizures. Facilities for electroencephalographic studies are now available at the New Hampshire State Hospital if so indicated. A clinician and a physician of the Hospital Staff are already trained respectively to take and interpret the readings. These facilities are also available for use in determining organic neurologic conditions of the brain, such as tumors for patients both within and without the Hospital.

In conjunction with the setting up of these clinics for convulsive seizures, it might be well to recommend a State survey of epileptics, which might include also a survey of backward children in the schools, with the view in mind of testing them by a psychologist for their I. Q., which would prove of value to their respective teachers.

The recent advances in treatment in neuropsychiatry by means of electroshock and insulin therapy and narcotherapy have aided materially in shortening hospitalization time of certain types of psychiatric patients, more noticeably depressive types and catatonic types of schizophrenia. The members of the Committee believe that if better facilities were available in general hospitals, a number of patients might be treated by these methods and thus prevented the necessity of entering a psychiatric or mental hospital for treatment there. It is thus recommended that in every newly built hospital, or where addition to a hospital is being contemplated, several beds, or preferably a small section, be set apart for the type of treatment mentioned above, in the belief that the patient probably would respond rapidly and favorably to it.

The problem of the care of feeble-minded children under the age of five, especially those afflicted with severe organic cerebral disorders, has come to the fore in view of the inability of the State School in Laconia to care for such patients. Individual county hospitals should be made to assume such responsibility as a last resort, or a more scientific medical approach to the problem would be for the State to build a special pavilion at the Laconia State School for such cases. The addition of the residential home in Concord for the intramural psychiatric study of certain psychiatric problems in children with normal intelligence will not alleviate in any way the need for special facilities for the care of the above group of cases.

The Committee recommends that a more intensive use of the sterilization laws might be of value in rehabilitation of certain cases of mentally ill and mentally defective persons to the point where they might be paroled from the institutions where they are now under treatment to proper environmental situations with suitable follow-up work by social agencies, because every available agency or interested person should be approached in any state hygiene program that may be instigated.

The State has come to recognize the chronic inebriate as a mentally sick person and now has a board that considers the problems from all angles. It hopes eventually to have proper facilities to care for the inebriate, staffed by a psychiatrist who would be a medical director, a psychologist and a clerical force and the proper amount of personnel. However, it seems to this Committee that the board should include as one of its members a psychiatrist, as well as the physician now on the board, who views the individual inebriate from a physiologic standpoint.

Shortly, it appears, from rising public interest, particularly in the courts, that the State must approach the problem of persons termed psychopaths more from a medical angle than ever before, and this should call for the appointment of a committee, which might emanate from the Governor and Council, to study this problem thoroughly and to render suggestions.

In conclusion, the members of the Mental Hygiene Committee feel that they, as well as the State in general, have met with a severe loss in the death of Dr. Charles H. Dol-

loft. He served as chairman of the Committee for many years. As a result of his interest and efforts, New Hampshire is in the vanguard in the institutional care of psychotic patients. He was also instrumental in organizing the State system of Mental Hygiene Clinics.

ARTHUR B. HOWARD, *Chairman*  
EDWARD S. MORRIS  
SIMON STONE

Dr. Sycamore moved that a copy of the paragraph in the report regarding facilities in general hospitals be sent to the president of the New Hamp-

shire Hospital Association, with the request that it be read at the next meeting of that association.

This motion was duly seconded and was carried.

Dr. Sycamore, for the Committee on Officers' Reports, also moved that the House of Delegates express its approval of a state survey of epileptic and psychopathic persons.

This motion was duly seconded and was carried.

(To be continued)

## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

EDITH E. PARRIS, *Assistant Editor*

### CASE 34401

#### PRESENTATION OF CASE

A forty-four-year-old woman was admitted to the hospital because of a tumor in the right side of the abdomen.

One month before entry the patient first experienced a dull pain in the right upper quadrant of the abdomen, which on the first day radiated to the umbilicus and the right costovertebral angle. There was no nausea, vomiting, anorexia, weight loss, change in bowel habits or urinary symptom accompanying the pain. After three days without relief the patient saw a physician and was subsequently admitted to another hospital. Barium studies and a Graham test were said to show a mass in the region of the right kidney extrinsic to the gall bladder and bowel. She was discharged from the hospital feeling well except for marked anxiety, depression and nervousness, these complaints being relieved by sedation. She had lost 10 pounds while on a restricted-calorie diet at home.

The patient had apparently always been well, there being no history of serious illness or previous operations. She had two deliveries, seven and five years before entry, without difficulty.

Physical examination disclosed a well developed, well nourished woman in no acute distress. The positive physical findings were limited to the abdomen where there was a smooth, firm mass below the right kidney and adjacent to the vertebral column. There was no costovertebral-angle or abdominal tenderness. Neither the spleen nor the liver edge could be felt and the contour of the

abdomen was normal. There was a question whether or not the right kidney could be felt.

The temperature, pulse and respirations were normal. The blood pressure was 110 systolic, 70 diastolic.

The blood hemoglobin was 13.8 gm, the white-cell count 7000, the prothrombin time 18 seconds (control, 16 seconds), the nonprotein nitrogen 22



FIGURE 1 Plain Film of the Abdomen, Showing a Lobular Mass in the Right Upper Quadrant. Arrow points to the straight line mentioned in the discussion.

mg and the total protein 6.4 gm per 100 cc. The urinary sediment showed a rare red cell, an occasional white cell and 30 epithelial cells per high-power field. The specific gravity was 1.020.

An intravenous pyelogram disclosed the presence of an ovoid mass of homogeneous density, showing a smooth, only slightly undulating margin situated in the right upper abdomen (Fig. 1). Its upper portion did not appear to be entirely included in the

films obtained. The mass measured at least 15 by 10 cm. Pyelography showed good kidney function and no evidence of intrinsic involvement of the urinary tracts or kidneys. However, the right kidney was displaced upward, its lower pole also being displaced medially, and the kidney being rotated on its vertical axis so that the ureter entered the renal pelvis more laterally than usual. The spleen may have been very slightly increased in size. There was no evidence of ureteral obstruction, and the bladder appeared normal.

On the fourth hospital day an operation was performed.

### DIFFERENTIAL DIAGNOSIS

DR LAURENCE L. ROBBINS. I assume that you do not have the x-ray films taken at the other hospital?

DR BENJAMIN CASTLEMAN. No.

DR ROBBINS. In summary, we have a forty-four-year-old woman whose complaint was pain in the right upper quadrant of one month's duration and the presence of a mass. That is just about as far as I am going to get in this discussion. First of all, it would be a tremendous help to know the relation of this mass to the gall bladder because one consideration would certainly have to be a hydrops of the gall bladder. It is not unusual to see a hydrops of the gall bladder in extreme cases do just what happened here. We must assume that the gall bladder was filled on the other examinations. What we see here is that the right kidney has been pushed upward and the lower pole rotated medially by a mass, the upper limits of which we cannot definitely define. Certainly, the greater portion of the mass is apparent, with suggestive lobulation at its inferior border and definitely something abnormal below and lateral to what we define as the edge of the lobular mass. We do see the kidney outline in its entirety so it would be unlikely that this arose from the kidney itself, unless we assume it arose from the anterior surface or posteriorly and worked around on a long, thin pedicle. These areas of calcification appear to be outside the mass and are probably nodes within the abdomen. The only abnormality in the intravenous pyelogram is the deformity of the inferior calyx, which can occur from extrinsic pressure.

Of the various things that we have to consider, I suppose one has to think of a dermoid cyst, which occasionally occurs in this area. If this was a dermoid cyst, it did not have the characteristic x-ray findings, such as the density of fat and areas of calcification within it.

So far as an inflammatory process such as tuberculosis is concerned, one has to think about the possibility that something extended downward from the region of the thoracic spine. But we have nothing to go on regarding that. This could have been an echinococcus cyst of the liver, but again,

we have nothing characteristic by x-ray examination. We would like a few flecks of calcification and something in the history to suggest it.

Of the various tumors in this region, a tumor of the adrenal gland is unlikely. I have already said I do not believe that it arose from the kidney. It is unlikely to be a primary tumor of the gall bladder in the absence of stones. However, we are assuming again that the Graham test previously noted was normal. Of the tumors of the liver, I do not believe it would be likely to be carcinoma because we have nothing to suggest it in either the history or the x-ray findings. There was questionable slight enlargement of the spleen, but it is unlikely to have been significant. A fair portion of the spleen could be seen, and it was not particularly enlarged. Hemangioma of the liver with hemorrhage intrigues me no end for two reasons: the apparent mass and the suggestion of some edema in the flank, which might possibly be the result of hemorrhage.

Another thing that is of some interest to me—nothing very definite—is that although the colon is displaced downward somewhat by this mass, one has the impression that the greatest pressure is on the proximal transverse colon and still we see something abnormal producing the straight line just above the iliac crest (Fig. 1), which I cannot explain unless it is due to hemorrhage or edema, which is possibly pushing the attachment of the ascending colon and hepatic flexure inferiorly. One other thing that goes along with the possibility of hemorrhage is the loss of the preperitoneal fat line. That is also present with edema or inflammation. From the clinical findings we have nothing to suggest an inflammatory process.

Can it possibly have been a lymphoma? It might have been, but I have never seen one with this appearance.

We come now to a group that is not too uncommon, the retroperitoneal connective-tissue tumors, and certainly they have to be given major consideration. The bulk of the mass, however, as we see it in these films, protrudes into the abdomen. There is preservation of the psoas outline and of the kidney outline, which is slightly against a typical retroperitoneal tumor.

I said at the beginning that I was going to come to the conclusion that there was a mass. I feel quite elated that I can see the mass because in many cases of abdominal masses it is not possible to demonstrate them on the films. I frankly cannot make a definite diagnosis, and I certainly think that surgery was indicated to determine the nature of the lesion.

DR CASTLEMAN. Do you not want to give us your first hunch?

DR ROBBINS. My first hunch would have to be what I ended with—a retroperitoneal connective-tissue tumor. The other possibility, heman-

gioma of the liver is not very good statistically

DR CASTLEMAN Dr Miller, will you tell us what Dr Sweet thought about this before operation?

DR CARROLL C MILLER Dr Richard H Sweet approached the case with an open mind. He had no definite idea what the mass was, but it was generally believed that it was probably in the liver because it was so very easily palpable beneath the anterior abdominal wall. We were not aware of any external edema in the flank tissues on palpation. There was no tenderness in this area. It did not seem to us to be an inflammatory process. The operation was done purely on the basis of making a diagnosis and treating the condition if that were possible.

#### CLINICAL DIAGNOSIS

Tumor of liver.

#### DR ROBBINS'S DIAGNOSIS

Retroperitoneal connective-tissue tumor?  
Hemangioma of liver?

#### ANATOMICAL DIAGNOSIS

*Congenital cyst of liver*

#### PATHOLOGICAL DISCUSSION

DR MILLER When the abdomen was first opened the mass presented itself readily. For a few minutes it was difficult to tell what the mass was. It was obviously a cystic tumor, and Dr Sweet thought this might be an enlarged hydroptic gall bladder because he could not find the gall bladder. After a bit more dissection all around the mass he found that the gall bladder lay medially, the tip of it being in normal apposition to the liver. The tumor was attached to the undersurface of the liver and protruded in the same way a hydroptic gall bladder would, except that it was a little more lateral to it. There was a very distended capsule over the cyst. With rapid dissection the capsule was stripped off the cystic mass, and the mass was easily removed. We were not able to get a clear idea of the tissue surrounding this area. In other words, we could not corroborate Dr Robbins's guess that there may have been edema. If there was, it was retroperitoneal, running out laterally in the flank. I do not believe much of any edema was present—certainly, no hemorrhage. The denuded area on the undersurface of the liver was closed easily, as one would close a gall-bladder bed. The abdomen was drained.

DR ROBBINS May I add one thing? I intended to include the possibility of lymphangioma of the liver and also meant to say that by x-ray the mass apparently was not so firm as it seemed clinically because there was a definite change in the shape of this lesion on some of the films. It was one reason why I thought of hemangioma of the liver as a very definite possibility.

DR CASTLEMAN The cyst that we received was multilocular, made up of four or five daughter cysts, the largest one about 6 cm in diameter. The entire mass was 13 by 7 by 8 cm. It was well encapsulated and filled with a clear straw-colored fluid, with no hemorrhage in it, and no evidence of infection—at least, no recent infection. The wall in several places was thickened, in most places it was rather thin. On microscopical examination a definite epithelium was found, very similar to the epithelium of the bile duct, and I therefore feel quite certain that this was a cyst of liver origin and probably arose from the bile ducts.

There are several theories regarding the etiology of cysts of the liver—that is, the nonparasitic cysts, most of which are on a congenital basis. The cysts arise from the bile-duct epithelium owing either to intrahepatic obstruction or, according to Moschowitz,\* to obstruction in a congenitally aberrant extrahepatic bile duct. One reason for believing the latter is that most of these cysts of the liver extend out from the liver on its inferior surface, protruding out just like a hydroptic of the gall bladder, suggesting that it was an extrahepatic rather than an intrahepatic bile duct that occurred congenitally in an aberrant fashion, which was blocked to produce the cyst. I think that was true in this case. Dr Robbins's second choice of hemangioma of the liver was pretty close, I do not recall ever seeing a hemangioma of the liver this large.

DR ROBBINS I understand from the literature that they can occur this large. One would have liked to find a phlebolith to confirm the diagnosis of hemangioma, although they do not always occur. They do tend to grow with increasing age.

DR CASTLEMAN The angiomas that we see at autopsy are usually small.

The other type of cyst that one occasionally sees in the liver is that associated with polycystic kidneys. They are usually much smaller and multiple, I do not believe there was any evidence in this case of polycystic kidney disease.

DR ROBBINS No, I did not consider a cyst of the liver because there were no changes in the films that suggested polycystic disease of the kidneys.

### CASE 34402

#### PRESENTATION OF CASE

*First admission* A nineteen-year-old unmarried secretary entered the hospital complaining of jaundice of four months' duration.

Seven months before admission she was in bed for a week with a "streptococcal throat" and a maximum temperature of 103°F, which cleared up without chemotherapy. One month later she had a tooth extracted, followed by considerable

\*Moschowitz, E. Non parasitic cysts (congenital) of liver with and without aberrant bile duct. *J. M. Sc.* 131:644, 1906.

bleeding Five months before admission she had "trench mouth," with tender, bleeding gums It responded initially to sodium perborate but later recurred At about the same time she noted the onset of painless jaundice Her physician advised a "fat-free" diet She continued to work, and the jaundice continued Two months before admission the jaundice became marked for about a week, and a transient swelling of the ankles followed She gained 15 pounds during the two months before admission She had noticed dark urine and light stools For about four months she had epistaxis about once each week

There was no nausea, vomiting, abdominal pain, melena or previous jaundice There was no history of exposure to sulfonamides, arsenic or solvents Before the onset of jaundice her alcohol intake was limited to an occasional cocktail The menses stopped two months before admission

Physical examination showed the patient to be slightly overweight, and the scleras were slightly icteric The head, neck, shoulders and arms were covered by a fine maculopapular, erythematous, dry, scaling rash The teeth were carious, and the gums infected and raw A systolic murmur was present at the apex and in the pulmonic area A systolic thrill was palpable at the third interspace The abdomen was tense On deep inspiration the liver was tender, and the edge was felt two finger-breadths below the costal margin Most observers felt the spleen on deep inspiration There was minimal ankle edema

The temperature was 98.6°F, the pulse 72, and the respirations 20 The blood pressure was 130 systolic, 70 diastolic

Examination of the blood disclosed a white-cell count of 7100, on one examination the differential was 70 per cent neutrophils, 17 per cent lymphocytes, 3 per cent monocytes, 8 per cent eosinophils, 1 per cent basophils and 1 per cent myelocytes The hemoglobin ranged between 13.5 and 8.8 gm The urine was amber colored, with a specific gravity of 1.020 Urobilinogen was present, varying from 1.280 to 1.24 on different examinations Bile was present, sugar, albumin and Bence-Jones protein were not observed The stools were tan and guaiac negative A blood Hinton test was negative The serum bilirubin was 3.65 mg per 100 cc direct, 5.85 mg total The phosphorus was 5.0 mg, the nonprotein nitrogen 18 mg, the serum albumin

2.0 gm, and the serum globulin 7.8 gm per 100 cc The alkaline phosphatase was 50 units The cephalin-flocculation test was ++++ in twenty-four hours Serum vitamin A and carotenoids were 0 units per cubic centimeter The prothrombin time ranged between 36 and 42 seconds (control, 15 seconds) The bromsulfalein test demonstrated 55 per cent retention of the dye in the serum The cholesterol was 123 mg, and the esters 46 mg per 100 cc X-ray examination of the chest and a gastrointestinal series were negative except for a small hiatus hernia

The patient was hospitalized for three months, was afebrile and was maintained on a high-carbohydrate, high-protein and low-fat diet supplemented by methionine, hykinone, components of the vitamin B complex and liver extract She received repeated blood transfusions Toward the latter part of the course all her teeth were removed because of abscesses and severe caries At the time of discharge the clinical and laboratory status had not altered markedly from the findings on admission The prothrombin time was 29 seconds (control, 19 seconds), the serum van den Bergh 2.1 mg per 100 cc direct, 2.9 mg indirect, the cephalin-flocculation test ++++ in twenty-four hours, the serum albumin 2.06 and the globulin 9.94 gm per 100 cc, and the nonprotein nitrogen 21 mg per 100 cc The vitamin A was 1.4 units and the carotenoid 0.8 units per cubic centimeter

*Second admission* (fifteen months later) During the interval the patient was followed carefully and maintained on a high-calorie, high-protein, low-fat diet, with supplementary vitamins Her activities were limited She felt better, and the jaundice was minimal There was no ascites or edema The laboratory data did not change remarkably One week before admission a mild cold began, followed in a day by moderate amounts of green sputum, chilly sensations and temperature rises up to 103°F Five days before admission the ears became tender, and a purulent, bloody exudate appeared Three days later she had a severe, sharp pain in the right chest on deep inspiration

Physical examination showed a moderately obese and pale woman, who complained of severe pain in the right chest with respiration Spider angiomas were present on the dorsal surfaces of the hand and neck The scleras were muddy There was marked conduction deafness, and the eardrums were red

and beefy, with landmarks obscured. There were dullness and diminished breath sounds at the right base, and bronchial breathing over the right middle lobe. An inspiratory friction rub was heard over the right lower lobe. Examination of the abdomen was unsatisfactory because of limitation of breathing. There was no ascites, but there was very slight pitting edema over the ankles.

The temperature was 99°F, the pulse 100 and the respirations 32. The blood pressure was 135 systolic, 70 diastolic.

Examination of the blood disclosed a red-cell count of 2,300,000 with a hemoglobin of 8.9 gm, and a white-cell count of 13,800 with 86 per cent neutrophils. The urine was amber and gave a + test for albumin and a +++ test for bile. Blood and throat cultures were negative. The serum albumin was 1.83 gm and the globulin 8.68 gm per 100 cc. The van den Bergh reaction was 2.2 mg per 100 cc direct, 2.9 mg indirect. The cholesterol was 89 mg, the cholesterol esters 31 mg, and the alkaline phosphatase 10 units per 100 cc. An esophagram demonstrated no varices.

On penicillin therapy the local signs and symptoms in the ears and right chest slowly subsided. The patient was discharged after three weeks of hospitalization.

*Final admission* (fifteen months later). One month before admission stiffness and pain in the knee joints, shoulders and the proximal interphalangeal joints of the right hand developed. Aspirin relieved the joint symptoms readily. Aside from joint pain the patient was asymptomatic. There was no ascites, but slight edema developed toward the end of the day. About three weeks before admission she fell and cut her right knee, but it healed promptly. Eight days before admission she awoke with a tender right calf and groin. The leg became swollen below the knee, and "blood blisters" appeared on the ankle, sole, left elbow and coccyx. She became restless, and the temperature became elevated. She lost her appetite, the abdomen became distended.

Physical examination showed the patient to be mildly icteric. A few scattered spider angiomas were present. There were coarse inspiratory rales at both bases posteriorly. The heart was not enlarged. The pulmonic second sound was louder than the aortic. Grade II pulmonic systolic and apical systolic murmurs were present. The abdomen

was distended, and a fluid wave was elicited. The liver edge was percussed two fingerbreadths below the costal margin. Peristalsis was active. The right leg was tense, swollen, tender and reddened below the knee. There was marked calf tenderness but no thigh or groin tenderness. The foot was swollen and tender, with several superficial erosions on the sole.

The temperature was 99.5°F, and the pulse 84.

Examination of the blood disclosed a white-cell count of 18,300, with 81 per cent neutrophils, and a hemoglobin of 10.5 gm. The urine contained bile. The stools were guaiac negative. The serum albumin was 1.65 gm, the globulin 6.80 gm, the cholesterol 109 mg, the nonprotein nitrogen 21 mg, the fasting blood sugar 90 mg, the calcium 8 mg, the phosphorus 3 mg per 100 cc, and the sodium 129 milliequiv and the chloride 100 milliequiv per liter. The alkaline phosphatase was 6.2 units per 100 cc. The van den Bergh reaction was 1.4 mg per 100 cc direct, 1.9 mg indirect. The prothrombin time was 26 seconds (control, 16 seconds). The cephalin-flocculation test was +++ in twenty-four and forty-eight hours.

X-ray examination of the chest demonstrated elevation of both leaves of the diaphragm. In the abdomen there was considerable fluid, there were gas-filled loops of small bowel but no definite evidence of organic obstruction.

On the third hospital day an abdominal paracentesis yielded 8500 cc of light-yellow, cloudy fluid, with a specific gravity of 1.008. Two days later the patient suddenly noticed steady upper abdominal pain, with some radiation to the back, relieved only partially by codein and demerol. On the following day she became nauseated and vomited bright-red-blood-stained material. The vomiting of blood continued intermittently. Seven transfusions were given over several days. The white-cell count reached 21,800, with 84 per cent neutrophils. The blood pressure ranged from 70 systolic, 40 diastolic, to 110 systolic, 60 diastolic. The pulse was rapid.

On the sixth hospital day, after thirty-six hours of coma, deepening jaundice and pulmonary congestion, the patient died.

#### DIFFERENTIAL DIAGNOSIS

DR. MARIA N. ROPES. I cannot make a diagnosis in this case but probably the most profitable way

bleeding Five months before admission she had "trench mouth," with tender, bleeding gums It responded initially to sodium perborate but later recurred At about the same time she noted the onset of painless jaundice Her physician advised a "fat-free" diet She continued to work, and the jaundice continued Two months before admission the jaundice became marked for about a week, and a transient swelling of the ankles followed She gained 15 pounds during the two months before admission She had noticed dark urine and light stools For about four months she had epistaxis about once each week

There was no nausea, vomiting, abdominal pain, melena or previous jaundice There was no history of exposure to sulfonamides, arsenic or solvents Before the onset of jaundice her alcohol intake was limited to an occasional cocktail The menses stopped two months before admission

Physical examination showed the patient to be slightly overweight, and the scleras were slightly icteric The head, neck, shoulders and arms were covered by a fine maculopapular, erythematous, dry, scaling rash The teeth were carious, and the gums infected and raw A systolic murmur was present at the apex and in the pulmonic area A systolic thrill was palpable at the third interspace The abdomen was tense On deep inspiration the liver was tender, and the edge was felt two finger-breadths below the costal margin Most observers felt the spleen on deep inspiration There was minimal ankle edema

The temperature was 98.6°F, the pulse 72, and the respirations 20 The blood pressure was 130 systolic, 70 diastolic

Examination of the blood disclosed a white-cell count of 7100, on one examination the differential was 70 per cent neutrophils, 17 per cent lymphocytes, 3 per cent monocytes, 8 per cent eosinophils, 1 per cent basophils and 1 per cent myelocytes The hemoglobin ranged between 13.5 and 8.8 gm The urine was amber colored, with a specific gravity of 1.020 Urobilinogen was present, varying from 1.280 to 1.24 on different examinations Bile was present, sugar, albumin and Bence-Jones protein were not observed The stools were tan and guaiac negative A blood Hinton test was negative The serum bilirubin was 3.65 mg per 100 cc direct, 5.85 mg total The phosphorus was 5.0 mg, the nonprotein nitrogen 18 mg, the serum albumin

2.0 gm, and the serum globulin 7.8 gm per 100 cc The alkaline phosphatase was 50 units The cephalin-flocculation test was ++++ in twenty-four hours Serum vitamin A and carotenoids were 0 units per cubic centimeter The prothrombin time ranged between 36 and 42 seconds (control, 15 seconds) The bromsulfalein test demonstrated 55 per cent retention of the dye in the serum The cholesterol was 123 mg, and the esters 46 mg per 100 cc X-ray examination of the chest and a gastrointestinal series were negative except for a small hiatus hernia

The patient was hospitalized for three months, was afebrile and was maintained on a high-carbohydrate, high-protein and low-fat diet supplemented by methionine, hykinone, components of the vitamin B complex and liver extract She received repeated blood transfusions Toward the latter part of the course all her teeth were removed because of abscesses and severe caries At the time of discharge the clinical and laboratory status had not altered markedly from the findings on admission The prothrombin time was 29 seconds (control, 19 seconds), the serum van den Bergh 2.1 mg per 100 cc direct, 2.9 mg indirect, the cephalin-flocculation test ++++ in twenty-four hours, the serum albumin 2.06 and the globulin 9.94 gm per 100 cc, and the nonprotein nitrogen 21 mg per 100 cc The vitamin A was 1.4 units and the carotenoid 0.8 units per cubic centimeter

*Second admission* (fifteen months later) During the interval the patient was followed carefully and maintained on a high-calorie, high-protein, low-fat diet, with supplementary vitamins Her activities were limited She felt better, and the jaundice was minimal There was no ascites or edema The laboratory data did not change remarkably One week before admission a mild cold began, followed in a day by moderate amounts of green sputum, chilly sensations and temperature rises up to 103°F Five days before admission the ears became tender, and a purulent, bloody exudate appeared Three days later she had a severe, sharp pain in the right chest on deep inspiration

Physical examination showed a moderately obese and pale woman, who complained of severe pain in the right chest with respiration Spider angiomas were present on the dorsal surfaces of the hand and neck The scleras were muddy There was marked conduction deafness, and the eardrums were red

of pneumonia. The fluid is consistent with the generalized anasarca that the patient had at the time of the last admission.

The joint symptoms that occurred at the time of the third admission are again not consistent with an uncomplicated liver disease. Furthermore, the final episode, although probably associated with the underlying liver disease, does not sound as though it was related to bleeding varices, although this has to be considered. The degree of pain and the relatively slow bleeding even in the presence of a low prothrombin would be unusual in bleeding varices. The type of bleeding and pain suggests the possibility of slow perforation of the stomach. It seems less likely to have been associated with the underlying liver disease.

So I should think that the final problem is to determine whether the patient had merely primary liver disease with some associated complications or whether the liver disease was part of a generalized process. The fact that makes one wonder most about a generalized process is the high globulin. One would think immediately about granulomatous diseases or other diseases causing elevation of globulin, such as sarcoid, tuberculosis, syphilis and possibly brucellosis, they elevate globulin although rarely to this height. One does not need to consider too seriously a malignant neoplastic process such as lymphoma or myeloma as the cause of the entire picture. The course over three years would be unusual for such a diagnosis. Also, one does not need to consider the group of connective-tissue diseases, such as disseminated lupus erythematosus or periarteritis nodosa. Some of them, particularly rheumatoid arthritis, develop high globulin levels in this range. However, the rest of the picture offers nothing, or practically nothing, in support of these diseases. Similarly, amyloid disease, which one thinks of always in the presence of hyperglobulinemia, has little to support it other than that and the presence of liver involvement.

So I am left with no possible evidence for any of the types of conditions that come to mind as the cause of liver disease as part of a generalized process. To be sure the liver involvement, the eosinophilia, the arthralgia and the high globulin are consistent with sarcoid. However in the absence of the more characteristic or specific lesions of this disease, it seems unwise to make such a diagnosis. The only diagnosis that I can make is parenchymatous liver

disease progressing to a chronic state with the development of cirrhosis. Whether or not it was part of an underlying generalized disease such as sarcoid, I think there is no evidence to determine.

DR TRACY B MALLORY: Dr Ellis, will you tell us what you thought about this case?

DR DANIEL S ELLIS: There is no one here today who followed the patient throughout the entire illness, although she spent most of it in this hospital. I saw her on several occasions in the various clinics, Medical Grand Rounds and Gastrointestinal Rounds. We were puzzled by the same things that Dr Ropes has pointed out. There were many different opinions about the etiology of the disease. One possibility that Dr Ropes did not mention, suggested by one member of the staff, was that this patient had some vascular disturbance in the form of thrombosis in the major circulation in the liver to account for some of the picture. Then in the final episode I am told that she was admitted to the hospital with a diagnosis of thrombophlebitis. It was believed by some that this might tie in with what had gone on several years before. We were puzzled by the high globulin. Most of the people who saw her decided that she had hepatitis and treated her from that standpoint. On one occasion I suggested that here was a patient who had had arthritis, serositis (pleurisy), jaundice, dermatitis with eruption, fever and high globulin and wondered if she might not at some time have fitted in with the picture of disseminated lupus. The urinary findings did not fit the picture of disseminated lupus, however. I am sure that this patient had a disease that involved more of her organs than the liver. I thought the liver was a part of the picture but probably not primary. Whether or not Dr Mallory will be able to tell us the underlying disease I do not know, but I think we were right in treating her for hepatitis because that was the one thing we could focus on and that was the basis on which we moved throughout the three years of illness.

Two liver biopsies were taken when she was first seen and again on the second admission. Dr Mallory will tell about the biopsies in relation to what the final picture showed.

#### CLINICAL DIAGNOSES

Cholemia

Varices of esophagus, with hemorrhage

Toxic cirrhosis of unknown cause

Thrombosis of veins of left leg

to approach it is to consider the involvement of the various systems separately and then to see if they can be related. The most apparent involvement is that of the liver, which started three years before death and persisted until the time of death. The entire course during the first two and a half years can be explained, I think, by hepatitis going into a chronic state with the development of cirrhosis. Usually in liver disease there is a great deal of difficulty in using the laboratory findings to differentiate obstructive jaundice and parenchymatous involvement. In this case the laboratory tests were entirely consistent with parenchymatous liver disease. The ++++ cephalin-flocculation test, the prolongation of prothrombin time to 42 seconds with lack of response to vitamin K, the low carotenoids, the low vitamin A, the very low cholesterol, with extremely low percentage of esters, the urobilinogen varying in amounts but found in the urine and the high bromsulfalein retention are all entirely consistent with liver-cell disease. The serum bilirubin gave more of the direct than the indirect reaction, in the neighborhood of 60 per cent, but this is lower than that ordinarily found in obstructive jaundice. So the laboratory tests are more consistent than those in the majority of cases with parenchymatous disease. I neglected to say that the alkaline phosphatase at the first admission was also normal. There is, however, one laboratory finding that to me was very surprising: the high globulin. One expects with hepatitis or liver-cell damage to get a lowering of albumin and some elevation of globulin, with reversal of the ratio. An increase up to 8 or 10 gm. of globulin is surprising, however, and unusual in uncomplicated liver disease. The course following the first admission, as I said before, is consistent to my mind with liver-cell damage progressing into a chronic state and with the development of cirrhosis. This took some two and a half or three years to occur. However, there are a good many findings in the total picture that are not explained by such a diagnosis. In the first place, we have no definite evidence of the cause of this hepatitis. Of course, infectious hepatitis has to be considered, and there is nothing to rule it out. We know that this patient was not exposed to some of the causes of liver-cell damage, but we have no further information about other toxins or of the possible role various cosmetics played in damaging the liver. Furthermore, the presence of

the very high globulin raises the question of some other generalized condition as the cause of the liver damage.

Now to consider a few of the other systems involved in the course of the disease, I think the rash that was present at the first admission and, I judge, not present at other admissions, was not part of the picture of liver disease, but with no further information I cannot offer any explanation for it. At the time of the second admission the patient had, I judge, bilateral otitis media and what I am interpreting as pneumonia. Whether or not she had underlying pulmonary disease is significant, and I think we should see the x-ray films to determine whether there was any involvement of the hilar lymph nodes or evidence of pulmonary disease other than pneumonia at the time of the second admission.

DR JAMES J. McCORT: This examination of the chest was made at the time of the second admission. The film taken on the day of admission shows an area of increased density in the medial segment of the middle lobe, which has the appearance of pneumonia. There is no enlargement of the hilar lymph nodes and no other evidence of pneumonitis that I can see. The film taken one week later shows a slight resolution of the pneumonic process in the middle lobe. However, at that time there is a definite suggestion of fluid in the right base posteriorly. The film taken two weeks after admission shows the pneumonitis to have undergone almost complete resolution. There is still a small amount of fluid in the right base. The right leaf of the diaphragm is slightly higher than it should be in this examination, possibly owing to the pressure of the liver.

DR ROPES: Is the chest entirely clear except for elevation of the diaphragm on the last admission?

DR McCORT: No. There is a slight amount of fluid in the left pleural cavity. There is also basal atelectasis, which I believe is due to the high diaphragm. The lungs are otherwise clear, and there is no mediastinal adenopathy.

DR ROPES: The gastrointestinal series shows nothing but the hiatus hernia, which I assume was not related to the rest of the picture.

DR McCORT: The gastrointestinal series was done at the second admission.

DR ROPES: I judge we have no evidence of underlying pulmonary disease — only the one episode

# The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established 1828

Official Organ of

THE MASSACHUSETTS MEDICAL SOCIETY

and

THE NEW HAMPSHIRE MEDICAL SOCIETY

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND  
PUBLISHED WEEKLY UNDER THE JURISDICTION  
OF THE COMMITTEE ON PUBLICATIONS

Richard M. Smith, M.D., *Chairman*

James P. O'Hare, M.D.  
Oliver Cope, M.D.

Conrad Wesselhoeft, M.D.  
John Fallon, M.D.

Joseph Garland, M.D., *Editor*

*Associate Editors*

Thomas H. Lanman, M.D.

Henry Jackson, Jr., M.D.

Donald Munro, M.D.

Clara D. Davies, *Executive Editor*

Robert O'Leary, *Assistant Editor*

*Editorial Board*

C. Guy Lane, M.D.  
Henry R. Viets, M.D.  
Robert M. Green, M.D.  
Dwight O'Hara, M.D.  
Fletcher H. Colby, M.D.  
Robert L. Goodale, M.D.  
Chester M. Jones, M.D.  
Harvey R. Morrison, M.D.

Maxwell Finland, M.D.  
James M. Faulkner, M.D.  
Carroll B. Larson, M.D.  
Francis D. Moore, M.D.  
C. Stuart Welch, M.D.  
Vernon P. Williams, M.D.  
Benjamin Castleman, M.D.  
Hugh R. Leavell, M.D.

**SUBSCRIPTION TERMS** \$7.00 per year in advance, postage paid, for the United States (medical students \$4.00 per year). Canada \$8.00 per year (Boston funds) \$9.50 per year for all foreign countries belonging to the Postal Union.

**MATERIAL** should be received not later than noon on Thursday, three weeks before date of publication.

**THE JOURNAL** does not hold itself responsible for statements made by any contributor.

**COMMUNICATIONS** should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts. Telephone KE 6-2094.

**NEW ENGLAND ADVERTISING REPRESENTATIVE** Edwin B. Tyler, 89 State Street, Boston, Massachusetts. Telephone LA 3-5516.

## PRIZE ESSAY COMPETITION

In acknowledgment of the support of more than 4000 student subscribers, the *Journal* announces a prize essay contest open to all members of the class of 1949 registered in any medical school approved by the Council on Medical Education and Hospitals of the American Medical Association.

The subject chosen for this year's competition is "Recent Advances in Preventive Medicine."

Manuscripts are to be between four and five thousand words in length, clearly typewritten in English, double or triple spaced with references listed at the end in numerical arrangement according to the form used by the *Quarterly Cumulative Index Medicus*. They must be in the hands of the editor

by March 15, 1949. All manuscripts will become the property of the *Journal*.

A cash prize of \$100 will be paid for the best essay of those found to be suitable for consideration; the paper will be published in the "Medical Progress" series that forms a regular part of the contents of the *Journal* and the author will receive a hundred free reprints.

A second prize will consist of a two-year subscription to the *Journal*.

The editors wish to emphasize that in establishing this competition they are as much interested in encouraging good medical writing as they are in promoting the collection of scientific material. In judging papers that may be submitted, particular attention will accordingly be paid to clarity, simplicity and general literary excellence.

The quality of medical writing needs at present more encouragement than the quantity of its production does.

## CHILD SAFETY

IN CO-OPERATION with the United States Children's Bureau, the American Academy of Pediatrics and the National Safety Council, the Metropolitan Life Insurance Company has undertaken an intensive campaign to prevent accidents in children. A special packet of material, which is available on request for use in local organized programs, includes copies of recent statistical studies, prepared talks and suggested area releases, as well as a twelve-page illustrated booklet, *Help Your Child to Safety*, addressed to parents and emphasizing the value of co-operation among all members of the family to combat physical hazards and unsafe practices resulting in injuries to children.

As previously pointed out in these columns, accidents account for an unwarranted number of deaths among persons of all ages each year.<sup>1</sup> However, the situation among children is even more discouraging; accidents now rank as the leading cause of death, as well as an outstanding cause of injury and permanent disability among children from one to fifteen years of age. The prevention of this enormous toll offers a challenge to all agencies interested in the health and welfare of children. To encourage parents, other adults and older chil-

## DR ROPES'S DIAGNOSIS

Hepatitis, chronic, with cirrhosis

## ANATOMICAL DIAGNOSES

*Cirrhosis of liver, postatrophic type*

*Adenoma of liver*

*Esophageal varices, with rupture*

Cholelithiasis

Bronchopneumonia

Anasarca

## PATHOLOGICAL DISCUSSION

DR MALLORY I do not know that I can give a satisfactory answer to this case, although I can describe the somewhat unusual findings at autopsy. As Dr Ellis said, we had two biopsies, one within six months of the first symptom, and one approximately a year after that. At the very first biopsy cirrhosis of the liver was already established. It was apparently of the type that follows regeneration from a severe degree of atrophy, quite consistent with a primary infectious hepatitis, but I would not be at all dogmatic about it. The second biopsy a year later had changed slightly, and we were very interested in finding great numbers of plasma cells in the stroma on that occasion. Although present in the first biopsy, they had not been numerous enough to excite our notice, but by the second time the patient had a high globulin, and we naturally tended to correlate this with the great numbers of plasma cells present. When she died the liver was still enlarged, weighing nearly 1900 grams, which is quite unusual for the type of cirrhosis that follows a healed atrophy. On the other hand, the gross appearance of the liver was otherwise characteristic. It was coarsely nodular, many of the nodules ranging from 1 to 2 cm in diameter. These nodules were very irregularly distributed, and there were large masses of tissue in which no nodules were found. There was one single nodule very much larger than any others that measured 5 cm in diameter in the middle of the right lobe, the center of which was soft and gelatinous. We did not find much else in the rest

of the body that seemed of interest. There were some shallow mucosal erosions in the esophagus.

On microscopical examination we found enlarged veins in the submucosa, and one of these erosions seemed to be communicating with a dilated vein so that I am confident that the terminal hemorrhage was due to rupture of a varix.

The spleen was only slightly enlarged, weighing a little over 400 gm, but in view of the massive hemorrhage it may have shrunk considerably in the last hours of life. There was a terminal very extensive bronchopneumonia. The gall bladder contained numerous small stones, but none were found in the duct system. The terminal pain may have been biliary colic, but unexplained abdominal pain is not unusual in cirrhosis.

From the histologic point of view the liver was characteristic of the postatrophic type of cirrhosis with the single exception of the plasma cells, which were more numerous than they are in most such cases. The very large nodule appeared to be composed entirely of liver cells. We could find no traces of bile ducts or portal veins in it. It contained very large amounts of fat, with some fatty acids. This was such a very large nodule, and completely devoid of normal liver architecture, that one had to classify it as a tumor. I could see no evidence of malignancy, and I would call it an adenoma of the liver. The bone marrow showed very marked erythroblastic hyperplasia, with a great many immature cells of the red-cell series. A few but not many plasma cells were present. It would have been quite impossible to make a diagnosis of multiple myeloma on the basis of the post-mortem findings so that all we have is a rather unusual type of cirrhosis with a great many more plasma cells in the scarred areas than we commonly see. These may or may not have had something to do with the unusual chemical findings, especially the high globulinemia.

DR JAMES T HEYL Because of the prolonged prothrombin time I am curious to know whether or not there was a thrombophlebitis.

DR MALLORY Large areas of hemorrhagic extravasation were found in the calf muscles, but no thrombi were seen in the major veins.

# The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established 1828

Official Organ of

THE MASSACHUSETTS MEDICAL SOCIETY

and

THE NEW HAMPSHIRE MEDICAL SOCIETY

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND

PUBLISHED WEEKLY UNDER THE JURISDICTION

OF THE COMMITTEE ON PUBLICATIONS

Richard M. Smith, M.D., Chairman

James P. O'Hare, M.D.

Oliver Cope, M.D.

Conrad Weisbroeck, M.D.

John Fallon, M.D.

Joseph Garland, M.D., Editor

ASSOCIATE EDITORS

Thomas H. Lanman, M.D.

Henry Jackson, Jr., M.D.

Donald Munro, M.D.

Clara D. Davies, Executive Editor

Robert O'Leary, Assistant Editor

EDITORIAL BOARD

C. Guy Lane, M.D.

Henry R. Viets, M.D.

Robert M. Green, M.D.

Dwight O'Hare, M.D.

Fletcher H. Colby, M.D.

Robert L. Goodale, M.D.

Chester M. Jones, M.D.

Harvey R. Morrison, M.D.

Maxwell Finland, M.D.

James M. Faulkner, M.D.

Carroll B. Larsen, M.D.

Francis D. Moore, M.D.

C. Stuart Welch, M.D.

Vernon P. Williams, M.D.

Benjamin Castleman, M.D.

Hugh R. Leavell, M.D.

SUBSCRIPTION TERMS \$7.00 per year in advance, postage paid, for the United States (medical students, \$4.00 per year) Canada \$8.00 per year (Boston funds) \$9.50 per year for all foreign countries belonging to the Postal Union.

MATERIAL should be received not later than noon on Thursday three weeks before date of publication

THE JOURNAL does not hold itself responsible for statements made by any contributor

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts. Telephone KE 6-2094

NEW ENGLAND ADVERTISING REPRESENTATIVE Edwin B. Tyler, 89 State Street, Boston, Massachusetts. Telephone LA 3-5516

## PRIZE ESSAY COMPETITION

In acknowledgment of the support of more than 4000 student subscribers, the *Journal* announces a prize essay contest open to all members of the class of 1949 registered in any medical school approved by the Council on Medical Education and Hospitals of the American Medical Association.

The subject chosen for this year's competition is "Recent Advances in Preventive Medicine."

Manuscripts are to be between four and five thousand words in length, clearly typewritten in English, double or triple spaced with references listed at the end in numerical arrangement according to the form used by the *Quarterly Cumulative Index Medicus*. They must be in the hands of the editor

by March 15, 1949. All manuscripts will become the property of the *Journal*.

A cash prize of \$100 will be paid for the best essay of those found to be suitable for consideration, the paper will be published in the "Medical Progress" series that forms a regular part of the contents of the *Journal*, and the author will receive a hundred free reprints.

A second prize will consist of a two-year subscription to the *Journal*.

The editors wish to emphasize that in establishing this competition they are as much interested in encouraging good medical writing as they are in promoting the collection of scientific material. In judging papers that may be submitted, particular attention will accordingly be paid to clarity, simplicity and general literary excellence.

The quality of medical writing needs at present more encouragement than the quantity of its production does.

## CHILD SAFETY

IN CO-OPERATION with the United States Children's Bureau, the American Academy of Pediatrics and the National Safety Council, the Metropolitan Life Insurance Company has undertaken an intensive campaign to prevent accidents in children. A special packet of material, which is available on request for use in local organized programs, includes copies of recent statistical studies, prepared talks and suggested area releases, as well as a twelve-page illustrated booklet, *Help Your Child to Safety*, addressed to parents and emphasizing the value of co-operation among all members of the family to combat physical hazards and unsafe practices resulting in injuries to children.

As previously pointed out in these columns, accidents account for an unwarranted number of deaths among persons of all ages each year.<sup>1</sup> However, the situation among children is even more discouraging: accidents now rank as the leading cause of death, as well as an outstanding cause of injury and permanent disability, among children from one to fifteen years of age. The prevention of this enormous toll offers a challenge to all agencies interested in the health and welfare of children. To encourage parents, other adults and older chil-

dren to recognize the hazards confronting younger children, to provide and maintain safe conditions in the home and at play and to help the child, by example and guidance, to develop safe practices, the field force of the Metropolitan Life Insurance Company will participate in the child-safety programs of more than three thousand communities.

Physicians, who occupy a position of unique importance in the community, are urged to engage wholeheartedly in this campaign to reduce the number of injuries and deaths suffered by children. The efforts of general practitioners (who see the major portion of preschool children<sup>2</sup>) and pediatricians will be of particular value.

#### REFERENCES

- 1 Editorial. Leading causes of death. *New Eng J Med* 239 71, 1948
- 2 Hubbard J P and Zibit, S. Review of private practice pediatricians and general practitioners. *Pediatrics* 1 379 386, 1948

### PENICILLIN IN SYPHILIS

A REPORT on the status of penicillin in the treatment of syphilis dated December 1, 1947 was recently published by the Syphilis Study Section of the National Institute of Health.\* It was estimated by the United States Public Health Service statisticians that at least 500,000 patients with syphilis in various stages have been treated with penicillin since the first report of its beneficial effects was made in 1943. A significant proportion of these cases form the basis of this report, the purpose of which is to summarize for the practicing physician the facts regarding penicillin in syphilis that are of clinical importance. The observations contained in this report should be of great practical help to all who are likely to be concerned with such therapy, and they should read this summary in detail. Only a few points are brought out here.

It is stated categorically that penicillin G, which is now available in crystalline form, is the most effective type in man. This is the final upshot of the intensive studies undertaken after irregular results had been encountered that proved to be due to the changing character of commercial penicillin. The poor results are traced to the appearance of increasing proportions of the less effective penicillin K, and this has not been corrected.

\*Status of penicillin in treatment of syphilis. *J A M A* 136 873 879 1948

As to the method of administration, the single intravenous injections are considered to be of little or no value because of the extremely rapid absorption and excretion cycle. The continuous intravenous drip, likewise, is of little practical value because of the necessity of continuous confinement of the patient to bed and the frequent occurrence of thrombophlebitis. Continuous intramuscular or subcutaneous administration has the same disadvantage, and, furthermore, it produces rather painful local reactions. The usual method employed and the one recommended is the use of intermittent intramuscular injections of aqueous solutions containing 50,000 to 100,000 units per cubic centimeter of either sterile water or isotonic sodium chloride solution. Intraventricular, intracisternal or intraspinal administration should be avoided both because of possible dangerous toxic reactions and because intramuscular therapy alone is effective in the treatment of neurosyphilis and no additional benefit is derived from the intrathecal route. The oral route likewise is not advised, but the use of prolonging agents, like penicillin in beeswax and peanut oil (and presumably the more recent procaine penicillin preparations), appears to offer a practical method that permits intramuscular injections to be given only once daily.

Of the toxic reactions the one that particularly concerns the treatment of syphilis is the Jarisch-Herxheimer reaction. This is encountered in about 50 per cent of patients with primary and secondary syphilis, but in such cases it is seldom if ever alarming and does not interfere with subsequent treatment. About 25 per cent of patients treated for latent or late syphilis experience a mild febrile reaction. Therapeutic shock, which may be serious and occasionally results in death, has been considered as possibly resulting from penicillin in occasional infants with congenital syphilis and in patients with cardiovascular syphilis or neurosyphilis. There is no indication that penicillin causes abortion in pregnant women.

There is little clear-cut evidence to indicate the existence of penicillin-resistant syphilis analogous to the familiar arsenic-resistant or bismuth-resistant syphilis or sulfonamide-resistant gonorrhea.

Attention is also called to the fact that when early syphilis and gonorrhea are acquired simultaneously penicillin given for the latter may delay or perhaps even suppress the lesions of syphilis. Patients treated for gonorrhea should therefore be followed over a period of at least four months with monthly serologic tests for syphilis. A sharp febrile reaction within the first twenty-four hours after the use of penicillin for gonorrhea should suggest concurrent early syphilis. If a diagnosis of syphilis is later established, the patient should be given a full course of treatment as indicated.

The results of penicillin alone seem satisfactory enough in early syphilis so that adjuvant therapy with arsenic or bismuth preparations or fever is not advised in the first course of treatment, but they may be used to advantage in patients in whom the original course of penicillin has failed. In dementia paralytica the use of fever or malaria to supplement the penicillin therapy may be expected to give better results than penicillin alone.

Details are given for the dosage and duration of penicillin treatment and the precautions to be taken for each of the various types of syphilis. This report may therefore serve as a useful guide to all physicians who undertake the treatment of this disease. Without doubt many of the details of the report, particularly those concerning dosage, will require modification as further experience accumulates. In the meantime, this is the most concise and authoritative summary available.

#### "PASSENGERS WILL PLEASE REFRAIN —"

THE *Journal of the American Medical Association*\* has made editorial comment on a potential health hazard that must have occurred as a possibility to many persons, without necessarily stimulating any number of them to a crusading pitch of activity. This hazard is the impartial distribution of toilet wastes along railroad lines — except, usually, in stations.

The practical difficulty of attaching a swiftly moving train to any permanent sewage system is obvious, the public-health implications, apparently, have been under consideration for a number of years. Recently the Joint Committee on Railway

Sanitation of the Association of American Railroads has tuned in on the problem and, in March and December, 1947, issued a technical and a supplementary report.

Research was carried out on the heavily traveled New York to Washington run of the Pennsylvania Railroad, and in the course of the investigation "the toilet habits of 2 000 persons were studied over a total of 6,201 passenger hours and 320,000 passenger miles." Since such a project of necessity covered a considerable area, in the interests of accuracy the wastes were collected in sealed containers carried underneath the cars.

Certain estimates were possible. Approximately 276,000 pounds (dry weight) of the material under discussion was spread per year along 226 miles of roadbed, or 0.694 pounds per linear yard. Found in the collection, although not included in the statistical analysis, were orange peelings, cigars and cigarette butts, cigarette packages, miniature whisky bottles, beer bottles, men's handkerchiefs and women's handbags.

Whether epidemic disease has actually resulted from this impartial and not inconsiderable contamination of roadbeds is problematical, certainly the possibilities are present. Perhaps the advice of the popular song, not originally intended for mixed company, should be reversed and passengers exhorted to use the station toilets and spare the rolling landscape.

#### MASSACHUSETTS MEDICAL SOCIETY COMMITTEE ON MEMBERSHIP

The following list of twenty-one names of members of the Massachusetts Medical Society, who are to be deprived of membership, together with their last known addresses, is published at the request of the Committee on Membership.

Any information concerning the correct addresses of these fellows will be appreciated by the secretary of the Society, 8 Fenway, Boston 15 Massachusetts.

Edward T. Abrahams (Berkshire), 511 North Street Pittsfield.

Victor Baer (Middlesex South), 276 Commonwealth Avenue, Boston.

Arthur J. Bischoff (Middlesex East), New England Sanitarium and Hospital Stoneham.

Chester E. Bromwell (Suffolk), 11 Gloucester Street Boston.

Martin F. Buell (nonresident), Dearborn Department of Health, Dearborn Michigan.

William B. Davidson (Worcester), 8 Howland Terrace, Worcester.

\*Current Comment. Railroad toilet wastes. *J A M A* 137 11:4 1948.

Winnifred P Davis (Worcester North), 79 Main Street, Ashburnham  
 David D Greene (Middlesex South), 117 Brackett Road, Newton  
 Herbert I Harris (Norfolk), 84 Reservoir Road, Brookline  
 Earle L Hussey (Essex South), 32 Cedar Street, Lynn  
 Gordon R Lamb (Norfolk), 4B Putney Road, Wellesley Hills  
 David I Levine (Norfolk South), Los Angeles, California  
 Arthur P Long (Norfolk), Office of Surgeon General, War Department, Washington, D C  
 Donald H MacDonald (Middlesex South), 425 Beacon Street, Boston  
 Theodore B Massell (nonresident), 1982 Comstock Avenue, Los Angeles Calif  
 Walter L McClintock (Norfolk South), 1245 Hancock Street, Quincy  
 Donald McNeil (nonresident), P O Box 168, Sacramento, Calif  
 Edward B Ormsby (Norfolk), 504 Talbot Avenue, Dorchester  
 Bernard W Rothblatt (Middlesex South), 65 Crosby Road, Newton  
 Roy W Smith (Worcester), 34 Chestnut Street, Worcester  
 Elton R Yasuna (Worcester), 340 Walnut Avenue, Roxbury

## MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

### WEEKLY RATES FOR CARE OF PATIENTS IN DEPARTMENT HOSPITALS

Owing to greatly increased costs of hospital care during the past few years, it has been necessary to revise charges for the care of patients in institu-

This provided authorization for payment for patients expecting to be confined on or before April 4, 1948, as well as for retroactive cases—that is, cases in which the patient had been delivered between September 3, 1943, and April 4, 1948, even though the application was not submitted at the time care was given

However, in May, 1948, the Government ruled that no authorization for payment for maternity care could be issued after June 30, 1948

These limitations were publicized to the professional and lay public

Outstanding bills for care already authorized continue to come in covering payment for medical, hospital and ancillary services. More than 2000 cases are still incomplete. Letters and telephone calls for information or assistance are numerous and the depleted staff is kept busy

### Infant Cases

Care is still available for eligible infants born on or before April 4, 1948. The number of cases naturally is decreasing, but authorization for payment for care will continue to be issued to cover all illnesses, including medical, hospital and other care, such as immunizations, until these infants become one year of age (in April, 1949)

TABLE 1

INSTITUTION	TYPE OF DISEASE	AGE OF PATIENTS	TOTAL WEEKLY CHARGE	
			BY PATIENT	BY CITY OR TOWN
Rutland and Westfield (Tuberculosis Section) North Reading	Pulmonary tuberculosis	17 yr and over	\$14	\$14
	Pulmonary tuberculosis	Under 17 yr	\$14	\$14
	Rheumatic heart disease	Under 17 yr	\$14	\$14
Lakeville	Extrapulmonary tuberculosis	All ages	\$14	\$21*
	Poliomyelitis (convalescent)	All ages	\$35	\$21*
Pondville and Westfield (Cancer Section)†	Cancer	All ages	\$21	\$40

\*\$14 if patient is under 21 yr of age

†Outpatient clinic (regardless of who pays bill) no charge for examination and \$3 per visit for treatment.

tions of the Massachusetts Department of Public Health. Table 1 presents the list of rates, effective July 1, 1948, as revised under the provisions of Section 66, Chapter 111 of the General Laws, as amended by Chapter 630 of the Acts of 1947

### LIQUIDATION OF EMERGENCY MATERNAL AND INFANT CARE PROGRAM

The Emergency Maternal and Infant Care Program is gradually being liquidated in the following manner

#### Maternity Cases

In May, 1947, the federal Government notified the states that payment for maternity care was limited to wives of men in the four eligible pay grades who became pregnant prior to July 1, 1947

#### Volume of Cases and Expenditures

For the period from September 3, 1943 (when the program began in Massachusetts), until July 1, 1948, a total of 43,541 cases were authorized. Of these, 33,486 were maternity, and 10,055 were infant cases. This does not include numerous individual separate authorizations for ante-partum and post-partum complications and nonobstetric conditions in maternity cases or for additional illness of many infants cared for by the same physician, nor does it include authorizations for consultant, nursing and other services. Rejections totaled 4934 cases, chiefly for noneligibility

The amount of money spent in this period was \$4,082,883.65. This expenditure was for cases only covering payment for hospital, medical and ancillary care. Administration funds were not included in this amount.

## LUE CROSS-BLUE SHIELD

### LUE CROSS APPLICATIONS

Membership in Blue Cross will again be available to all members of the Massachusetts Medical Society not now enrolled, as of December 1, 1948

For membership to be effective on that date all applications must be filed with Blue Cross not later than November 1, 1948

Thereafter, while applications will be received at any time, enrollments will become effective each quarter on March 1, June 1, September 1 and December 1 To become effective on these dates, however, applications must be received thirty days in advance

Those who desire to join should communicate with John H McLaughlin, enrollment representative, 38 Chauncy Street, Boston 11

## CORRESPONDENCE

### ACTION ON SPECIALTY BOARDS

To the Editor As advance information to the members of the Society I would remind them that the Hampden District Medical Society endorsed a resolution that can be found in the spring issue of the *Hippocrat* and was sent to all councilors This resolution is perhaps poorly drawn and I have since found on page 886 of the *Journal of the American Medical Association* of July 3, 1948, a more comprehensive resolution passed unanimously by the New York Medical Society and brought up under new business at the meeting of the American Medical Association

In the House of Delegates of the American Medical Association this resolution was referred to a reference committee on miscellaneous business, which re-referred it to a special committee of the Board of Trustees—that on Medical Practice and Hospitals, headed by Dr E Hess of Erie, Pennsylvania Dr Hess will give a report of his committee at the St. Louis meeting on November 30, 1948

The New York Society has 15 per cent of the national membership, the Massachusetts Medical Society is sixth in size in the nation, and the problems of the New York Society are ours No mention of instructions by the Massachusetts Medical Society to its delegates to the American Medical Association—Drs Phippen, Sullivan, and Curley—have as yet been noted Inasmuch as the subject matter of this resolution is vitally important to orderly medical practice I am preparing a presentation for action in the matter at the meeting of the Council on October 6 I hope that the councilors will come to the meeting informed sufficiently to express an opinion on the subject of specialty boards

W A R CHAPIN M D

121 Chestnut Street  
Springfield, Massachusetts

## BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender Books that appear to be of particular interest will be reviewed as space permits Additional information in regard to all listed books will be gladly furnished on request

*The Acute Bacterial Diseases Their diagnosis and treatment* By Harry F Dowling M D, clinical professor of medicine, George Washington University School of Medicine, and chief George Washington Medical Division Gallinger Municipal

Hospital With the collaboration of Lewis K Sweet M D chief medical officer in pediatrics and infectious diseases Gallinger Municipal Hospital, adjunct clinical professor of pediatrics, George Washington University School of Medicine and Georgetown University School of Medicine, and Harold L Hirsh, M D, assistant professor of medicine, Georgetown University School of Medicine, and director, Bacteriology and Immunology Laboratory, Georgetown University Hospital 8°, cloth, 465 pp, with 55 illustrations and 52 tables Philadelphia W B Saunders Company, 1948 \$6 50

This new book on infectious diseases is intended as a practical guide for the practicing physician and presents the up-to-date knowledge on these diseases The individual diseases are classified according to the etiologic agents Diseases that are clinically similar have been grouped together whenever possible The work is based principally upon more than 7000 cases observed at Gallinger Municipal Hospital The text is divided into four parts The first deals with diagnosis and treatment in general, including the current use of the sulfonamides, penicillin and streptomycin The second part describes the diseases caused by the cocci, the third those caused by the bacilli, and the fourth, those in which exotoxins are a major factor Only the acute forms of tuberculosis are discussed because they are the ones most likely to be confused with other acute bacterial infections and because the chronic forms are usually treated in institutions by specialists The text is well written, and the book well published The volume is recommended for all medical schools and to the general practitioner

*Biology of Disease* By Eli Moschowitz, M D, physician, Mt Sinai Hospital, New York City 4°, cloth, 221 pp New York Grunc and Stratton, 1948 \$4 50

This book may be characterized as a series of essays on the evolution of certain chronic diseases or conditions in which the biologic factors are not too obvious The author points out that many chronic conditions present a distinct evolutionary progression from a primitive stage to the final form He classifies diseases into two great divisions those in which there is a well established pathogenesis, and those that can be classified on a grouping of clinical phenomena The diseases and syndromes discussed include hypertension, arteriosclerosis, periarthritis nodosa, Libman-Sacks disease, polycythemia vera leukemia, follicular lymphoblastoma, myeloma, Graves's disease, toxic hepatitis, Laennec or portal cirrhosis, glomerulonephritis, obesity, peptic ulcer, achlorhydria in relation to anemia, cardiopasm, sprue syndrome, emphysema, uremia, nephrosis and the hyperkinetic diseases Also there is a chapter on psychosomatic medicine The essays are scholarly and well written A selected list of references is appended to each chapter A good index concludes the volume The publishing is excellent The book is recommended for all medical libraries and to all physicians interested in chronic forms of disease

*The 1947 Year Book of Endocrinology, Metabolism and Nutrition "Endocrinology"* Edited by Willard O Thompson, M D clinical professor of medicine, University of Illinois College of Medicine, attending physician (senior staff), Henry Hospital, and attending physician, Grant Hospital of Chicago "Metabolism and Nutrition" Edited by Tom D Spies, M D, chairman, Department of Nutrition and Metabolism Northwestern University School of Medicine, and director Nutrition Clinic, Hillman Hospital Birmingham, Alabama 12°, cloth, 575 pp, with 86 illustrations Chicago The Year Book Publishers, Incorporated, 1948 \$3 75

This second issue of a standard reference work covers the literature on its subjects for the period from November, 1946, to October, 1947 The literature on the pancreas has been transferred from "Endocrinology" to "Metabolism and Nutrition" The text comprises abstracts of original articles on various topics selected for their importance The citations to original sources are printed as footnotes on the appropriate pages Good indexes of subjects and authors conclude the volume The text is well printed with good type on coated paper The book is recommended as an essential reference work for all medical libraries and to all persons interested in the subjects covered

Winnifred P Davis (Worcester North), 79 Main Street, Ashburnham

David D Greene (Middlesex South), 117 Brackett Road, Newton

Herbert I Harris (Norfolk), 84 Reservoir Road, Brookline

Earle U Hussey (Essex South), 32 Cedar Street, Lynn

Gordon R Lamb (Norfolk), 4B Putney Road, Wellesley Hills

David I Levine (Norfolk South), Los Angeles, California

Arthur P Long (Norfolk), Office of Surgeon General, War Department, Washington, D C

Donald H MacDonald (Middlesex South), 425 Beacon Street, Boston

Theodore B Massell (nonresident), 1982 Comstock Avenue, Los Angeles Calif

Walter L McClintock (Norfolk South), 1245 Hancock Street, Quincy

Donald McNeil (nonresident), P O Box 168, Sacramento, Calif

Edward B Ormsby (Norfolk), 504 Talbot Avenue, Dorchester

Bernard W Rothblatt (Middlesex South), 65 Crosby Road, Newton

Roy W Smith (Worcester) 34 Chestnut Street, Worcester

Elton R Yasuna (Worcester), 340 Walnut Avenue, Roxbury

## MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

### WEEKLY RATES FOR CARE OF PATIENTS IN DEPARTMENT HOSPITALS

Owing to greatly increased costs of hospital care during the past few years, it has been necessary to revise charges for the care of patients in institu-

This provided authorization for payment for patients expecting to be confined on or before April 4, 1948, as well as for retroactive cases—that is, cases in which the patient had been delivered between September 3, 1943, and April 4, 1948, even though the application was not submitted at the time care was given

However, in May, 1948, the Government ruled that no authorization for payment for maternity care could be issued after June 30, 1948

These limitations were publicized to the professional and lay public

Outstanding bills for care already authorized continue to come in covering payment for medical, hospital and ancillary services More than 2000 cases are still incomplete Letters and telephone calls for information or assistance are numerous and the depleted staff is kept busy

### Infant Cases

Care is still available for eligible infants born on or before April 4, 1948 The number of cases naturally is decreasing, but authorization for payment for care will continue to be issued to cover all illnesses, including medical, hospital and other care, such as immunizations, until these infants become one year of age (in April, 1949)

TABLE I

INSTITUTION	TYPE OF DISEASE	AGE OF PATIENTS	TOTAL WEEKLY CHARGE	
			BY PATIENT	BY CITY OR TOWN
Rutland and Westfield (Tuberculosis Section) North Reading	Pulmonary tuberculosis	17 yr and over	\$14	\$14
	Pulmonary tuberculosis	Under 17 yr	\$14	\$14
	Rheumatic heart disease	Under 17 yr	\$14	\$14
Lakeville	Extrapulmonary tuberculosis	All ages	\$14	\$21*
	Poliomyelitis (convalescent)	All ages	\$35	\$21*
Pondville and Westfield (Cancer Section)†	Cancer	All ages	\$21	\$40

\*\$14 if patient is under 21 yr of age

†Outpatient clinic (regardless of who pays bill) no charge for examination and \$3 per visit for treatment

tions of the Massachusetts Department of Public Health Table 1 presents the list of rates, effective July 1, 1948, as revised under the provisions of Section 66, Chapter 111 of the General Laws, as amended by Chapter 630 of the Acts of 1947

### LIQUIDATION OF EMERGENCY MATERNAL AND INFANT CARE PROGRAM

The Emergency Maternal and Infant Care Program is gradually being liquidated in the following manner

#### Maternity Cases

In May, 1947, the federal Government notified the states that payment for maternity care was limited to wives of men in the four eligible pay grades who became pregnant prior to July 1, 1947

#### Volume of Cases and Expenditures

For the period from September 3, 1943 (when the program began in Massachusetts), until July 1, 1948, a total of 43,541 cases were authorized Of these, 33,486 were maternity, and 10,055 were infant cases This does not include numerous individual separate authorizations for ante-partum and post-partum complications and nonobstetric conditions in maternity cases or for additional illness of many infants cared for by the same physician, nor does it include authorizations for consultant, nursing and other services Rejections totaled 4934 cases, chiefly for noneligibility

The amount of money spent in this period was \$4,082,883 65 This expenditure was for cases only covering payment for hospital, medical and ancillary care Administration funds were not included in this amount

## NOTICES (Concluded from page 530)

- NOVEMBER 3 and 4. Annual Meeting of National Committee for Mental Hygiene Inc Page 282 issue of August 12.
- NOVEMBER 3-5 Seventh New England Postgraduate Assembly Copley 222 Hotel Boston
- NOVEMBER 4-6. American Society of Anesthesiologists Page 418 issue September 9
- NOVEMBER 8-12 American Public Health Association Page 420 issue March 18
- NOVEMBER 10-11 Association of Military Surgeons of the United States Page 722 issue of May 17
- NOVEMBER 20-23 American Academy of Pediatrics Annual Meeting ballroom Haddon Hall Hotel Atlantic City New Jersey
- NOVEMBER 30 Hampden District Medical Society Page 492 issue of September 23
- DECEMBER 2. Suffolk Censors Meeting Page 492, issue of September 23
- DECEMBER 7-9 Southern Surgical Association Annual Meeting Page 543 issue of April 8
- DECEMBER 9 and 10 New York State Society of Anesthesiologists Page 34 issue of July 1
- FEBRUARY 4, 1949 American Board of Obstetrics and Gynecology Inc. Page 244 issue of August 5
- MARCH 28-April 1 1949 American College of Physicians Page 1 8 issue of July 22.
- MAY 16-19 1949 American Urological Association Biltmore Hotel Los Angeles
- MAY 26-28 1949 American Gopher Association Hotel Lorraine Madison Wisconsin
- NOVEMBER 11-17 1949 Third Inter-American Congress of Radiology Page 158 issue of July 22.

## DISTRICT MEDICAL SOCIETIES

## HAMPDEN

NOVEMBER 30 8 30 p.m. Academy of Medicine Springfield Cardiothoracic of the Breast. Dr Grantley W Taylor

## NORFOLK

SEPTEMBER 28 Specialty Night

## SUFFOLK

OCTOBER 9 Fall Dinner

DECEMBER 2. Suffolk Censors Meeting

## Valleyhead Hospital

CONCORD, MASSACHUSETTS

For the treatment of psychoneuroses, alcoholism, mild mental disorders and chronic diseases. Pleasant pastoral setting near historic Concord. Accepted modern therapies used. Complete occupational and recreational facilities available including outdoor swimming pool and tennis court.

S. GAGNON, M.D.  
Superintendent

J. BUTLER TOMPKINS, M.D.  
Director of Clinical Psychiatry

J. P. THORNTON, M.D.  
Consultant in Neuro-psychiatry

IRVING KAUFMAN, M.D.  
Psychiatrist

Post Office, Box 151, Concord, Mass Tel Concord 1600

## Washingtonian Hospital

41-43 WALTHAM STREET, BOSTON MASS

Incorporated 1859

Conditioned Reflex, Psychotherapy, Semi-Hospitalization  
For Rehabilitation of Male Alcoholics

Treatment of Acute Intoxication and Alcoholic Psychoses  
Included

Outpatient Clinic and Social-Service Department for  
Male and Female Patients

JOSEPH THIMANN, M.D., Medical Director

Visiting Psychiatric and Neurologic Staff  
Consultants in Medicine, Surgery and the Other Specialties  
Telephone HA 6-1750

## Xenopus laevis FROG test

1 day

## PREGNANCY TEST

Complete reading in twenty-four hours, with a positive result often obtained in eight hours.

The *Xenopus laevis* test is well established as a quick, accurate and economical test for pregnancy.

*New Eng J Med* 234 784 1946

Correctly designed mailing cases for all laboratory tests are promptly furnished on request. Results are telephoned to physicians anywhere in New England, followed by a written report.

**JAMES QUINN LABORATORY**  
471 Commonwealth Avenue  
Boston 15, Mass. Ken. 1356

★ A NEW SERVICE for  
YOUR ALLERGY PATIENTS

- Gladown Pillows
- Rubber Mattresses
- Allergy-free Covers for Pillows
- Mattresses Box Springs
- Gladown Comforters
- Rubber Pillows
- Allergy-free Box Springs
- Rubber Carpeting
- Allergy-free Insecticide

FAST, EFFICIENT MAIL ORDER SERVICE  
Brochures available for distribution to patients

AMERICAN ALLERGY AIDS COMPANY

230 BOSTON STREET BOSTON MASS  
CO 6-5855

## HARVARD MEDICAL SCHOOL

Courses for Graduates

## MEDICAL DIAGNOSIS AND TREATMENT

October 6, 1948 to May 25 1949

Wednesdays, 2 to 4 p.m.

Tuition — \$100

## CARDIOLOGY

October 27, 1948 to January 12 1949

Wednesdays, 10 a.m. to 1 p.m.

Tuition — \$75

For further information write to  
Assistant Dean Courses for Graduates  
Harvard Medical School Boston 15 Mass

## NOTICES

## ANNOUNCEMENTS

Dr H Myer Bloomenthal announces the removal of his office from 1396 to 1460 Commonwealth Avenue, Brighton, for the practice of medicine and surgery

Dr A G Israelian announces the removal of her office to 520 Boylston Street, Boston

Dr Abraham L Rubin announces the removal of his office to 252 Gallivan Boulevard, Dorchester, for practice limited to diseases of the eye

## HARVARD MEDICAL SOCIETY

A meeting of the Harvard Medical Society will be held in the amphitheater of Building D, Harvard Medical School, on Tuesday, October 12, at 8 p m

Dr Arturo Rosenblueth, director, Physiological Laboratory, National Institute of Cardiology, Mexico City, and Dr Norbert Wiener, professor of mathematics, Massachusetts Institute of Technology, will speak on "The Shape of the Spike Potential of Nerve"

## METROPOLITAN STATE HOSPITAL

The following change in the schedule of the course in Pediatric Neuropsychiatry (child psychiatry) of the Fourteenth Postgraduate Seminar in Neurology and Psychiatry at the Walter E Fernald State School, announced in the September 9 issue of the *Journal*, has been made: this course will be given on Tuesdays, October 26, and November 9, 1948, and on Mondays, November 22 and December 6, 1948, and from March 14 until May 9, 1949, every second week from 6 00 to 9 30 p m

## NEW ENGLAND DERMATOLOGICAL SOCIETY

A regular meeting of the New England Dermatological Society will be held in the Skin Out-Patient Department of the Massachusetts General Hospital, at 2 p m on Wednesday, October 20. The meeting is open to members and invited guests only

## NEW ENGLAND DIABETES ASSOCIATION

The fall meeting of the New England Diabetes Association will be held in the Cheever Amphitheater of the Boston City Hospital on Wednesday, October 20, at 8 00 p m

The speaker of the evening will be Dr George W Thorn, whose subject will be "Some Fundamental Endocrine Relations in Diabetes"

After the clinical program there will be an important business meeting of the Association to discuss future policies

NEW ENGLAND  
PEDIATRIC SOCIETY

The fall meeting of the New England Pediatric Society will be held in Boston on Wednesday, October 27, 1948

Dr Lawson Wilkins, of Johns Hopkins Hospital, will be the speaker

A detailed program will be announced at a later date

AMERICAN SOCIETY FOR THE STUDY OF  
ARTERIOSCLEROSIS

A scientific meeting of the American Society for the Study of Arteriosclerosis will be held at the Hotel Knickerbocker, Chicago, on October 31 and November 1

AMERICAN BOARD OF OBSTETRICS  
AND GYNECOLOGY, INC

The following changes in Board requirements and regulations were made at the annual meeting of the Board held in Washington, D C, May 16 to May 22: the ruling that applicants must receive adequate training in both obstetrics and gynecology has been defined as meaning a minimum of six months, full time, in the branch of either obstetrics or gynecology relegated to a minor role in a candidate's training and preference for practice, acceptable preceptorship, training is defined, the present regulation requiring at least six months of practice in the specialty following the completion of an acceptable training period has now been extended, effective December 31, 1949, to a requirement of two years' post-training practice limited to the specialty; specific requirements for approval of hospital services for residency training are outlined, and effective immediately there will be no further temporary approvals of hospital services for residency training—it is planned that all hospitals holding any type of residency-training approval will soon be either resurveyed or initially surveyed by the Council on Medical Education and Hospitals of the American Medical Association so that all future approvals, new and old, will be based entirely upon inspection following application. It is expected also that certain resurveys will result in withdrawal of present residency approval from institutions where the educational and training standards are not being maintained

## SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING  
THURSDAY, OCTOBER 7

## FRIDAY OCTOBER 8

- \*9 00 a m-12 00 m Combined Medical and Surgical Staff Report  
Peter Bent Brigham Hospital
- \*12 00 m Clinicopathological Conference Margaret Jervett Hill  
Mt Auburn Hospital Cambridge
- 12 00 m-1 00 p m Clinicopathological Conference (Boston Foreign Hospital) Joseph H Pratt Diagnostic Hospital

## WEDNESDAY OCTOBER 13

- \*11 00 a m-12 00 m Medical Clinic Amphitheater Children's Hospital
- \*12 00 m Clinicopathological Conference (Children's Hospital) Amphitheater Peter Bent Brigham Hospital
- \*2 00-3 00 p m Combined Clinic by the Medical, Surgical and Orthopedic Services Amphitheater Children's Hospital

\*Open to the medical profession

- OCTOBER 1 and 2 American Society of Anesthesiologists Inc. Page 352, issue of September 2
- OCTOBER 1-MAY 20 Metropolitan State Hospital Page 418 issue of September 9
- OCTOBER 3-7 Medical Society of the State of Pennsylvania Page 491, issue of September 23
- OCTOBER 4 South Boston Medical Society Page 452, issue of September 16
- OCTOBER 4-15 New York Academy of Medicine. Page 492, issue of September 23
- OCTOBER 6-9 American Board of Ophthalmology Page 170 issue of January 29
- OCTOBER 9 Suffolk District Medical Society Page 452, issue of September 16
- OCTOBER 12 Harvard Medical Society Notice above
- OCTOBER 14 The Practical and Clinical Sides of the Management of the Rb Problem in Pregnancy Dr William C. Moloney Pentecost Association of Physicians 8 30 p m. Haverhill.
- OCTOBER 15 American Trudeau Society Page 418 issue of September 9
- OCTOBER 18-22 American College of Surgeons Page 417 issue of September 9
- OCTOBER 20 New England Diabetes Association Notice above
- OCTOBER 20 New England Dermatological Society Notice above.
- OCTOBER 27 New England Obstetrical and Gynecological Society Annual Meeting Hotel Somerset, Boston
- OCTOBER 27 New England Pediatric Society Notice above
- OCTOBER 31 and NOVEMBER 1 American Society for the Study of Arteriosclerosis Notice above
- NOVEMBER 1-3 American Clinical and Climatological Association Page 582 issue of April 15

(Notices concluded on page viii)

# The New England Journal of Medicine

Copyright 1948 by the Massachusetts Medical Society

Volume 239

OCTOBER 7, 1948

Number 15

## THE USE OF THE RICE DIET IN THE TREATMENT OF HYPERTENSION IN NONHOSPITALIZED PATIENTS\*

ANDREW W. CONTRATTO, M.D.,† AND MIRIAM B. ROGERS

BOSTON

THIS report covers the first six months of a study of a group of ambulatory or nonhospitalized patients with hypertension who were treated with the rice diet. With the work of Kempner<sup>1-4</sup> as a guide but unlike his series in which all but a few patients were initially confined to a hospital, our patients were not hospitalized. So far as possible, nothing was changed in the daily routine of the patient except the diet. If he was ambulatory and working, this activity was continued. Patients who, when first started on the regime, were inactive because of their illness, continued on this routine except for the diet until improvement, if it did occur, warranted a more strenuous life. Moreover,

Of the 55 patients with essential hypertension who were started on the diet, 18 were excluded from the study because of nonco-operation. Some of these failed to return for subsequent visits after having been advised to follow the diet. Others after a few days, expressed unwillingness to remain on the diet, and still others, who did not admit their dietary divergence, were excluded because their twenty-four-hour urinary chloride excretions

TABLE 1 Use of Rice Diet in 67 Cases

DIAGNOSIS	NO. OF CASES
Hypertension with renal failure*	4
Cardiac failure with edema	3
Coronary artery disease with marked angina and no hypertension	5
Coronary artery disease with hypertension	1
Essential hypertension	55
Nonco-operative patients	18
Patients who developed coronary occlusion early in treatment and were excluded from series	3
Patients with essential hypertension available for study	34

\* All these cases were failures

these people were all private patients, and we supervised their treatment, with exceptions that will be discussed later.

Sixty-seven patients were originally started on the rice diet (Table 1). Of this number, 4 had hypertension with renal failure, 3 had cardiac failure with edema, 5 had coronary-artery disease with severe angina pectoris and no hypertension, 1 had severe coronary-artery disease with hypertension, and 55 had essential hypertension. The study and results in the group with essential hypertension largely constitute this report.

TABLE 2 Age and Sex Distribution of 34 Patients with Essential Hypertension\*

AGE	MALE PATIENTS	FEMALE PATIENTS
yr		
30-39	1	0
40-49	5	6
50-59	5	10
60-69	5	5
	16	21
Systolic blood pressure of 150 or below after therapy		
30-39	0	0
40-49	3	1
50-59	1	7
60-69	2	2
	6	10
Drop of 30 mm or more in systolic and 20 mm or more in diastolic blood pressure		
30-39	0	0
40-49	0	2
50-59	2	2
60-69	0	2
	2	6

\*The rice diet benefited a total of 24 patients or 70 per cent.

(expressed as sodium chloride) were so high as to make it obvious that they were not adhering to the regime. Also 3 patients developed coronary occlusion within the first few days or weeks after having been started on the diet and were therefore excluded. Thus, there were 34 patients with essential hypertension who co-operated and were considered satisfactory for the report.

These 34 patients had had well established, known hypertension for at least three or more years. Many of them had been under personal observation during this time, others had been under the care of other physicians. Of this number 21 were

\*Presented at the annual meeting of the Massachusetts Medical Society, Boston, May 26, 1948.

†Assistant in medicine, Harvard Medical School physician, Department of Hygiene, Harvard University, associate physician, Peter Bent Brigham Hospital.

---

# BRIEF HISTORICAL NOTES ON MEAD'S CEREAL, PABLUM AND PABENA

---

**H**AND in hand with pediatric progress, the introduction of Mead's Cereal in 1930 marked a new concept in the function of cereals in the child's dietary. For 150 years before that, since the days of "pap" and "panada," there had been no noteworthy improvement in the nutritive quality of cereals for infant feeding. Cereals were fed principally for their carbohydrate content.

The formula of Mead's Cereal was designed to supplement the baby's diet in minerals and vitamins, especially iron and thiamine. How well it has succeeded in these functions may be seen from two examples:

(1) As little as one-sixth ounce of Mead's Cereal\* supplies over 50% of the iron and 20% of the thiamine minimum requirements of the 3-months-old infant. (2) One-half ounce of Mead's Cereal furnishes all of the iron and 60% of the thiamine minimum requirements of the 6-months-old baby.

That the medical profession has recognized the importance of this contribution is indicated by the fact that cereal is now routinely included in the infant's diet as early as the third or fourth month instead of at the sixth to

twelfth month as was the custom only a decade or two ago.

In 1933 Mead Johnson & Company went a step further, improving the Mead's Cereal mixture by a special process of cooking, which rendered it easily tolerated by the infant and at the same time did away with the need for prolonged cereal cooking in the home. The result is Pablum, an original product which offers all of the nutritional qualities of Mead's Cereal, plus the convenience of thorough scientific cooking.

During the last twelve years, these products have been used in a great deal of clinical investigation of various aspects of nutrition, which have been reported in the scientific literature.

Many physicians recognize the pioneer efforts on the part of Mead Johnson & Company by specifying Mead's Cereal and PABLUM—and also the new Pablum-like oatmeal cereal known as PABENA.

---

\*Pablum, the precooked form of Mead's Cereal, has practically the same composition: wheatmeal (farina), oatmeal, cornmeal, wheat embryo, beef bone, brewers yeast, alfalfa leaf, sodium chloride, and reduced iron.

# The New England Journal of Medicine

Copyright 1948 by the Massachusetts Medical Society

Volume 239

OCTOBER 7, 1948

Number 15

## THE USE OF THE RICE DIET IN THE TREATMENT OF HYPERTENSION IN NONHOSPITALIZED PATIENTS\*

ANDREW W. CONTRATTO, M.D.,† AND MIRIAM B. ROGERS

BOSTON

THIS report covers the first six months of a study of a group of ambulatory or nonhospitalized patients with hypertension who were treated with the rice diet. With the work of Kempner<sup>1-4</sup> as a guide but unlike his series in which all but a few patients were initially confined to a hospital, our patients were not hospitalized. So far as possible, nothing was changed in the daily routine of the patient except the diet. If he was ambulatory and working, this activity was continued. Patients who, when first started on the regime, were inactive because of their illness, continued on this routine except for the diet until improvement, if it did occur, warranted a more strenuous life. Moreover,

Of the 55 patients with essential hypertension who were started on the diet, 18 were excluded from the study because of nonco-operation. Some of these failed to return for subsequent visits after having been advised to follow the diet. Others, after a few days, expressed unwillingness to remain on the diet, and still others, who did not admit their dietary divergence, were excluded because their twenty-four-hour urinary chloride excretions

TABLE 1 Use of Rice Diet in 67 Cases

DIAGNOSIS	No. of Cases
Hypertension with renal failure*	4
Cardiac failure with edema	3
Coronary artery disease with marked angina and no hypertension	5
Coronary artery disease with hypertension	1
Essential hypertension	55
Nonco-operative patients	18
Patients who developed coronary occlusion early in treatment and were excluded from series	3
Patients with essential hypertension available for study	34

\* All these cases were failures

these people were all private patients, and we supervised their treatment, with exceptions that will be discussed later.

Sixty-seven patients were originally started on the rice diet (Table 1). Of this number, 4 had hypertension with renal failure, 3 had cardiac failure with edema, 5 had coronary-artery disease with severe angina pectoris and no hypertension, 1 had severe coronary-artery disease with hypertension, and 55 had essential hypertension. The study and results in the group with essential hypertension largely constitute this report.

TABLE 2 Age and Sex Distribution of 34 Patients with Essential Hypertension\*

Age	MALE PATIENTS	FEMALE PATIENTS
30-39	1	0
40-49	5	6
50-59	5	10
60-69	2	5
	13	21
Systolic blood pressure of 150 or below after therapy		
30-39	0	0
40-49		1
50-59	1	7
60-69	2	2
	6	10
Drop of 0 mm. or more in systolic and 20 mm. or more in diastolic blood pressure		
30-39	0	0
40-49	0	2
50-59	2	2
60-69	0	2
	2	6

\*The rice diet benefited a total of 24 patients or 70 per cent.

(expressed as sodium chloride) were so high as to make it obvious that they were not adhering to the regime. Also 3 patients developed coronary occlusion within the first few days or weeks after having been started on the diet and were therefore excluded. Thus, there were 34 patients with essential hypertension who co-operated and were considered satisfactory for the report.

These 34 patients had had well established known hypertension for at least three or more years. Many of them had been under personal observation during this time, others had been under the care of other physicians. Of this number 21 were

\*Presented at the annual meeting of the Massachusetts Medical Society, Boston, May 26, 1948.

†Assistant in medicine, Harvard Medical School, physician, Department of Hygiene, Harvard University, associate physician, Peter Bent Brigham Hospital.

women, and 13 were men. They varied in age from 35 to 69 years (Table 2)

### METHODS

Before being started on the diet, each patient had a physical examination that included an electrocardiogram, blood counts, urinalysis and determinations of twenty-four-hour urinary chloride excretion, blood cholesterol, blood urea nitrogen, total protein, albumin-globulin ratio and blood chloride. Each patient received a copy of the rice diet,\* as devised by Kempner,<sup>5</sup> which contains in 2000 calories not more than 5 gm of fat and about 20 gm of protein derived from rice and fruit and not more than 200 mg of chloride and 150 mg of sodium.

A patient takes an average of 250 to 350 gm of rice (dry weight) daily, any kind of rice may be used provided no sodium, chloride, milk, etc has been added during its processing. All fruit juices and fruits are allowed, with the exception of nuts, dates, avocados and any dried or canned fruit or fruit derivatives to which substances other than white sugar have been added. Usually no water is given and the fluid intake is limited to 700 to 1,000 cc of fruit juice per day.

Supplementary multiple vitamins were added, usually 2 unicaps per day, and iron when the patient was menstruating. Modified diets were outlined, mimeographed and ready for the patients' use as soon as their condition indicated. Directions for collecting the twenty-four-hour specimen of urine were also printed. It was believed that it was necessary to see these patients in the early part of the regime at least every two weeks to collect the twenty-four-hour specimen of urine for urinary chloride determinations as advised by Kempner,<sup>1-4</sup> secondly, merely to establish the diet in some cases and, thirdly, as in most cases, to maintain the diet and keep it varied. Patients who were perhaps too ill at the time, who for some other reason were unable to report for a regular two-week checkup or who because of psychologic reasons were having difficulty following the regime were seen by a volunteer worker (M. B. R.) at regular intervals in their homes. She answered any question about the use and preparation of the diet, collected the urine and blood specimens, recorded the blood pressure and pulse and took an electrocardiogram when it was considered necessary. One of her important duties on these visits was reassurance to the patient, making it understood that in most cases the diet was effective, that it was not necessarily a permanent one

and that although they might have periods of extreme weakness and fatigue, and even depression, they would soon feel better. This plan worked very well, and it is believed that many patients who would otherwise not have adhered to the diet followed the regime faithfully and even cheerfully.

All sedation and medication were withdrawn from these patients as soon as possible, especially from those who were taking sodium pentobarbital or phenobarbital. The patients were expected to remain rigidly on the strict rice diet for a period of three months unless a satisfactory drop in blood pressure occurred before that time. With some patients, because of their age or for psychologic reasons, it was necessary to modify the diet before the three-month period had elapsed. Patients who, during this period, had remained strictly on the diet and who also had satisfactory urinary chloride excretions but whose blood pressure did not show significant drop were considered "failures," and the diet regime was concluded.

The diet was gradually modified for patients whose blood-pressure readings dropped satisfactorily. The first modification was the addition of one egg once a week, half a cup of nonleguminous vegetables (carrots, broccoli, celery, cabbage, asparagus, beets, spinach and so forth), boiled without salt, once a day and, if desired, a cup of coffee or tea once a day, with sugar, but without milk or cream, no salt or fat was included in any of the modifications, all of which contained the amounts of rice specified above. The patient stayed on this regime for two weeks to a month. If the blood-pressure readings were satisfactory at the end of this time, 4 ounces of lean meat, fish, liver or chicken three times weekly was added to the diet, the egg being taken three times a week and the nonleguminous vegetable once a day. The meat or fish was boiled or broiled, without salt or salt-containing substances. At this time, some patients were allowed salt-free bread,<sup>†</sup> two slices daily. If progress was satisfactory after another month, the diet was again modified, to allow 4 ounces of meat and so forth as mentioned above at one meal daily, half a cup each of two nonleguminous vegetables, one egg, either boiled or poached, three times weekly, and a baked or boiled white or sweet potato twice weekly. The fourth modification of the diet<sup>‡</sup> was advised only for those patients whose blood-pressure readings had remained satisfactory after having been on the third modification for a month. This addition consisted of one egg daily if desired,

<sup>†</sup>Through the courtesy of Mr. Herbert Carlough this bread which contains only flour, yeast, sugar, vegetable shortening and water was made available by the Betty Bakerie Company.

<sup>‡</sup>This consisted of 1 egg three times a week (boiled or poached), ½ lb of lean meat, fish, chicken or liver four times a week (4 ounces with one meal), a small amount of nonleguminous vegetable seven times a week (½ cup), a small amount of white or sweet potatoes seven times a week (½ cup), boiled without salt and 1 slice of salt free bread with each meal.

No fluids except those listed with the rice diet were included. Vitamins and iron were continued.

Other alterations on discretion of physician.

\*Breakfast consisted of 2 or 3 ounces of rice (uncooked weight) with sugar or honey, two thirds of a glass of prune juice, a baked apple and a baked grapefruit. At 10 a.m. half a glass of orange juice was included with grapes and an orange. Lunch consisted of rice (as at breakfast) with sugar or honey, five eighths of a glass of orange juice, one split banana with six slices of apple, a good many raisins and a baked slice of fresh pineapple with a cherry in the center. At 3 p.m. half a glass of orange juice, apple with a cherry and an apple were taken. Supper consisted of the rice, dried soft peaches, two thirds of a glass of orange juice and a fruit plate with sugar or honey. At 9 p.m. half a glass of orange juice was taken.

meat and so forth once daily, any of the nonleguminous vegetables as desired, and a baked or boiled potato each day.

The blood-pressure readings were always taken in the same manner. Three readings were taken at intervals of five or ten minutes with the patient in the recumbent position. A mercury sphygmomanometer was always used, and the readings taken from the right arm. An average of the three readings was considered the actual reading for that visit. In the beginning of the regime, the patients were seen every two weeks for an accurate check on the blood pressure and for collection of a twenty-four-hour urine specimen. Determinations of the blood urea nitrogen, blood chloride, total protein, albumin-globulin ratio and blood cholesterol were done at monthly intervals.

### RESULTS

All the patients lost weight during the first and second months. The amount of weight loss depended upon the weight initially, but a loss of 10 to 15 pounds during this period was not unusual. The average weight of the patients was 155 pounds at the beginning, 146 pounds six weeks later and 144 pounds after three months — an average loss of 11 pounds per patient (Fig 1). Although after six months the average weight of the group was only 139 pounds, it did not mean that the patients were continuing to lose weight during the entire period, but rather that the failures had been excluded after three months. None of these patients were obese. In this series, the obese patients failed to co-operate.

The urinary chloride determinations averaged 8.6 gm before the diet was started. This dropped rapidly, going below 1 gm within the first two weeks and less than 0.5 gm within the first six-week period (Fig 1), and in some patients as low as 0.1 gm. As the diet was modified, the urinary chloride began to rise, reaching an average of 1.10 gm shortly after the three-month period, and 1.31 gm at the end of the six-month period.

The blood-pressure readings in the patients with essential hypertension averaged 210 systolic, 120 diastolic, before the regime was started, the highest being 260 systolic, 160 diastolic, and the lowest, 190 systolic, 102 diastolic. At three months, the average figure read 158 systolic, 100 diastolic. The same average figures were obtained at the end of the six-month period.

The systolic blood pressure dropped to 150 or below and the diastolic to 100 or below in 16 patients (10 women and 6 men). The blood pressure dropped 50 or more systolic and 20 or more diastolic in 8 patients (2 men and 6 women) (Table 2). Twenty-four patients, or 70 per cent, showed a definite and persistent drop in blood pressure.

The lowest readings were observed between the sixth week and the third month of the regime, while the patient was on the strict rice diet. As the diet was modified, a slight elevation of the blood pressure was observed, but in none of the successful cases did the pressure return to its original level.

The blood-pressure figures show no change from those obtained at the end of the third and sixth months, although the 10 cases of failure were excluded from the study after the three-month period (Fig 1). This is explained by the fact that the average blood-pressure readings in the successful group were lower at the three-month period while the patients were on the strict rice diet than

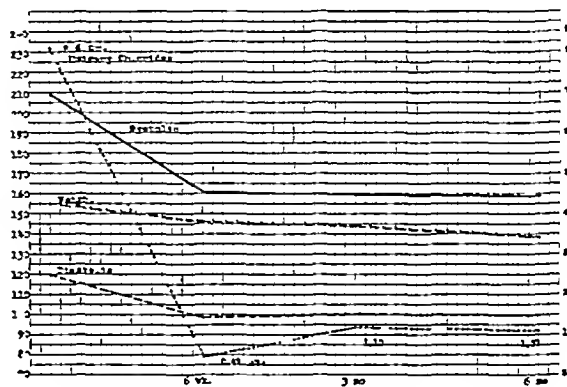


FIGURE 1 Blood-Pressure Readings in 34 Cases of Essential Hypertension (including Failures)

at the sixth-month period after the diet had been modified.

The blood chemistry was determined in each case every month for the first three months. None of the patients showed any change, with the exception of a decrease in the average cholesterol concentration in some cases. None of the patients observed developed a sodium or a chloride deficiency. During the hot summer months, these patients suffered no more from the heat than persons on normal diets. As a matter of fact, several of them maintained that they had a better summer than they had had in years.

All the patients experienced a period of weakness, which generally occurred from about the tenth to the twenty-first day and in some cases was even accompanied by a psychologic depression that required much understanding on the part of the physician and the volunteer worker. This period was only temporary, however, lasting at the most two or three weeks, and although no change was made in the diet, the patient began to feel stronger, and because of the reduction in blood pressure and absence of symptoms, all the patients felt increasingly better — far better than they had felt before the diet. It was very gratifying to find an absence

of headaches, when they had been the predominating complaint, much less tension and nervousness, these people were finally able to relax, rest and sleep well without sedation

### CASE REPORTS

**CASE 1** V L, a 49-year-old man, was first seen in 1937 for an unrelated illness. At this time, his blood-pressure reading was 130/80 (Fig 2). The patient was seen at various intervals, but it was not until some time in 1943, when his chief complaint was severe headache, that he was found to have hypertension, with a reading of 190/110. He was admitted to the hospital, where all findings were normal except for hypertension. During subsequent years, his blood pressure continued to be elevated. On April 5, 1947, when it was found to be 220/120, he was placed on the rice diet. One month later, his blood pressure was 180/120, and the headache had somewhat abated. His blood pressure continued to drop, and on June 14 it was 140/95. He was started on the second modification of the diet and was advised that he could eat one slice of salt-free bread with each meal, but through some misunderstanding ate regular bread. When he was next seen on September 20, his blood pressure had risen to 160/100. The patient, at his next visit on December 13,

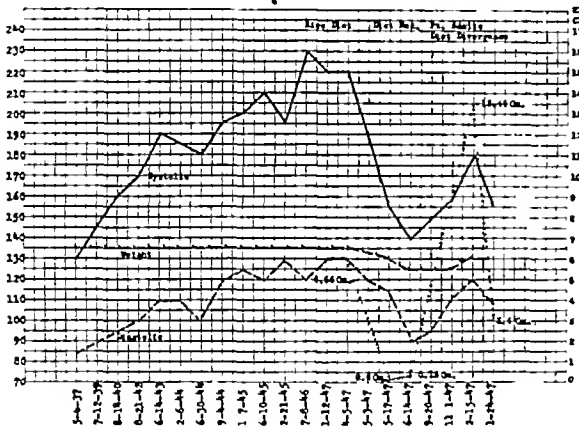


FIGURE 2 Blood Pressure and Other Data in Case 1

admitted to irregularities in his diet, which were quite obvious. His blood pressure had risen to 180/120, and the urinary chloride excretion, which had been 3 gm, was now 13.48 gm. He had also had a recurrence of severe headache. He was advised to return to his diet, which he did, and when he was last seen on January 24, 1948, his blood pressure was 155/110, and the urinary chloride excretion was 3.48 gm. His headache had again disappeared.

**CASE 2** R M, a 45-year-old woman, was first seen in 1945. She had been admitted to the Peter Bent Brigham Hospital for a surgical condition in 1943, when her blood pressure was 164/118. In the intervening years, her blood pressure varied from 180/96 to 200/115 (Fig 3). She was readmitted to the hospital for study of the hypertension in April, 1946, when her blood pressure was 180/100. All other findings were normal and she was discharged. On December 26 her blood pressure was 190/110. She was started on the rice diet on June 24, when her blood pressure was 204/110. From this date her blood pressure dropped spectacularly. On July 24, 1947, it had decreased to 150/85, and she had lost 13 pounds from her former weight of 153 pounds. Because of this favorable response, she was allowed the third modification of the diet. During a vacation, she indulged in food other than the diet, and on September 18, her blood pressure was found to be 155/92 and her urinary chloride excretion, which had been below 1 gm, had increased to 4.5 gm. She was again placed on the strict rice diet, and by January 6, 1948, her blood pres-

sure had decreased to 135/86, and the urinary chloride excretion to 0.4 gm.

**CASE 3** A P, a 65-year-old woman, was first seen in June, 1943, when her blood pressure was 210/110, with a history of known hypertension for 10 years before this visit. Her

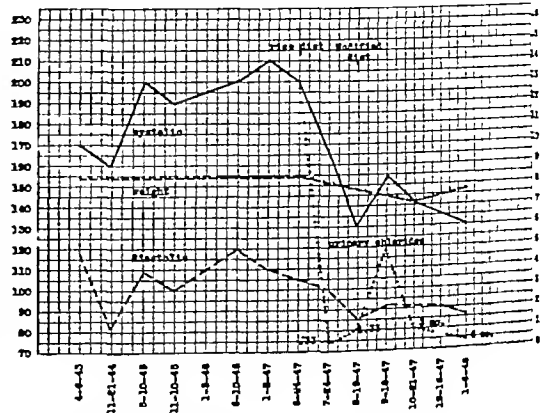


FIGURE 3 Blood Pressure and Other Data in Case 3

main complaint was a "pressure band" across the back of her head, which she stated had been present for approximately 15 years. A period of rest and small doses of phenobarbital were advised. At yearly examinations, her blood pressure readings varied between 198/118 and 230/110. In June, 1947, her blood pressure was 230/130, and she was started on the rice diet. After 2 weeks, her blood pressure was 180/110. After 6 weeks on the diet, her blood pressure had decreased to 150/90, and she felt much improved. She no longer complained of the pressure sensation in her head. Upon her next examination (August 16, 1947), her blood pressure was 130/90, and she was placed on a modified diet, which included meat, fish, vegetables and salt-free bread. The patient looked and felt markedly improved, and was capable of much more physical exertion than she had been for years. On September 16 her blood pressure was 150/100. These

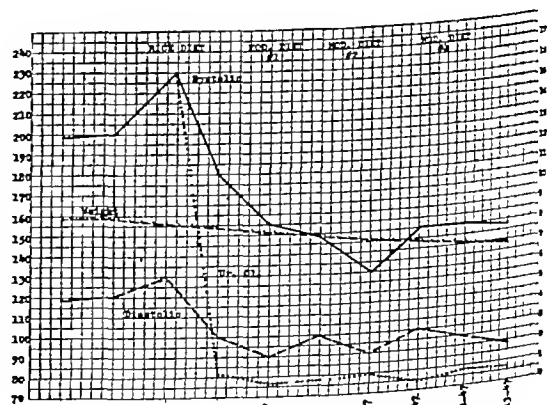


FIGURE 4 Blood Pressure and Other Data in Case 4

figures have been maintained (Fig 4), and although her diet has been modified to allow meat, vegetables and salt-free bread each day, the urinary chloride excretion has remained below 0.7 gm.

**CASE 4** T R, a 53-year-old woman with known hypertension since 1937, was first examined in 1943, 6 months after

a cerebral accident with left-sided hemiplegia. At this time, her blood pressure was 230/150. Kidney-function tests were negative, and she had no cardiac symptoms. She weighed 180 pounds and was advised to go on a diet. During the following year she lost 15 pounds, with only a slight decrease in blood pressure. She was started on the rice diet on April 20, 1947, when her blood pressure was 190/140 and the urinary chloride excretion was 118 gm. Two months later, her blood pressure had decreased to 138/102, and the urinary chloride excretion to 0.103 gm. The diet was modified at this time and despite an elevation of the urinary chloride excretion, her blood pressure has remained satisfactory (Fig 5). When she was last examined on December 13, 1947, the blood pressure was 142/105.

CASE 5 F G, a 69-year-old man, demonstrated a rapid drop in blood pressure and urinary chloride excretion with a subsequent rise in both after the diet was modified. When first seen he had a blood pressure of 220/110 and a urinary chloride excretion of 11.65 gm. During the previous 6 months, he had experienced precordial pain, suggestive of angina pectoris, and breathlessness on exertion. Kidney-function tests were negative. Although the patient was not working he was ambulatory, and no other change in his routine was prescribed with the exception of the rice diet. Ten days later, his blood pressure had decreased to 174/92, and the urinary chloride excretion to 0.79 gm. On November

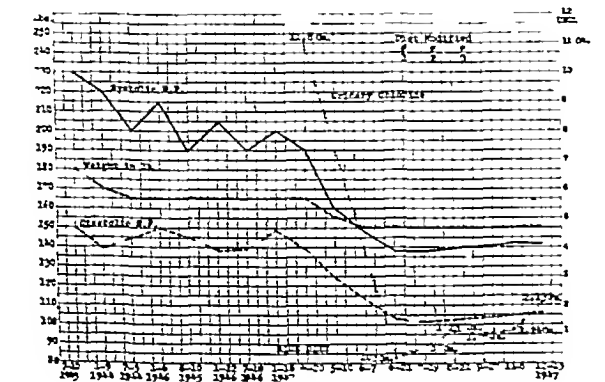


FIGURE 5 Blood Pressure and Other Data in Case 4

16 1947, his blood pressure was 128/80, the urinary chloride excretion was 0.20 gm, and the patient had lost 14 pounds. The diet was modified at this time, and on December 30, his blood pressure was 148/85, and the urinary chloride excretion was 2.08 gm. The chart on this patient ends with the December date (Fig 6). However, he has been checked twice since that time, which brings his record up to a six-month interval. On February 24, 1948, the blood pressure was 150/84, and the urinary chloride excretion was 4.77 gm. On April 7, when the patient was last seen, the blood pressure was 176/92, and the urinary chloride excretion was 4.31 gm. Although this patient admitted to some slight deviations from his diet, which might very well account for the increase in the urinary chloride excretion, it was decided to allow him to continue on the modified regime since he was feeling so much better and had returned to work.

DISCUSSION

The rice diet has been found to be a practical, inexpensive and simple method for reducing blood pressure. It requires, however, understanding and co-operation on the part of the patient to maintain it strictly, since it is a rigid departure from what is usually considered a "normal" diet. Nevertheless, of the total number of patients who have

been advised to go on the rice diet, the number of those who have refused to co-operate has been relatively small. All the patients lost weight more or less markedly during the first ten to twenty days, depending on their initial weight and the amount of edema present (Fig 1). In most cases, the loss of weight was welcomed and, at a certain place in the regime, became stabilized. Patients who were

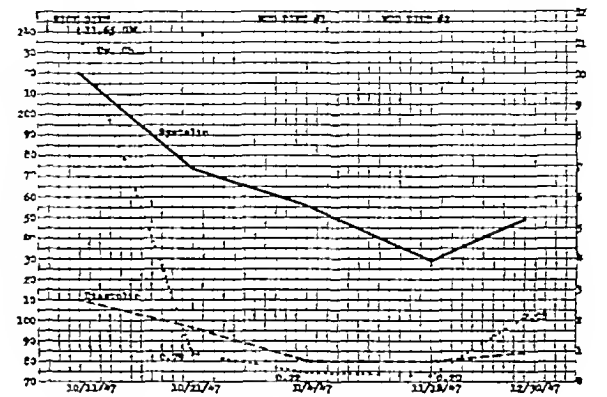


FIGURE 6 Blood Pressure and Other Data in Case 5

underweight initially lost less than those who were overweight, but this condition likewise became adjusted as the routine progressed. It is my opinion that loss of weight has little or nothing to do with a drop in blood pressure, for several of the patients who were overweight had formerly been placed on low-calorie diets, and their blood pressure had not measurably altered. On the subject of weight loss, Kempner<sup>1</sup> has the following to say:

It is not unusual for the weight to decrease more or less markedly during the first twenty days. The reason for this weight loss may be that the amount of food given does not cover the caloric requirements, in such cases, the amount of food must be increased, unless reduction of weight is indicated. Another reason may be that the patient does not eat the full amount of his diet during the first period of adjustment. The most frequent cause is the loss of visible edema, one patient with marked edema for example, lost 65 lbs. within the first sixteen days on the diet.

Urinary chloride determinations done before the patients were started on the diet averaged 8.6 gm, the lowest being 3.2 gm and the highest 13 gm. The great majority who adhered strictly to the diet had an excretion of less than 1 gm after the first two weeks. At the end of one month, the determinations were between 0.2 and 0.15 gm.

Too much emphasis cannot be placed on the necessity for obtaining the urinary chloride determinations at two-week intervals. Aside from the value to the physician, scientifically it is a valuable psychologic aid in maintaining the patient on the strict rice diet. Since it is obviously natural for patients to desire other food than that prescribed, it is carefully explained that any deviation from the

of headaches, when they had been the predominating complaint, much less tension and nervousness, these people were finally able to relax, rest and sleep well without sedation

### CASE REPORTS

**CASE 1** A L, a 49-year-old man, was first seen in 1937 for an unrelated illness. At this time, his blood-pressure reading was 130/80 (Fig 2). The patient was seen at various intervals, but it was not until some time in 1943, when his chief complaint was severe headache, that he was found to have hypertension, with a reading of 190/110. He was admitted to the hospital, where all findings were normal except for hypertension. During subsequent years, his blood pressure continued to be elevated. On April 5, 1947, when it was found to be 220/120, he was placed on the rice diet. One month later, his blood pressure was 180/120, and the headache had somewhat abated. His blood pressure continued to drop, and on June 14 it was 140/95. He was started on the second modification of the diet and was advised that he could eat one slice of salt-free bread with each meal, but through some misunderstanding ate regular bread. When he was next seen on September 20, his blood pressure had risen to 160/100. The patient, at his next visit on December 13,

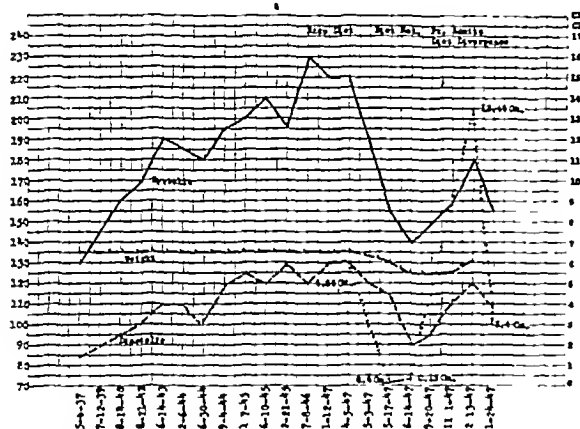


FIGURE 2 Blood Pressure and Other Data in Case 1

admitted to irregularities in his diet, which were quite obvious. His blood pressure had risen to 180/120, and the urinary chloride excretion, which had been 5 gm, was now 13.48 gm. He had also had a recurrence of severe headache. He was advised to return to his diet, which he did, and when he was last seen on January 24, 1948, his blood pressure was 155/110, and the urinary chloride excretion was 3.48 gm. His headache had again disappeared.

**CASE 2** R M, a 45-year-old woman, was first seen in 1945. She had been admitted to the Peter Bent Brigham Hospital for a surgical condition in 1943 when her blood pressure was 164/118. In the intervening years, her blood pressure varied from 180/96 to 200/115 (Fig 3). She was readmitted to the hospital for study of the hypertension in April, 1946, when her blood pressure was 180/100. All other findings were normal and she was discharged. On December 26 her blood pressure was 190/110. She was started on the rice diet on June 24 when her blood pressure was 204/110. From this date her blood pressure dropped spectacularly. On July 24, 1947, it had decreased to 150/85, and she had lost 15 pounds from her former weight of 155 pounds. Because of this favorable response, she was allowed the third modification of the diet. During a vacation, she indulged in food other than the diet, and on September 18, her blood pressure was found to be 155/92 and her urinary chloride excretion, which had been below 1 gm, had increased to 4.5 gm. She was again placed on the strict rice diet, and by January 6, 1948 her blood pres-

sure had decreased to 135/86, and the urinary chloride excretion to 0.4 gm.

**CASE 3** A P, a 65-year-old woman, was first seen in June 1943, when her blood pressure was 210/110, with a history of known hypertension for 10 years before this visit. Her

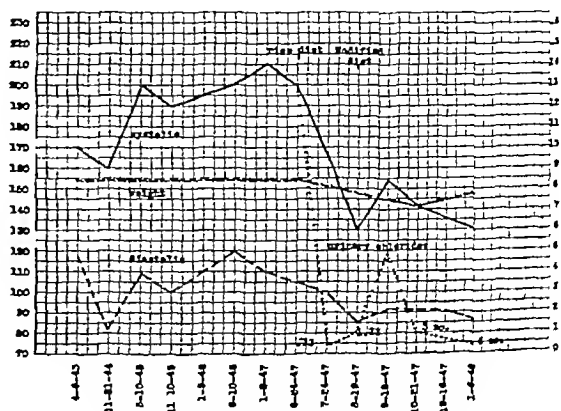


FIGURE 3 Blood Pressure and Other Data in Case 2

main complaint was a "pressure band" across the back of her head, which she stated had been present for approximately 15 years. A period of rest and small doses of phenobarbital were advised. At yearly examinations, her blood pressure readings varied between 198/118 and 230/130. In June, 1947, her blood pressure was 230/130, and she was started on the rice diet. After 2 weeks, her blood pressure was 180/110. After 6 weeks on the diet, her blood pressure had decreased to 150/90, and she felt much improved. She no longer complained of the pressure sensation in her head. Upon her next examination (August 16, 1947), her blood pressure was 130/90, and she was placed on a modified diet, which included meat, fish, vegetables and salt-free bread. The patient looked and felt markedly improved, and was capable of much more physical exertion than she had been for years. On September 16 her blood pressure was 150/100. These

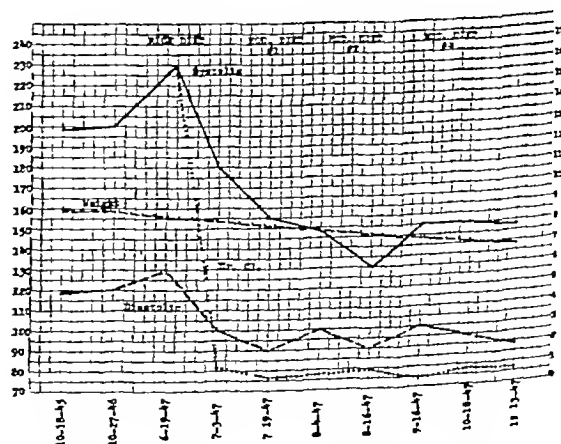


FIGURE 4 Blood Pressure and Other Data in Case 3

figures have been maintained (Fig 4), and although her diet has been modified to allow meat, vegetables and salt-free bread each day, the urinary chloride excretion has remained below 0.7 gm.

**CASE 4** T R, a 53-year-old woman with known hypertension since 1937, was first examined in 1945, 6 months after

a cerebral accident with left-sided hemiplegia. At this time, her blood pressure was 230/150. Kidney-function tests were negative, and she had no cardiac symptoms. She weighed 180 pounds and was advised to go on a diet. During the following year she lost 15 pounds, with only a slight decrease in blood pressure. She was started on the rice diet on April 20, 1947, when her blood pressure was 190/140 and the urinary chloride excretion was 118 gm. Two months later, her blood pressure had decreased to 138/102, and the urinary chloride excretion to 0.103 gm. The diet was modified at this time, and despite an elevation of the urinary chloride excretion, her blood pressure has remained satisfactory (Fig 5). When she was last examined on December 13, 1947, the blood pressure was 142/105.

CASE 5 F G, a 69-year-old man, demonstrated a rapid drop in blood pressure and urinary chloride excretion with a subsequent rise in both after the diet was modified. When first seen he had a blood pressure of 220/110 and a urinary chloride excretion of 11.65 gm. During the previous 6 months, he had experienced precordial pain, suggestive of angina pectoris, and breathlessness on exertion. Kidney-function tests were negative. Although the patient was not working he was ambulatory, and no other change in his routine was prescribed with the exception of the rice diet. Ten days later, his blood pressure had decreased to 174/92, and the urinary chloride excretion to 0.79 gm. On November

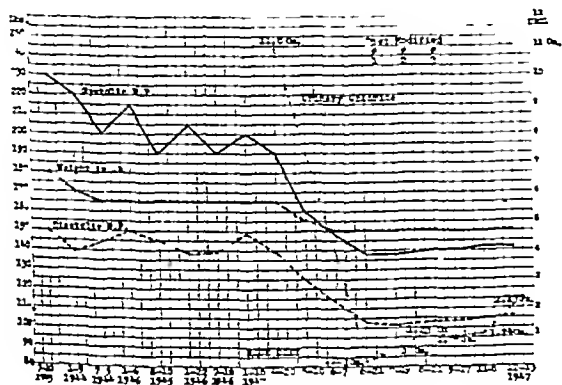


FIGURE 5 Blood Pressure and Other Data in Case 4

18, 1947, his blood pressure was 128/80, the urinary chloride excretion was 0.20 gm, and the patient had lost 14 pounds. The diet was modified at this time, and on December 30, his blood pressure was 148/85, and the urinary chloride excretion was 2.08 gm. The chart on this patient ends with the December date (Fig 6). However, he has been checked twice since that time, which brings his record up to a six-month interval. On February 24, 1948, the blood pressure was 150/84, and the urinary chloride excretion was 4.77 gm. On April 7, when the patient was last seen, the blood pressure was 176/92, and the urinary chloride excretion was 4.51 gm. Although this patient admitted to some slight deviations from his diet, which might very well account for the increase in the urinary chloride excretion, it was decided to allow him to continue on the modified regime since he was feeling so much better and had returned to work.

### DISCUSSION

The rice diet has been found to be a practical, inexpensive and simple method for reducing blood pressure. It requires, however, understanding and co-operation on the part of the patient to maintain it strictly, since it is a rigid departure from what is usually considered a "normal" diet. Nevertheless, of the total number of patients who have

been advised to go on the rice diet, the number of those who have refused to co-operate has been relatively small.

All the patients lost weight more or less markedly during the first ten to twenty days, depending on their initial weight and the amount of edema present (Fig 1). In most cases, the loss of weight was welcomed and, at a certain place in the regime, became stabilized. Patients who were

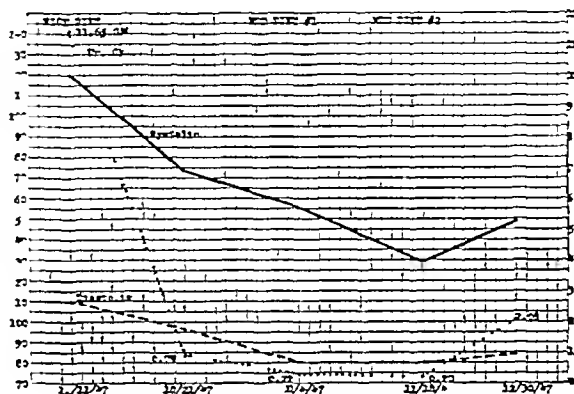


FIGURE 6 Blood Pressure and Other Data in Case 5

underweight initially lost less than those who were overweight, but this condition likewise became adjusted as the routine progressed. It is my opinion that loss of weight has little or nothing to do with a drop in blood pressure for several of the patients who were overweight had formerly been placed on low-calorie diets, and their blood pressure had not measurably altered. On the subject of weight loss, Kempner<sup>1</sup> has the following to say:

It is not unusual for the weight to decrease more or less markedly during the first twenty days. The reason for this weight loss may be that the amount of food given does not cover the caloric requirements, in such cases, the amount of food must be increased, unless reduction of weight is indicated. Another reason may be that the patient does not eat the full amount of his diet during the first period of adjustment. The most frequent cause is the loss of visible edema: one patient with marked edema for example, lost 65 lbs within the first sixteen days on the diet.

Urinary chloride determinations done before the patients were started on the diet averaged 8.6 gm, the lowest being 3.2 gm and the highest 13 gm. The great majority who adhered strictly to the diet had an excretion of less than 1 gm after the first two weeks. At the end of one month, the determinations were between 0.2 and 0.15 gm.

Too much emphasis cannot be placed on the necessity for obtaining the urinary chloride determinations at two-week intervals. Aside from the value to the physician, scientifically, it is a valuable psychologic aid in maintaining the patient on the strict rice diet. Since it is obviously natural for patients to desire other food than that prescribed it is carefully explained that any deviation from the

strict diet will be easily observed in these tests. This advice, in my experience, has proved an inhibitory factor in some patients whose need and desire for a varied menu was greater than that in others.

I have learned many things from my experience with a rather large number of patients on this diet. One of the most conspicuous problems is that it is difficult if not impossible to have a patient revert to the strict rice diet if the results on the modified diet have proved unsatisfactory. In the future, it will be necessary to maintain certain patients for a longer period on the strict rice diet. Also, the modified diets have been considerably altered to eliminate eggs, liver and certain nonleguminous vegetables high in sodium content—notably, spinach, beets and kale. The new modified diets add considerably less in quantity at each modification, and there are six diets instead of four. The results of these changes will be discussed in a subsequent publication.

Although these observations cover a limited period, it is my belief that the rice diet for hyper-

tension offers the greatest hope so far for the medical treatment of a disease in which, to date, the therapeutic results have been notoriously poor.

The mechanism through which the reduction of blood pressure is achieved is not known, but it is difficult to escape the notion that the sodium ion<sup>6-8</sup> plays a role in a manner not yet clear.

99 Bay State Road

## REFERENCES

1. Kempner W. Treatment of kidney disease and hypertensive vascular disease with rice diet. *North Carolina M J* 5:125-133 and 71, 1944.
2. *Idem*. Compensation of renal metabolic dysfunction: treatment of kidney disease and hypertensive vascular disease with rice diet. *North Carolina M J* 6:61-87 and 117-161, 1945.
3. *Idem*. Some effects of rice diet treatment of kidney disease and hypertension. *Bull New York Acad Med* 7:358-370, 1946.
4. *Idem*. Treatment of cardiac failure with rice diet: history of patient with myocardial aneurysm. *North Carolina M J* 8:128-131, 1947.
5. *Idem*. Treatment of hypertensive vascular disease with rice diet. *Am J Med* 4:545-577, 1948.
6. Bryant J M and Blecha E. Low sodium forced fluid management of hypertensive vascular disease and hypertensive heart disease. *Proc Soc Exper Biol & Med* 65:227-229, 1947.
7. Grollman A and Harrison T R. Effect of rigid sodium restriction on blood pressure and survival of hypertensive rats. *Proc Soc Exper Biol & Med* 60:52-55, 1945.
8. Schroeder H A. Low salt diets and arterial hypertension. *Am J Med* 4:578-587, 1948.

## THYROID THERAPY IN GYNECOLOGIC ABNORMALITIES\*

C L BUXTON, M D,† AND F H VANN, M D‡

NEW YORK CITY

FOR a number of years it has been the impression of obstetricians and gynecologists that lack of thyroid activity has a definite influence on the production of menstrual and obstetric abnormalities.

It has been said that "the relation of the thyroid gland to the sex organs is the most ancient and classical interrelation of the functions of the glands of internal secretion. Known to the ancients and a subject of daily gossip, it has passed down through the ages."<sup>1</sup>

In 1926 Litzenberg<sup>2</sup> noted the frequency of low basal metabolic rates in patients complaining of sterility and menstrual abnormalities, and in 1929 Litzenberg and Carey<sup>3</sup> reported 91 cases of sterility with low basal metabolic rates in 52. Of these, 36 per cent had abnormal menstruation, and 30 per cent conceived after thyroid medication. There were 2 abortions. Somewhat similar results were published by Haines and Mussey<sup>4</sup> in 1935 on 74 cases, some of which had been reported before, with menstrual abnormalities and low basal metabolic rates but no evidence of myxedema. This type of

case has come to be known, correctly or not, by the name of "subclinical hypothyroidism."

Of their 74 patients, 59 complained of amenorrhea or oligomenorrhea, and 15 of menorrhagia. The basal metabolic rates varied in these patients, but none were less than -30 per cent and no patient had symptoms of myxedema. The resumption of normal menstruation following thyroid therapy occurred in about 60 per cent of patients with hypomenorrhea and in 53 per cent of those with menorrhagia.

It will be noted that 80 per cent of the menstrual abnormalities in these patients consisted of a decrease in menstrual activity as measured by amount, duration and frequency of menstrual flow.

On the other hand, Mason<sup>5</sup> found, in patients with so-called "subclinical hypothyroidism," frequent abnormal menstruation rather than actual amenorrhea, and Hamblen and his co-workers,<sup>6</sup> although finding no significant change in the actual bleeding from secretory endometrium in hypothyroidism, noticed a greater infrequency of menstrual periods. In discussing the apparent increased incidence of abortion in hypothyroid patients, the authors speak of the possible gametopathic effect of lowered oxygen metabolism due to lack of thyroid activity.

In discussions of papers in the gynecologic-endocrine literature it has become almost a common-

\*From the Department of Obstetrics and Gynecology, Columbia University College of Physicians and Surgeons and the Sloane Hospital for Women.

†Director Sterility and Endocrine Clinic, Vanderbilt Clinic, New York City, associate attending obstetrician and gynecologist, Sloane Hospital, New York City.

‡Staff member Sterility and Endocrine Clinic, Vanderbilt Clinic, New York City, attending obstetrician, Englewood Hospital, Englewood, New Jersey.

place to state that thyroid medication is still the only trustworthy and efficacious hormonal preparation available for the treatment of menstrual disturbances. Furthermore, it is the general opinion of many gynecologists that the menstrual disturbances of hypothyroidism are those of hypomenorrhea — that is, absent or decreased menstruation — rather than profuse menstrual flow. On the other hand, the impression that decreased thyroid activity results in menorrhagia is a common one among internists, and Means<sup>7</sup> states this to be so in discussing menstrual abnormalities and diseases of the thyroid gland. In the same textbook, however, he quotes the observation of Haines and Mussey that hypomenorrhea is four times more frequent than hypermenorrhea in "subclinical hypothyroidism."

In an effort to determine experimentally the effect of hypothyroidism on menstruation, Engle<sup>8</sup> carried out thyroidectomies on 3 monkeys that had previously had normal menstrual cycles. Amenorrhea occurred in hypothyroid monkeys with intact

it more closely and to evaluate the result of thyroid therapy.

A review and analysis were therefore made of 550 consecutive patients seen in the sterility and

TABLE 1 *Classification of Patients According to Diagnosis and Basal Metabolic Rate*

DIAGNOSIS	BASAL METABOLIC RATE			TOTALS
	NO OF CASES 0 to -10%	NO OF CASES -11 to -20%	NO OF CASES -21 to -30%	
Sterility	11	11	2	24
Hypomenorrhea	9	0	5	14
Hypermenorrhea	2	2	—	4
Dysmenorrhea	1	3	—	4
Habitual abortion	1	3	—	4
Totals	24	20	7	61

endocrine clinic of the Sloane Hospital for Women who had complained of sterility or menstrual abnormalities or both. In an effort to evaluate the effects of thyroid therapy on the symptoms only patients

TABLE 2 *Primary and Secondary Gynecologic Complaints and Results of Treatment with Thyroid*

COMPLAINT	NO OF CASES	COMPLAINT CORRECTED		FULL TERM PREGNANCY		ABORTIONS	
		NO	PERCENTAGE	NO	PERCENTAGE	NO	PERCENTAGE
Sterility							
Primary complaint	24	—	—	10	41.6	1	—
Secondary complaint	9	—	—	—	—	—	—
Totals	33	—	—	10	30.3	1	3.0
Average							
Hypomenorrhea							
Primary complaint	23	16	70.0	—	—	—	—
Secondary complaint	17	—	—	—	—	—	—
Totals	40	16	40.0	—	—	—	—
Average							
Hypermenorrhea							
Primary complaint	4	4	100.0	—	—	—	—
Secondary complaint	1	—	—	—	—	—	—
Totals	5	4	80.0	—	—	—	—
Average							
Dysmenorrhea							
Primary complaint	6	5	83.3	—	—	—	—
Secondary complaint	5	—	—	—	—	—	—
Totals	11	5	45.5	—	—	—	—
Average							
Habitual or threatened abortion							
Primary complaint	4	—	—	4	100.0	—	—
Secondary complaint	3	—	—	—	—	—	—
Totals	7	—	—	4	57.1	—	—
Average							
Total primary complaints	61	39	(63.9)	—	—	—	—
All complaints	106	64	(61.3%)	—	—	—	—

ovaries, normal cyclic menstruation being re-established by thyroid administration.

Since there is some question regarding not only the actual clinical entity of this group of patients who have slightly low basal metabolic rates and menstrual abnormalities but also just what their menstrual abnormalities are, it was decided to review a number of cases from the Sloane Hospital sterility and endocrine clinic in an attempt actually to identify this type of clinical picture, to define

who received thyroid medication were considered in this review. One hundred and fourteen patients, or 20.7 per cent, had received medication in addition to thyroid, so that they could not be considered in the results. Fifty-three of these cases were not followed. Sixty-one patients, or 11 per cent of the original 550, had received thyroid medication exclusively and their progress had been sufficiently observed to warrant accurate conclusions about results. Their classification accord-

ing to diagnoses and basal metabolic rates is presented in Table 1. Serum cholesterol studies were made in 35 of these patients. Of these, only 6 were above 225 mg per 100 cc.

It must be stressed that these patients were actually a selected group in that they were given thyroid medication during their course of investigation and treatment in the clinic. It is therefore assumed that the clinician who saw them believed that thyroid medication was indicated. The great majority of the 550 cases reviewed did not receive thyroid therapy. This is especially significant in the small groups in this series, such as the cases of dys-

menstrual disturbances, that there is a fairly common condition of mild thyroid deficiency, usually known as "subclinical hypothyroidism," that is amenable to thyroid therapy. This condition, which is sort of "twilight zone" between the normal gland and a state of myxedema, is characterized by symptoms suggestive of decreased metabolic activity such as weight gain, lassitude, dry skin, brittle fingernails, coarse hair and, what is most important to gynecologists, menstrual abnormality—decreased menstrual activity in the great majority of cases. Furthermore the basal metabolic

TABLE 3 *Thyroid Therapy in Gynecologic Abnormalities*

SERIES	TOTAL NO OF CASES	STERILITY		TOTAL NO OF CASES	MENSTRUAL ABNORMALITIES			
		NO OF PREGNANCIES	NO OF ABORTIONS		CASES OF HYPOMENORRHEA	CURES	CASES OF HYPERMENORRHEA	CURES
Litzenberg and Carey <sup>2</sup>	52	17 (30%)	2	—	—	—	—	—
Haines and Mussey <sup>4</sup>	—	—	—	74	59	60	15	53
Buxton and Vann	33	13 (39.4%)	3	55	50	62	5	100

menorrhea and habitual abortion. Most patients with similar complaints were treated by other techniques so that the few who fell into the category of thyroid-treated cases are thought to have more significance than their numerical paucity admits.

The results of thyroid therapy are shown in Table 2. It would be incorrect to ascribe all pregnancies and all cures in these different groups to thyroid therapy alone. Certainly, in the cases of sterility there must be a certain percentage of patients who would have become pregnant during the course of investigation without any therapy whatever (3 out of 13 in a recent series of 52 cases of sterility). However, the patients placed on thyroid therapy had all finished their investigation, and the sterility had lasted from fourteen months to ten years.

Of the menstrual abnormalities it is certainly true that spontaneous remissions—or resumption of menstruation in cases of amenorrhea—occur, and undoubtedly a certain percentage of these patients would have spontaneously resumed normal menstruation. Most of them, however, had received therapy of various sorts elsewhere or in our clinic without success before receiving thyroid.

Table 3 compares our results with those reported elsewhere. It will be seen that for the most part the figures are fairly comparable.

### DISCUSSION

The cases presented add corroborative evidence to the impression long held by physicians treating

rates and blood cholesterol determinations are, for the most part, not significantly abnormal.

Not the least of the significant relations between possible thyroid deficiency and this type of case is the appreciable number of patients improved by thyroid therapy. Not only in this series but also in others previously reported, there has been a fair percentage of cures in patients who received thyroid therapy only. This is especially true in the series of cases of sterility.

It seems legitimate to conclude, therefore, that thyroid therapy is advantageous in many cases of abnormal menstruation and sterility even in the presence of fairly normal basal metabolic rates. These patients do not have signs of myxedema and tolerate fairly large dosages of thyroid.

### REFERENCES

- 1 Marine D. Present status of functions of thyroid gland. *Physiol Rev* 2:521-551 1922.
- 2 Litzenberg J C. Relation of basal metabolism to sterility: preliminary report. *Am J Obst & Gynec* 12:705-709 1926.
- 3 Litzenberg J C and Carey J B. Relation of basal metabolism to gestation. *Am J Obst & Gynec* 17:550-552 1929.
- 4 Haines S F and Mussey R D. Certain menstrual disturbances associated with low basal metabolic rates without myxedema. *J A M A* 105:557-560 1935.
- 5 Mason L W. Hypothyroidism and its relation to gynecologic problems. *Tr Am Soc for Study of Sterility* 1:18-22 1946.
- 6 Hamblen E C, Pullen R L, and Cuyler W K. Clinical studies on thyrogonadal correlates: basal metabolic rates and endometrial responses. *J Clin Endocrinol* 1:523-527 1941.
- 7 Means J H. *The Thyroid and Its Diseases*. 602 pp. Philadelphia: J B Lippincott Co. 1937. P. 92.
- 8 Engle E T. Effect of hypothyroidism on menstruation in adult rhesus monkeys. *J Biol & Med* 17:59-66 1944.

## TRAUMATIC PARTIAL LOBECTOMY FROM GUNSHOT WOUND\*

## Report of a Case with Recovery and Personality Change

EDGAR M. HOLMES, M.D.†

BOSTON

IN THE following case the patient received a head injury similar to that in the famous crowbar-skull case, which has been written up in the past and the skull of which is on exhibition at the Harvard Medical School Museum. In that case, a miner while tamping a hole in the ground filled with blasting powder accidentally ignited the blast, which created a projectile of the tamping crowbar. The projectile entered the head just lateral to the angle of the left ramus of the mandible, traveling

consisting of increased profanity, obstinacy and狠fulness. In the last year of his life, the patient developed convulsions followed by others and death at thirty-eight years of age.

## CASE REPORT

A 45-year-old woman had a pyramiding depression, which terminated in a suicidal attempt. To execute this, she held a 12-gauge shotgun under her chin and pulled the trigger. She was found in an unconscious state with a hole of entry in the midline of her chin about 1.5 cm. behind the symphysis



FIGURE 1 Appearance of the Patient on Admission

A shows an area in the forehead covered by irregular epithelium beneath which there is scar tissue without dura, the brain being directly beneath. There is moderate loss of forehead skin associated with retraction of the remaining tissue. (Note the displacement of the left ascending process of the superior maxilla and the lacrimal bone with a slightly visible divergence of the pupils.) The nasal bones are absent. There is a hole in the nose. B demonstrates a point of entry in the soft tissues of the chin that has closed itself. In the palate is visible the hole that was shot out. On the forehead, the depression can be seen.

medially and superiorly to find its exit near the midline, where the parietal and frontal bones meet. This man, after a stormy convalescence lived for thirteen years and was able to go about the country as a living exhibit of this most unusual accident and injury. The only residual lesion that was noticeable to others was a changed personality.

\*From the Department of Plastic Surgery, Massachusetts Eye and Ear Infirmary.

†Assistant professor of otolaryngology, Boston University School of Medicine; instructor in otology, Harvard Medical School; associate surgeon for plastic operations, Massachusetts Eye and Ear Infirmary; chief of otolaryngology, Newton Hospital.

The hole carried up through the tongue, causing torn lacerations together with areas of complete loss of substance of that organ. It continued through the hard palate, the perpendicular plate of the ethmoid, both nasal bones, the frontal sinuses and part of the frontal bone as far as the hairline (Fig. 1). Some of the forehead scalp was lost. After débridement and the use of penicillin, the patient gradually recovered.

On admission to the Massachusetts Eye and Ear Infirmary, examination revealed that the frontal defect had granulated and epithelized over and was pulsating from the underlying brain. The forehead flaps had retracted laterally. A scar left in the soft tissue of the chin had closed over the floor of the mouth. The tongue had three points, and as a result of the laceration and scarring, it was bound down and immo-

bile. It was with much difficulty that the patient could talk or eat, since her tongue could not be pulled up to the roof of her mouth. The hole in the palate remained patent and

A psychiatrist believed that the patient was perfectly oriented, without a psychosis, and that she had probably performed a partial anterior lobectomy, which had cured her pyramiding depression. Her vision was within normal limits; there had been no change after the accident other than a small tear in the right choroid.

X-ray study revealed the losses mentioned above. In addition, there were some pellets that had sprayed into the brain, one going back near the occiput (Fig. 2).

The corrective problems in this case were sevenfold: the brain needed protection, the hole into the nose should be closed, the hole in the palate should be closed, the function of her tongue would improve if the fragments were joined into one and the tongue freed so that the patient could talk



FIGURE 2. Anteroposterior View of the Skull, Showing the Loss of the Frontal Sinus and Part of the Frontal Bone. Note the dispersed, small, lead shot.

round but was closed by an upper plate. The membrane had healed over the anterior and posterior remaining parts of the septum, but there was a hole where the nasal bones should

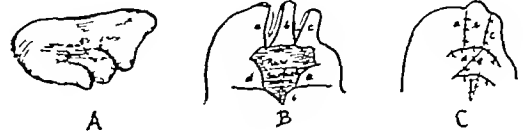


FIGURE 4. Correction of the Lacerated, Bound-Down Tongue. A represents an anterior top view of the tongue (Note the central scarred, bound down and immobile tongue with the three prongs of tissue — much of the tongue was shot away). B is a diagram of the under surface of the tongue, revealing the incisions and the raw area just after removal of much of the scar tissue and freeing of the tongue. C shows the method of closure of the under surface.

and eat with greater ease, the displaced ascending process of the left superior maxilla, the lacrimal bone and the ethmoid should be brought back in the midline in an attempt to enlarge the orbit and thus permit the eye to have a normal range of excursion and probably lessen some of the diplopia. The contour of the nose and forehead would be improved if brought out to their original level, and the left lacrimal sac must be opened and drained into the nose to correct tearing.

All operative procedures were conducted under local anesthesia except the one in which bone grafting was done, and this was performed with a general anesthetic (nitrous oxide, oxygen and ether).

The first stage consisted of exposure of the displaced left superior maxilla and ethmoid bones, which were then freed and placed back into normal position. At the same time,

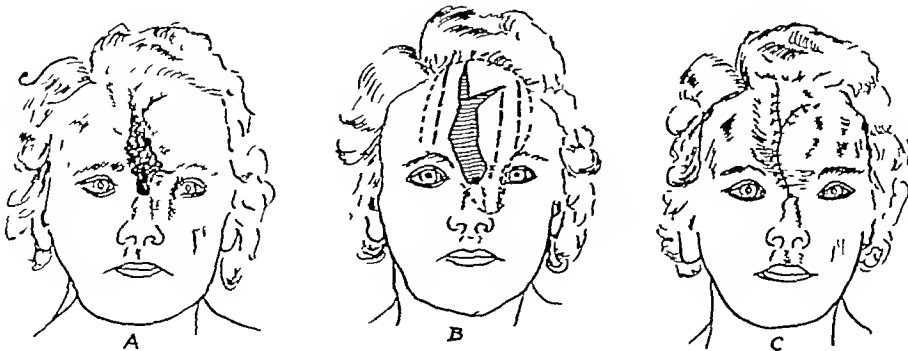


FIGURE 3. Steps in the First Operation. A shows the deformity. B demonstrates the incision (solid line), the extent of undermining (short dotted line), and the incision through the aponeurosis (long dotted line). C shows the method of closure.

have been, with a depression to the level of the inner canthus. The left ascending process, lacrimal and ethmoid bones were pushed laterally, causing a marked diplopia (Fig. 1a).

The forehead wound was closed, the epidermis that had grown over the brain being removed and the brain being covered with forehead flaps, which were freed so that they could

approximate. The opening in the nose was partially closed by direct approximation of the skin edges (Fig. 3). A few days later, the scarred and bound-down tongue was mobilized and the three points of the lacerated tongue were brought together. The scar on the undersurface was freed.

The diplopia improved objectively, but the patient still has double vision though it is less pronounced. She also continued after a couple of months, to have tearing and some infection in her left tear sac, so that a tear-sac operation was performed. As expected, there were no landmarks present,

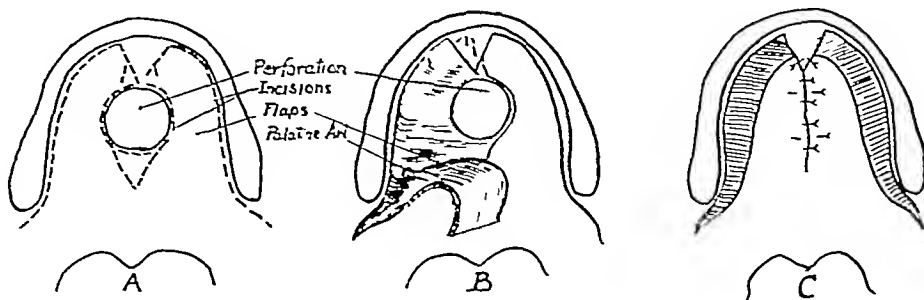


FIGURE 5 Closure of the Palatal Defect

A shows the lines of the incision (heavy dotted line). In B one palatal flap has been raised, and the palatine artery exposed and stretched from its caral. C demonstrates the method of closure.

and corrected by a "Z" plastic. This enabled the patient to talk and eat much more easily (Fig. 4). At a later stage, the hole in the palate was closed, two flaps being utilized, as in a case of cleft palate (Fig. 5). This further improved speech and facility in eating because the mouth was separated from the nose. The patient still had the hole through the dorsum

since the area of the lacrimal bone and sac were comminuted and filled with fragments of bone, callus and scarred tissue. What was left of the tear sac was freed, and this was opened and drained into the nose. Her tearing is less and the infection has gone.



FIGURE 6 The Postoperative Result

The forehead has been brought out to a normal contour. There is still some irregularity of the skin. The ascending processes and lacrimal bone and ethmoid are in place, and the nose is elevated. (Note the restoration of the nasal bone.)

of her nose and the depression caused by the loss of frontal and nasal bones. This condition was corrected by a bone graft taken from the ilium. It was unnecessary to employ skin grafting to obtain skin for the region of the glabella and the nasal dorsum (Fig. 6).

The patient is most appreciative of all that has been done for her and has resumed her place as an active member in her community.

330 Dartmouth Street

## INFECTIOUS MONONUCLEOSIS WITH PSYCHOSIS\*

## Report of a Case

R W RAYMOND, MD,† AND R L WILLIAMS, MD‡

ALBANY, NEW YORK

**I**NVOLVEMENT of the central nervous system in infectious mononucleosis has been reported by a number of authors since the patients with meningitis described in 1931 by Johansen<sup>1</sup> and by Epstein and Dameshek.<sup>2</sup> However, cases of infectious mononucleosis associated with psychosis have not appeared up to the present time in the literature to our knowledge. Many cases of meningitis and peripheral-nerve palsies, occurring separately or together, have been reported.<sup>3-12</sup> Bernstein's<sup>13</sup> monograph summarized most of these early reports up to 1940. In 1941, while publishing the details of a case of meningeal involvement, together with ataxia, catatonia and slurred speech, Landes, Reich and Perlow<sup>14</sup> reviewed the literature with particular regard to central-nervous-system manifestations. Since that time cases of a similar nature have been added to the literature.<sup>15-25</sup> All these patients had serous meningeal findings or some other neurologic manifestation such as paralyses, convulsions or reflex changes. At times the picture simulated a Guillain-Barré syndrome.

Because the condition is rarely fatal, only a few cases of infectious mononucleosis have come to autopsy. Particular examples are those reported by Ziegler,<sup>26</sup> Allen and Kellner<sup>27</sup> and Peters et al.<sup>28</sup> All pointed out a nonspecific but definite involvement of the central nervous system with increased vascular reaction of the pia arachnoid, petechial hemorrhages in the brain and degenerative changes of the Purkinje cells. The literature since Bernstein's article has been summarized twice by Bethell et al.<sup>29, 30</sup> In reporting 2 additional cases Slade<sup>31</sup> completed a review of the literature up to 1946, which dealt with central-nervous-system involvement in infectious mononucleosis. In none of these reports can one find a case of psychosis associated with acute infectious mononucleosis.

The following case report is that of a psychotic episode resembling schizophrenia that occurred during the course of typical acute infectious mononucleosis and subsided during the regression of the disease.

## CASE REPORT

E T, a 25-year-old married college student was admitted to the Albany Hospital on December 11, 1947. He was placed on the psychiatric ward because he had become unmanageable in a neighboring hospital. The history obtained from his family revealed that he had developed general malaise,

anorexia, fatigue, headache, a temperature of 102°F and sweating, but no chills, about 16 days prior to admission. Entering the referring hospital on December 1, he had complained that his symptoms had grown progressively worse and that he had developed painful lymph nodes in his neck with some abdominal discomfort. At that time, physical examination revealed a well developed and well nourished man who was alert and co-operative with a blood pressure of 120/70, a temperature of 98.6°F and respirations of 20. Positive physical findings included injected scleras, a coated tongue, bilateral cervical lymphadenopathy in the posterior chain and several small inguinal lymph nodes. The rest of the physical examination was negative. Examination of the blood on December 1 showed a red-cell count of 4,800,000 with a hemoglobin of 90 per cent (Sahli), and a white-cell count of 4500, with 1 per cent basophils, 3 per cent eosinophils, 15 per cent stab forms, 20 per cent segmented neutrophils, 51 per cent lymphocytes and 4 per cent monocytes. Fifty per cent of the lymphocytes appeared large and abnormal. The urine was normal. On the 2nd day, heterophil-antibody agglutination was reported positive in a dilution of 1:40. Also a Widal test was reported positive in a dilution of 1:100 (the patient was a World War II veteran). No brucella agglutination was obtained.

On the fourth hospital day, repeated examination of the blood disclosed a red-cell count of 5,200,000, with a hemoglobin of 108 per cent (Sahli), and a white-cell count of 5900 with 2 per cent basophils, 1 per cent eosinophils, 10 per cent stab forms, 19 per cent segmented neutrophils, 61 per cent lymphocytes and 4 per cent monocytes. There were 2 young lymphocytes, and on this day heterophil-antibody agglutination was reported positive in a dilution of 1:60. On the 5th day the agglutination was positive in a dilution of 1:320. Examination of the spinal fluid showed a total protein of 15 mg per 100 cc. An x-ray film of the chest on admission revealed an area of increased density in the region of the hilus that was consistent with peribronchial infiltration, but not suggestive of pneumonia or tuberculosis. The course of the disease from time of entry on December 1 until transfer to the Albany Hospital was reported as most disturbing mentally. Review of the record showed that the patient was confused much of the time from the day of admission. The nurses reported that he became more irritable, often was overtalkative and showed "flight of ideas" in speech. He was demanding at times and on one occasion attempted to walk out of the hospital. He became belligerent, impulsive and unpredictable in his behavior, and once he threw a glass of water in the nurse's face. He received penicillin and sedatives during his stay, but as time passed, he became delusional, his speech was rambling, and he talked of his sex life much of the time. Because of his behavior, he was transferred to the Albany Hospital.

Physical examination was only slightly different from that previously reported. There was a papuloerythematous rash on the back. The pharynx was injected and there were dry patchy areas of denuded epithelium with a white exudate visible. The cervical lymph nodes were still enlarged but not tender. The remainder of the physical and neurologic examinations were completely within normal limits. The patient's mental status was definitely abnormal. He was overactive and overtalkative, impulsive and unpredictable. His thinking was rambling and irrelevant. He seemed preoccupied with thoughts of his family, childhood and health. No definite delusions or hallucinations were noted at this time, but his mood was often labile, and his affect seemed inappropriate. He was well oriented in time, place and person, but his insight and judgment were lacking.

The temperature was 101°F.

Urinalysis demonstrated a reaction of pH 6.5, a specific gravity of 1.020 and a trace of albumin. There was no sugar.

\*From the Department of Medicine and the Department of Neurology and Psychiatry, Albany Hospital.

†Assistant resident in medicine, Albany Hospital.

‡Assistant resident in neurology and psychiatry, Albany Hospital.

acetone or urobilinogen, and microscopical examination was negative. Examination of the blood showed a red-cell count of 4,320,000, with a hemoglobin of 108 per cent (Sahli), and a white-cell count of 16,050, with 1 per cent stab forms, 24 per cent segmented neutrophils and 75 per cent lymphocytes. Many of the lymphocytes showed large amounts of pale-blue cytoplasm, with large oval nucleoli. The blood sugar was 91 mg, and the blood nonprotein nitrogen 35 mg per 100 cc. The blood Wassermann test was negative. A heterophil-antibody agglutination was positive in a dilution of 1:1792. The spinal fluid was clear and showed no cells, the total protein was 42 mg, the chloride 760 mg, and the

DISCUSSION

There was considerable controversy regarding whether this was a case of toxic psychosis associated with infectious mononucleosis, or whether there was an actual schizophrenia precipitated by the febrile illness. The diagnosis of infectious mononucleosis was certain in view of the fever, enlarged lymph nodes, abnormal lymphocytes in increased

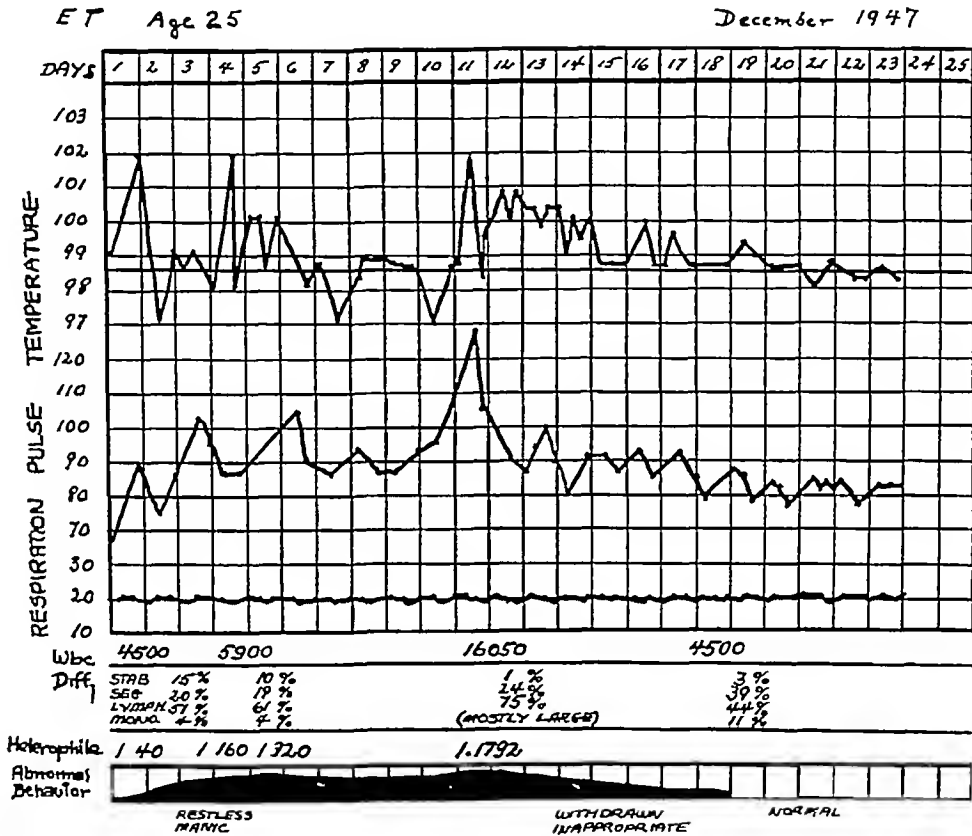


FIGURE 1 Clinical Course

sugar 66 mg per 100 cc. The spinal-fluid Wassermann test was negative, as was the colloidal-gold test.

The patient was treated symptomatically with adequate diet, fluids and sedatives. On several occasions he showed definite evidence of auditory and visual hallucinations and delusions. His behavior alternated from overactivity and excitement to withdrawal and loss of contact with his environment. The picture resembled an acute schizophrenic episode. On December 19 there was a dramatic change in his mental status. He became alert and co-operative. There was none of the overactivity or overtalkativeness. The delusions and hallucinations had completely disappeared. The temperature fell to normal on December 20 and 3 days later he was well enough to be discharged. The lymph nodes were still moderately enlarged, and the spleen was palpable three fingerbreadths below the costal margin. He was seen later for a follow-up examination, and no abnormality was found psychiatrically. The symptoms of infectious mononucleosis had subsided except for some fatigue. He went back to his college career and is doing very well leading an active social as well as scholastic life, according to a report 3 months later. The clinical course is demonstrated in Figure 1.

number and the rising titer of the heterophil-antibody agglutination. The absence of any neurologic manifestations, the failure to demonstrate pathologic changes in the cerebrospinal fluid and the dramatic resolution of the marked psychotic episode suggested that a toxic psychosis was the best explanation of the syndrome.

SUMMARY

The literature relating to central-nervous-system involvement in infectious mononucleosis is briefly reviewed and a case of this disease with a toxic psychosis resembling schizophrenia presented.

We are indebted to Dr. S. Eugene Barrera, neurologist and psychiatrist-in-chief, and to Dr. L. Whittington Gorham, physician-in-chief, Albany Hospital, for permission to report this case.

## REFERENCES

- 1 Johansen A H Serous meningitis and infectious mononucleosis *Acta med Scandinav* 76 269 272 1931
- 2 Epstein S H and Dameshek W Involvement of central nervous system in case of glandular fever *New Eng J Med* 205 1238 1241 1931
- 3 Marchal G Bargeton and Mahoudeau-Campoyer Angine a monocytes avec biopsie *Sang* 7 431-436 1933
- 4 Fledelius M Augenmuskellähmung als Komplikation der Mononucleosis infectiosa *Acta Ophth* 13 150-152 1935
- 5 Sucher A and Schwarz E Lymphatische Reaktion und Encephalomeningitis *Wien klin Wchnschr* 49 1417-1424 1936
- 6 Davidsohn I Serologic diagnosis of infectious mononucleosis *J A M A* 108 289 295 1937
- 7 Gsell O Meningitis serosa bei Pfeifferschem Drüsenfieber (mononucleosis infectiosa) *Deutsche med Wchnschr* 63 1759-1762 1937
- 8 Huber W Beitrag zur Meningitis serosa bei Pfeifferschem Drüsenfieber *Schweiz. med Wchnschr* 68 892 1938
- 9 Schmidt, V. and Nyfeldt A Über Mononucleosis infectiosa und Meningoencephalitis *Acta oto-laryng* 26 680-688 1938
- 10 Marshall E A Infectious mononucleosis *Am J Clin Path* 9 298-305 1939
- 11 Pietzonka H Meningitis serosa bei Pfeifferschem Drüsenfieber *Deutsches Arch f klin Med* 185 153-163 1939
- 12 Thomsen S and Vimtrup B Six fatal cases of infectious mononucleosis complicated by central respiratory paralysis. *Nord med (Hospitalsind)* 4 3295 3299 1939
- 13 Bernstein A Infectious mononucleosis *Medicine* 19 85-159 1940
- 14 Landes R. Reich, J P. and Perlow S Central nervous system manifestations of infectious mononucleosis report of case *J A M A* 116 2482 2484 1941
- 15 Thelander H E. and Shaw E. B Infectious mononucleosis with special reference to cerebral complications *Am J Dis Child* 61 1131-1145 1941
- 16 Leavell B S and McNeel, J O Infectious mononucleosis unusual manifestations *Virginia M Monthly* 69 180-187 1942
- 17 Richardson J S Serratus magnus palsy *Lancet* 1 618 1942
- 18 Zohman B L. and Silverman E. G Infectious mononucleosis and encephalomyelitis *Ann Int Med* 16 1233 1239 1942
- 19 Hiller R I and Fox M J Infectious neuritis associated with infectious mononucleosis *Marquette M Rev* 7 152 154 1943
- 20 Saksena H C. Paralysis of serratus anterior following glandular fever *Brit M J* 2 267 1943
- 21 Shafar J and Weir J C R Meningeal reaction in case of glandular fever *Brit M J* 1 218 1943
- 22 Coogan T J Martinson D L. and Matthews W H. Neurological symptoms of infectious mononucleosis *Illness M J* 87 296-300 1945
- 23 Gelheiter S Acute infectious mononucleosis complicated by encephalomyelitis report of case. *Lancet* 2 753 1946
- 24 Wechsler H F Rosenblum, A H and Sills C. T Infectious mononucleosis report of epidemic in army post. *Ann. Int Med.* 25 216-265 1946.
- 25 Field W W Infectious mononucleosis with severe central nervous involvement. *Am J Med* 4 154-157 1948
- 26 Ziegler E. E. Infectious mononucleosis report of fatal case with autopsy *Arch Path* 37 196-201 1944
- 27 Allen F H Jr and Kellner A Infectious mononucleosis autopsy report. *Am J Path.* 23 463-477 1947
- 28 Peters, C. H Wideman A. Blumberg A. and Rucker W A. Jr. Neurologic manifestations of infectious mononucleosis with special reference to Guillain-Barre syndrome *Arch Int. Med.* 80 366-373 1947
- 29 Bethell F H Sturgis C C., Hettug R. A. and Mallory O T. Jr. Blood review of recent literature. *Arch. Int Med.* 69 1031 1126 1942
- 30 Bethell, F H., Sturgis C. C. Rundles R. W. and Meyers M. C. Blood review of recent literature. *Arch. Int Med.* 77 80 119 1946
- 31 Slade, J deR. Involvement of central nervous system in infectious mononucleosis report of two cases *New Eng J Med* 234 753 757 1946

## MEDICAL PROGRESS

## BLOOD AND ITS DERIVATIVES\*

SAM T. GIBSON, M.D.†

BOSTON

SINCE prehistoric man first noticed the red fluid that issued from his wounds, much thought and energy have been expended toward the conservation, investigation and utilization of this life-symbolizing liquid—blood. The past decade has witnessed great advances along these lines impelled by the demands of the recent war. To summarize all aspects of this important subject, however, would involve a treatise on the major branches of medicine. This review is restricted to the following topics: whole blood—preservation, use, reactions, salvage of erythrocyte residues, physiology and procurement, plasma—homologous serum hepatitis and clinical use, plasma fractionation—methods, use of fractions and mechanism of action, blood substitutes, protein therapy—metabolism, administration and reactions, and laboratory methods—amino acids, total protein and protein fractions. One major subject—the Rh factor—is reserved for a separate review.<sup>1</sup>

It is intended that this will supplement previous reviews on blood and plasma proteins appearing

in the *Journal* since 1941.<sup>2-5</sup> These form a helpful background for the following general discussion. More detailed information can be obtained from many excellent reviews now available.<sup>6-18</sup>

## BLOOD

## Preservation

World War I initiated the use of blood transfusions on a large scale. Until World War II, however, technics changed little, and blood was given directly through a variety of devices or indirectly, sodium citrate being used as an anticoagulant.<sup>19</sup> The storage period of five to seven days permitted by this system was satisfactory for most hospitals, very few of which had banks, but it was totally inadequate for military use. Worldwide problems of logistics demanded a longer dating period and more stability. This difficulty was resolved early in the war by the development and use of dried plasma, dried serum and concentrated human serum albumin. Although these agents were extremely useful, increasing medical experience showed that no substitute approached the efficacy of blood in the severely wounded.<sup>6</sup> Accordingly, in 1944

\*From the Medical Clinic, Peter Bent Brigham Hospital and the Department of Medicine, Harvard Medical School.

†Milton Research Fellow in Medicine, Harvard Medical School, assistant in medicine, Peter Bent Brigham Hospital.

the Committee on Medical Research of the Office of Scientific Research and Development and the Army and Navy medical departments took up again the problem of preserving and shipping whole blood. The findings of the six major groups of investigators recently appeared simultaneously.<sup>20-31</sup>

Studying the effects of variations in reaction, temperature, buffers, concentration of glucose and volume of diluent, it was generally agreed that maximal preservation followed the use of a slightly acid citrate-dextrose solution,\* which was cooled to 4 to 10°C before the blood was collected and maintained there continuously thereafter. A formula utilizing these principles had already been proposed by Loutit and Mollison.<sup>22</sup> Using erythrocytes tagged with radioactive iron ( $Fe^{55}$  and  $Fe^{59}$ ) by feeding isotopic iron to donors, J. G. Gibson et al.<sup>20, 21</sup> were able to show that when blood was drawn as stated above, maintained at 4 to 10°C for twenty-one days and then transfused, 70 to 80 per cent of the transfused cells were viable at least five days after transfusion. To achieve the same survival under comparable conditions, blood in a neutral citrate glucose solution (diluent volume equal to blood volume) could be stored only fifteen days, and blood in sodium citrate could be stored only one to four days.<sup>25</sup> If the temperature rises above 15°C even once during storage, subsequent cooling fails to retard the rapid rate of deterioration thus initiated,<sup>22, 23</sup> though spontaneous hemolysis may not occur before transfusion. With 80 per cent survival, all the nonviable erythrocytes are removed from the circulation within twenty-four hours (most within two hours).<sup>22, 23</sup> All the iron from the nonvital cells is utilized to make new hemoglobin. Utilization is about twenty times that of equivalent amounts of iron given by mouth.

Although some thought a 7:3 blood diluent ratio optimal,<sup>26</sup> the practical aspects of smaller diluent volume led to the development of an improved ACD formula using 75 cc diluent for 500 cc of blood,† and achieving equal preservation. Strumia et al.<sup>31</sup> report the satisfactory routine hospital use of 5000 bottles of blood preserved with this formula.

The same investigators,<sup>21, 26, 30</sup> studying the preservation of erythrocytes discarded from plasma preparation, agreed that the best survival resulted when blood was collected in cooled bottles and immediately separated, and the cells resuspended in ACD solution if collected in sodium citrate, or stored undiluted if collected in ACD and diluted with a little hypertonic saline solution just prior to administration, 80 per cent survival was possible after ten to fifteen days' storage by this method.

\* Acid-citrate-dextrose solution (ACD-1) formula: sodium citrate  $Na_2C_6H_5O_7 \cdot 2H_2O$  — 1.33 gm. per 100 cc. citric acid ( $C_6H_8O_7$ ) — 0.47 gm. per 100 cc. dextrose (anhydrous) — 3.00 gm. per 100 cc. 25 cc. of the solution is used for each 100 cc. of blood.

† The revised formula of ACD-3 is as follows:  $Na_2C_6H_5O_7 \cdot 2H_2O$ , 1.60 gm. per 100 cc.  $C_6H_8O_7$ , 0.56 gm. per 100 cc. and dextrose (anhydrous), 1.50 gm. per 100 cc. 15 cc. of ACD-3 is used for each 100 cc. of blood.

## Use

Whole blood was originally transfused to replace that lost by hemorrhage.<sup>32</sup> It was also found to be effective in traumatic shock even when external blood loss had been minimal. This is to be expected from the currently accepted theories that the shock is a condition of diminished cardiac output depleted circulating blood volume and peripheral vascular collapse.<sup>7, 8, 11</sup> Evidence for and against a humoral or neurogenic origin, or both, is still confusing. Severe shock, however, often fails to respond to massive transfusions, thereby casting some doubt on the theory that deranged circulatory dynamics was the major physiopathology of shock. Seligman et al.<sup>24</sup> have sought to incriminate the liver. Perfusion of the liver by cross circulation with a donor dog (femoral artery to splenic vein) saved 8 of 9 dogs in standardized "irreversible" hemorrhagic shock, whereas femoral-artery to femoral-vein perfusion saved only 2 of 9 controls.

Seeking to make blood more effective, others have tried intra-arterial or intracardiac transfusions. Glasser and Page<sup>25</sup> revived 9 of 35 dogs kept in hemorrhagic shock for two and a quarter hours, then bled until pulse and respiration ceased and finally given intra-arterial blood and artificial respiration. Lefebure,<sup>36</sup> in France, was quite successful with intracardiac infusions of oxygenated blood in shocked cats or oxygenated intracardiac autotransfusions in drowned and electrocuted cats, drawing blood from the femoral vein, oxygenating it and giving it into the heart. He records the rumor that, using this method, Vladimir Negoski in Russia saved 12 of 51 soldiers considered otherwise lost. Iokhveds<sup>37</sup> reports 2 such cases, 1 of which was saved. Kay and Hacker<sup>38</sup> gave oxygenated blood into the ascending aorta and believed that a patient exsanguinated from a stabbed right internal mammary artery was saved thereby.

Two uses of transfusion, apart from shock treatment, have been featured recently. European workers<sup>39</sup> seem to believe that frequent small transfusions hasten convalescence from rheumatoid arthritis faster than the mere replacement of hemoglobin alone. Barsi<sup>40</sup> thinks this particularly effective if the donors are pregnant.

The most spectacular new use for blood has been the substitution therapy for erythroblastotic infants, reported by Wallerstein<sup>41, 42</sup> and others.<sup>43</sup> Since the newborn infant's total blood volume is only 250 cc, it is possible to infuse Rh— blood and withdraw the patient's blood simultaneously from a different vein for sixty minutes, leaving at the end only 36.7 per cent of the infant's blood in its circulation. Alternate removal and replacement of 50 cc of blood five times reduces the residual blood to 32 per cent and the addition of 100 cc of Rh— blood reduces this further to 25 per cent, thereby providing enough blood to live on until all the

circulating Rh agglutinins have been used up. Seven of 9 infants so treated were in satisfactory condition six months later. Wallerstein takes such infants off breast feedings, since Witebsky<sup>44</sup> has shown that it is possible to excrete Rh agglutinins in milk. Cathie,<sup>45</sup> however, denies that this is clinically significant.

Almost all blood is now given indirectly. Only one new device for direct transfusion has been described recently, and it is from Australia.<sup>46</sup>

### Reactions

The usual reactions to transfusions — pyrogenic and hemolytic — are now considerably less frequent owing to more careful preparation of equipment, better crossmatching and the use of more potent grouping serums. Several other types of reactions merit closer attention.

Although *homologous serum hepatitis* is much more common after plasma than blood transfusions, it does occur with the latter. Two fatal cases are reported<sup>47, 48</sup> in infants fifteen to sixteen weeks old who had received three blood transfusions each sixty to one hundred days before, and a fatal case in an adult is reported from Argentina.<sup>49</sup> The most complete follow-up survey yet done included 1050 patients receiving blood or plasma, or both, and 891 receiving blood alone<sup>50</sup>; 73 per cent of the first group and none of the second were considered to have had hepatitis. Nevertheless, no one should be used as a donor who has had jaundice, been exposed to jaundice or received any injections of blood or its derivatives in the preceding six months.

A case of transfusion-induced quartan malaria is reported by Fischer and York<sup>51</sup> from Providence, Rhode Island, occurring in a native, unexposed New Englander receiving three transfusions from donors who had had malaria in early life but had been symptom-free and living outside an endemic area for thirty, thirty-six and forty-two years respectively. These authors report from the literature 12 other cases of transfusion malaria in Massachusetts between 1929 and 1944, 10 of the donors having previously lived in endemic areas, and 5 of these having been symptom-free more than twelve years. The bloods in this case had been stored at 6°C for five, seven and twelve days. Coggeshall<sup>52</sup> also reports transmission from eight-day-old blood. It is important, then, to reject as donors all people who have ever had malaria, and if a would-be donor has lived in an endemic area or taken suppressive therapy, to wait at least two years<sup>52</sup> before use as a donor, and then only if no symptoms have developed. Even this procedure is not entirely safe, for Rogers<sup>53</sup> has recently reported a case of quartan malaria appearing in an eighteen-year-old London girl

eight weeks after receiving one ante-partum transfusion from a donor who had lived five months in a malarious area seven years before but had never shown any clinical symptoms of infection.

An interesting observation on the use of the *universal donor* — Group O — was made during J. G. Gibson's<sup>54</sup> cell-survival studies. A Group A recipient given radioactively tagged O blood had 800 cc of his own blood destroyed by the high anti-A agglutinin content of the donated blood. It was possible to show that the recipient's cells were the ones destroyed because there was no diminution in the number of tagged donated cells. A similar reaction, but with fatal outcome, is reported from England<sup>54</sup> in which a thirty-eight-year-old Group A man with a pistol shot wound received three transfusions of O blood, with severe hemolytic reaction and death from lower-nephron nephrosis. The donors were found to have anti-A agglutinin titers of 1 256, 1 512 and 1 4096. In the Red Cross, Army and Navy whole-blood program, 205,907 bottles of O blood were sent to the European theater and 181,555 bottles to the Pacific.<sup>55</sup> All blood had anti-A and anti-B titrations done, and the 20 per cent with the highest values were reserved for use in O recipients. The remaining 80 per cent had titers well below 1 64. Although a fair amount of pigment nephropathy and lower-nephron nephrosis was seen in North Africa and Italy — Snyder<sup>56</sup> reports 68 fatal cases in Fifth Army Hospitals in 1944-1945 — it was believed that this might well have been due to prolonged shock of severe degree before resuscitation rather than to the O blood. Perhaps this is true, since an analysis of 21,296 reports (part of the 171,564 bottles of O blood administered in the Pacific) failed to show any case with similar lesions.<sup>57</sup> (The total reaction rate in this series was only 3.1 per cent.) If O blood is to be used for universal transfusion, it should have an anti-A and anti-B agglutinin titer of 1 64 or less, or Witebsky's<sup>58</sup> A and B substances\* should be added before transfusion.

The *anuria* following hemolytic transfusion reactions has been treated<sup>59</sup> by the use of the artificial kidneys of Kolff<sup>60, 61</sup> and Murray<sup>62</sup> and the peritoneal irrigation of Frank, Seligman and Fine.<sup>63</sup> It is not yet possible to pass judgment on their effectiveness.

In the best Gallic tradition, Hustin and Rémy<sup>64</sup> studied transfusion-reaction rates in relation to sex. The over-all rate of 9.2 per cent for 864 transfusions given to 425 men and 439 women when broken down showed only 5.3 per cent reactions when donor and recipient were both

\*These are complex carbohydrate like compounds free from protein that seem to play an important part in the composition of isoagglutinogens and combine with isoagglutinins rendering them ineffective. Commercial preparations are obtained from pepsin, mucin, peptone, gastric juice, hog stomach and so forth.

men, and 17.3 per cent when both were women. When all donors were men the rate was 7.2 per cent, and when the sexes were mixed (man to woman or vice versa) the rate remained 7.7 per cent. The authors highly recommended the last procedure.

### *Salvage of Erythrocyte Residues*

Apart from a limited use of erythrocyte transfusions in anemia,<sup>65</sup> valuable for their small volume, little progress has been made toward salvaging the large quantity of erythrocytes accumulating from a plasma or plasma-fractionation program. Early interest in red-cell pastes<sup>66</sup> or dried preparations as stimulants for wound healing has waned and is now reported chiefly from Europe.<sup>67, 68</sup>

Van Slyke and his associates<sup>69-71</sup> have reported their experiences with the preparation and use of dried hemoglobin for transfusions. Following earlier work,<sup>69</sup> they evolved the following method. Cells are laked with distilled water, stroma precipitated by bringing the reaction to pH 5.7, most of the potassium removed by exchanging for the sodium of sodium zeolite, zeolite and stroma removed by centrifuging, physiologic concentration and reaction achieved through the addition of sodium chloride and sodium bicarbonate, and sterility obtained by Seitz filtration. This gives a solution of 95 to 98 per cent hemoglobin in the active form with no conversion to methemoglobin in solutions kept two and a half months at 4°C. If 99.7 per cent deoxygenated, it is readily lyophilized without developing methemoglobin. This material stored in vacuum retains all its oxygen-binding properties for one hundred and eighty days at 4° to 30°C, ninety-two days at 38°C and seven days at 56°C. After restoration in a vacuum, no methemoglobin is formed, and the material can then be kept in solution with impunity.

A 7 per cent hemoglobin solution was quite satisfactory for treating hemorrhagic shock in dogs.<sup>71</sup> A transitory depression in urea clearance in some of the dogs following hemoglobin treatment has led the Van Slyke group to recommend that hemoglobin not be used clinically until the significance of this is clarified. Since most reactions following hemoglobin administration have been shown to be due to methemoglobin<sup>72, 73</sup> and since this preparation contains practically no methemoglobin, stroma or lipids, it is quite possible that a safe, effective hemoglobin solution can soon be prepared.

Strumia et al.<sup>74, 75</sup> sought to avoid the dangers of methemoglobin and perfected a method for the preparation of modified globin. This is a moderately homogeneous preparation with a slightly asymmetric molecule weighing approximately 34,000<sup>74</sup> and having colloidal and nutritional properties quite similar to those of serum albumin. They concluded from studies on 7 surgical patients that globin could replace plasma in supplying protein

needs.<sup>76</sup> The "doubly depleted" dogs (anemic and hypoproteinemic) of Robscheit-Robbins and her co-workers<sup>77</sup> used this human globin to form hemoglobin and plasma proteins though dog globin was better tolerated.

### *Physiology*

The physiologic tagging of erythrocytes through the use of radioactive iron enabled investigators to study the *erythrocyte life cycle* in vivo as well as in vitro. The evidence from transfusion-survival studies<sup>21</sup> of a life cycle of one hundred to one hundred and twenty days (approximately 1 per cent per day disappearance) taken with the earlier results of Ashby and Wearn<sup>78</sup> using nonagglutinable cell technics, and Hawkins and Whipple,<sup>79</sup> who followed hemoglobin excretion, as well as the recent work of London, Shemin and Rittenberg,<sup>80-82</sup> who labeled the globin portion by feeding glycine containing N<sup>15</sup>, leaves little doubt that normal erythrocytes have a life span of one hundred and ten to one hundred and thirty days. It is difficult to understand the results recently reported in Scandinavia<sup>83, 84</sup> of thirty to fifty days (the figures most frequently quoted before the war). Perhaps the reticulocytes and elliptocytes used in these careful studies do not behave as normal adult erythrocytes do.

The *sludged-blood* report released by Knisely's group<sup>85</sup> summarizes their work for the past sixteen years in an important aspect of physiology. They have observed and photographed<sup>86</sup> the circulation of thousands of intact and dissected animals and, using a binocular dissecting microscope and oblique illumination, have studied the corneal and conjunctival vessels of hundreds of normal subjects and patients. They found that in the healthy organism no fluid leaks through capillaries, there is no erythrocyte agglutination or phagocytic removal of red cells, and blood flow is faster in the center of a blood vessel, the cells moving in concentric tubular layers with plasma next to the intima. There are numerous acute bottlenecks at arteriolar-capillary junctions, since the capillaries are only slightly larger than the erythrocyte diameter. The bottlenecks and capillaries are extremely labile and capable of complete self-occlusion. Even during occlusion in normal animals fluid leakage did not occur unless the capillaries were forcibly dilated—in which case the proteins always leaked out. In almost all diseased states (over 600 unanesthetized patients), including mild sinusitis or colds, the leukocytes rolled along and stuck to the blood vessel walls, and many capillaries were dilated and leaking and were packed with erythrocytes stuck to each other quite firmly by a clear tenacious substance. These "sludges" frequently obstructed vessels for hours. Their moving pictures of normal and sludged blood in

color are most instructive and are available for viewing.<sup>87</sup>

### Procurement

At present, whole blood is irreplaceable in modern therapeutics. To guarantee a continued supply in the quantities that came to be used during the war, several agencies have set up peace-time procurement plans. The National Association of Blood Donors in Italy seeks Government recognition.<sup>88</sup> The Ministry of Health in England supplies whole blood and plasma.<sup>89</sup> Besides the state blood and plasma programs of Michigan and New York<sup>90</sup> and the Massachusetts<sup>91</sup> program of whole blood and plasma fractionation, the American Red Cross initiated a nationwide peace-time procurement program in November, 1947.<sup>92</sup> Opening their first center in Rochester, New York, at that time, they hoped to establish twenty to twenty-five more this year, and in three to five years they plan to collect three million donations annually. This is in collaboration with existing state and local facilities and is to provide blood for transfusions, fractionation and research, all free of charge.

### PLASMA

#### *Homologous Serum Hepatitis*

The brilliant wartime career of plasma is now a well known and well documented story.<sup>11, 93</sup> Suggested by Ward<sup>94</sup> in 1918, first used by Filatov<sup>95</sup> in 1935 and reported in this country since 1938, this therapy became very popular with the establishment of plasma and serum programs in Britain and America to meet wartime needs. The details of collection, preservation and use need not be recounted again.<sup>11</sup> Having played an irreplaceable role in war medicine, plasma therapy now faces a serious threat to its future use—the danger of transmission of homologous serum hepatitis or jaundice. First reported in 1937,<sup>96-99</sup> this disease was thought to be of little consequence until, with more general use of plasma, larger pools and more donors, it was observed with increasing frequency in Britain and later in the United States.

The widespread use of plasma, the transient character of military-hospital populations and the long incubation period of the disease have seriously limited attempts to estimate the incidence of hepatitis following blood and plasma transfusions. The most complete survey yet reported is by Spurling, Shone and Vaughan.<sup>50</sup> They followed all patients surviving at least four weeks after receiving serum or plasma in 78 northwest London hospitals from 1940 to July, 1945, all receiving blood from January, 1944, to July, 1945, in 23 of these hospitals, and an equivalent number of controls matched as nearly as possible according to age, sex, ward and hospital but who received neither serum nor plasma. The authors were able to communicate with or study adequately 1054 of the 2040 receiving serum and plasma and 891 of the

1284 receiving blood alone (these patients received 2278 of 2468 bottles given). The serum-plasma group revealed 77 cases suggestive of homologous serum jaundice (7.3 per cent) and 1.3 per cent with jaundice of other origin. None of the blood recipients or the controls had jaundice in five months.

On June 1, 1945, the United States Army conducted a hepatitis survey in all its general hospitals in the United States.<sup>100</sup> Of 1762 patients with jaundice on that day, 500 gave a history of recent transfusions with blood or its derivatives. In the preceding thirty days, 9 of 15 patients dying of jaundice had been transfused previously.

Scheinberg et al.<sup>101</sup> followed 2443 transfusions from the blood bank of the Peter Bent Brigham and Children's hospitals in Boston between August, 1944, and August, 1945, and found 11 cases (0.45 per cent) of hepatitis, including 4 deaths.

Brightman and Korns<sup>102</sup> followed 649 recipients of surplus Army and Red Cross plasma in New York state and found 4.5 per cent hepatitis, with no hepatitis in 1597 household contacts (therefore, it was unlikely that the hepatitis was infectious). In six months 51 deaths from acute hepatitis were reported, 15 of these patients had been previously transfused, 12 with plasma alone.

Rosenthal<sup>103</sup> gave 695 units of blood and plasma to 98 patients in ten months with 4 cases of probable serum hepatitis (none with blood alone).

Grossman and Saward<sup>104</sup> from September, 1943, to September, 1945, had 8 cases of hepatitis (including 1 fatal case) in 501 infusions of commercial liquid plasma. Ginsberg<sup>105</sup> reported a fatal outcome in 2 of 14 cases.

Three cases following the administration of blood alone were discussed above.

A method of *destruction* of the etiologic agent has been reported in only one study. Wolf et al.<sup>106</sup> passed plasma in a thin, rapidly moving film under an Oppenheimer-Levinson source of ultraviolet radiation of 2537 angstrom units and 1849 angstrom units, exposing it for one-third second. They could demonstrate no consistent electrophoretic changes in the plasma and no harmful effects on recipients of it. They failed to present any data on hepatitis-virus survival, merely accepting the earlier work of Oliphant<sup>107</sup> that this amount of irradiation should be virucidal.

Gellis and his associates,<sup>108</sup> however, used 15 human volunteers and demonstrated that heating serum albumin at 60°C for ten hours (routine procedure with salt-poor albumin) actually inactivated known infective virus added to the albumin samples after fractionation.

*Prophylaxis and treatment* with serum gamma globulin (effective for infectious-hepatitis prophylaxis<sup>109-112</sup>) has been quite disappointing. Grossman et al.<sup>113</sup> treated alternate casualties returning to the United States from the European theater

Those treated and controls had received blood or its derivatives. Three hundred and eighty-four patients were given 10 cc of gamma globulin intramuscularly and 10 cc more thirty days later. The incidence of hepatitis among the 384 control patients was 11.5 per cent in the next six months whereas that in the treated group was only 2.9 per cent. Two subsequent investigations unfortunately failed to repeat this. Robinson and his co-workers<sup>114</sup> gave one injection of 10 cc of gamma globulin to 523 Army patients, with resulting hepatitis in 2.1 per cent. The incidence in 449 controls was 2.0 per cent. Duncan et al,<sup>115</sup> in a similar experiment, obtained an incidence of 1.2 per cent in 2406 treated patients and 0.9 per cent in 2374 controls. They observed, however, that Grossman had used two prophylactic injections instead of one, and that in their series the onset of the acute phase was delayed an average of eighteen days among the treated patients who contracted hepatitis.

Besides this difference in response to gamma globulin, Neefe et al<sup>116</sup> with human volunteers and Gauld<sup>117</sup> in a field epidemic of hepatitis in North Africa\* showed that there was no cross-immunization between the two agents. Since there is no cross immunity, since the epidemic virus attacks younger age groups and since the incubation periods vary (infectious twenty-one to forty and serum sixty to one hundred and eighty days<sup>118</sup>) many have sought to explain the survival and transmission of the agent of serum hepatitis, other than by parenteral transfer. Truelove and Hogben<sup>119</sup> suggest the possibility of a sperm-placenta transfer.

In the face of this evidence, the Committee on Blood and Blood Derivatives of the American Red Cross made the following recommendations to the Council on Pharmacy and Chemistry of the American Medical Association<sup>120</sup> that plasma be used only when nothing else is available, that the past history of all jaundice patients be carefully investigated that no blood donors be accepted who have had jaundice or lived with a patient with jaundice or received any parenteral injections of blood or its derivatives in the preceding six months. Until a proved reliable method for inactivating the hepatitis agent is presented, these recommendations should be carried out.

#### Use

Lozner et al<sup>121</sup> report on the safety of liquid plasma stored at room temperature for three years. As a colloidal solution, it is quite satisfactory but electrophoretically shows complete destruction of fibrinogen and gamma globulin and some reduction in beta globulin with a slight increase in osmotic pressure. Destruction of gamma globulins

\*The incidence of epidemic hepatitis in January 1944 among three groups of soldiers was as follows: 438 who had had yellow fever vaccine 11.6 per cent; 7500 who had been vaccinated in 1942 4.5 per cent; 48 per cent and 2500 who had not been vaccinated 4.5 per cent.

and associated antigens gives it an even lower reaction rate than that of dried plasma.

Prober<sup>122</sup> showed that drying to less than 1 per cent moisture made plasma noninfective even when it contained *Treponema pallidum*.

The question of the danger of mercurial preservatives remains unsettled. McNally<sup>123</sup> recommended a maximum of 4 liters of plasma containing mercurial preservatives in a short time to a patient without kidney damage, and less if damage is present. Individual tolerance is quite variable, however, as shown by Leamon's<sup>124</sup> patient who received 437 injections of mercupurin in five and a half years for congestive heart failure and yet showed no kidney damage at autopsy.

Although the use of concentrated plasma has never been too successful, two recent reports are of interest. Cleland<sup>125</sup> successfully treated traumatic pulmonary edema with 400 to 800 cc of triple concentrated plasma. Fearnley<sup>126</sup> kept a patient with subacute hepatic necrosis free from ascites for eight months using 25 units of twice-concentrated plasma.

### PLASMA FRACTIONATION

#### Method

The background, history and development of the plasma-fractionation program have been adequately recorded,<sup>9-12, 127-140</sup> the definitive documentation being now available.<sup>9</sup> Briefly outlined, they are as follows.

Early in World War II, global supply lines and overloaded transportation systems indicated that an effective, stable agent of small bulk for combating shock would be highly desirable, particularly for the Navy. Eventually the Army, Navy, National Research Council, Committee on Medical Research of the Office of Scientific Research and Development, Department of Physical Chemistry, Harvard Medical School, National Institute of Health, Massachusetts Department of Public Health, American Red Cross and seven commercial biologic laboratories collaborated to solve this problem. Until a better substitute was found, it was decided to separate the components of plasma and concentrate the albumin that was chiefly responsible for osmotic pressure, most stable, least antigenic and less viscous. Utilizing differences in solubility dependent on reaction, temperature and salt, protein and precipitant concentrations, Cohn selected ethanol as the precipitant best adapted to commercial use. As Hardy<sup>141</sup> and Melanby<sup>142</sup> had shown in 1905, ethanol does not denature protein at temperatures below 0 to -5°C. It can also be removed and recovered by vacuum drying (lyophilizing).

Originally five groups of more or less similar proteins were separated (Fractions I to V), the last being albumin. Later the second and third groups

were removed together (Fraction II plus III) and subfractionated, Fraction IV was removed in two steps, and a residue, Fraction VI, was left after albumin removal. Details of the method are adequately reviewed by Mulford.<sup>12</sup> Table 1 summarizes the variations in chemical conditions used for separation, and the electrophoretic composition of the principal fractions. Table 2 lists the components of the various fractions with relative amounts and specific interactions. Table 3 gives dimensions of the proteins obtained and of several suggested substitutes. Improved methods have produced at least twenty-seven components, and the old fraction-subfraction nomenclature is losing its usefulness. Plans are underway to re-

foam and thrombin instead of pleura to cover a bronchial stump after lobectomy. Quimby<sup>161</sup> found it to be a useful pack in 40 suprapubic prostatectomies.

There is now considerable literature comparing fibrin foam with oxycellulose<sup>162, 163</sup> and gelatin sponge.<sup>164</sup> Results are essentially the same<sup>165</sup> in neurosurgery,<sup>166, 167</sup> vascular and organ defects,<sup>168</sup> closure of bronchial wounds,<sup>169</sup> obliteration of dead spaces in orthodontics,<sup>160</sup> sinus and mastoid surgery,<sup>161</sup> and nephrostomy<sup>162</sup> and prostatectomy.<sup>164, 161</sup> Buchman and Blair<sup>165</sup> believed, however, that both oxycellulose and gelfoam interfered with the healing of fractures and bone cavities more than fibrin foam did and have abandoned all three for

TABLE 1 Separation and Electrophoretic Composition of Principal Fractions of Human Plasma by Method 6\*

FRACTION	REACTION	CONDITIONS OF SEPARATION				ELECTROPHORETIC COMPOSITION†					TOTALS
		IONIC STRENGTH	TEMPERATURE	ETHANOL	PROTEIN IN SYSTEM	ALBUMIN	ALPHA	BETA	GAMMA	FIBRIN OGLES	
	pH	$I/2$	°C	%	gm/liter	gm/liter	gm/liter	gm/liter	gm/liter	gm/liter	
Plasma	7.4	0.16	—	—	60.5	36.3	9.2	10.6	7.2	2.5	65.8
I	7.2	0.14	—3	9	51.1	0.2	0.4	0.5	0.3	2.1	3.4
II + III	6.8	0.07	—5	25	0.0	0.8	1.1	9.1	7.0	1.0	19.0
IV-1	5.2	0.07	—5	18	15.8	0	4.2	0.5	0.1	0	5.1
IV-2	5.8	0.07	—5	40	10.1	0.9	2.7	2.2	0	0	5.8
V	4.8	0.11	—5	40	7.5	29.9	1.3	0.3	0	0	31
VI	4.8	0.11	—5	40	0.2	0.6	0.2	<0.1	0	0	1.0
Totals	—	—	—	—	—	32.6	10.1	12.6	7.4	3.1	65.8

\*Adapted from Brand and Edsall.<sup>12</sup>

†Estimated in plasma. The figures in the top row are for measurements directly on plasma; those in the bottom row are summations from the distribution in the plasma fractions multiplying by the appropriate factor for the percentage of total plasma protein represented in the fraction.

vise the fractionation method entirely, precipitate the albumin and lipoproteins first, obtain better products and greater yields, designate the components by their chemical names and abandon the Fraction designations.<sup>144</sup> The preparation of so many fractions, with diverse uses, has exceeded in importance the original purpose of fractionation to obtain an agent for combating shock. Each component now has a variety of uses.

### Use of Fractions

**Fibrinogen (Fraction I-2) and Thrombin (Fraction III-2)** These clotting globulins were combined by Bering<sup>145</sup> into a light, sterile absorbable *fibrin foam*, which was originally used as a hemostatic agent in neurosurgery<sup>145, 146</sup> and more recently in other fields. Bailey et al.<sup>147</sup> found it to be an effective agent for stopping oozing and venous bleeding in 240 patients, including hemophiliacs, in whom it caused only slight tissue reaction. It was especially useful in tumor beds and on the cut surface of parenchymatous organs. Fallon and Crookery,<sup>148</sup> in 236 trials, also found fibrin foam valuable in general surgery. It can be employed with penicillin or sulfonamides and in infected cavities,<sup>149</sup> but has no effect on arterial bleeding. Kepl and Ahlquist<sup>150</sup> report the successful use of

dead-space obliteration. This might be due to the high acidity of oxycellulose, which Olwin and Wahl<sup>160</sup> found inactivated thrombin and could not be successfully buffered. The other two did not interfere.

**Fibrin film** prepared by Ferry and Morrison<sup>161</sup> from fibrinogen and thrombin was first used as a dural substitute.<sup>161, 168</sup> More recently it has been used to repair perforations in tympanic membranes and nasal septums.<sup>161</sup> The film has been studied considerably, and its physical characteristics can be altered to provide a "tailor-made" rigid or pliable substance of slow or fast absorption time with minimal tissue reaction.<sup>169-174</sup> Swenson and Gross<sup>175</sup> have utilized this material in the form of rigid tubes for blood-vessel anastomosis with a non-suture technic. With one end of a severed vessel threaded through the tube, that end is then turned back as a cuff over the tube, and this cuffed end is inserted into the other severed blood-vessel end, which is then held in place by a ligature around everything. In 27 dogs whose vena cava or jugular veins were severed and thus reunited all survived, no thromboses occurred, and all evidence of the tubes had disappeared in six or seven weeks. Arteries have also been joined in this manner.

*Fibrinogen and thrombin* injected separately into the renal pelvis, allowed to clot and removed by pelvotomy have brought out all the tiniest stones in 28 of 36 cases reported by Dees<sup>176</sup>

*Fibrinogen* intravenously has been successfully used by Diamond et al<sup>144</sup> to combat congenital hypofibrinogenemia

*Antihemophilic globulin (Fraction I)* The antihemophilic activity of Taylor's unidentified globulin

*Gamma globulin (Fraction II)* Most antibodies are selectively concentrated in this fraction,<sup>181</sup> and it has been used in prophylaxis and modification of measles with considerable success by groups headed by Stokes,<sup>182, 183</sup> Janeway,<sup>135, 184</sup> Rutstein<sup>185</sup> and others<sup>186, 187</sup> The measles antibodies are concentrated about twenty-five times those of pooled adult plasma and if given before the sixth day after exposure will usually prevent (dose 0.08 to 0.1 cc

TABLE 2 Protein Components of Human Plasma Separated and Concentrated in Diverse Fractions\*

PROTEIN COMPONENT	ESTIMATED AMOUNT IN 100 GM PLASMA PROTEIN	CONCENTRATED IN FRACTION†	APPROXIMATE ISO-ELECTRIC POINT	SPECIFIC CHEMICAL INTERACTION
Fibrinogen	500	I 2		Thrombin
Nonclottable protein insoluble at low temperature	0.1	I 1		
Antihemophilic globulin‡		I		
Antibody gamma globulins { Diphtheria antibodies‡ Measles antibodies‡ Mumps antibodies‡ Streptococci antitoxin‡ Influenza antibodies‡ Pertussis antibodies‡ Typhoid H agglutinins‡	0.001			
Antibody euglobulins { typhoid "O" agglutinins‡				
Isaagglutinins { anti-A, anti B‡ anti Rh antibodies‡	0.0	II	7	Antigen
Complement components { C'1 C'2	0.4	III-1	6.5	Antigens
Enzyme precursors { Prothrombin Plasminogen	0	III-1 III-2 III-3	6.5	Incompatible red blood cells
Serum enzymes { Thrombin‡ Plasmin‡ Amylase‡ Lipase‡ Peptidase‡ Phosphatase‡ (alkaline) Esterase‡	0.0	III-2 III-3 IV IV 5 IV-6	4.5	Antigen antibody complex Thromboplastin Streptokinase
Metal-combining beta pseudoglobulin crystallized	2	IV 7	5.6	Fibrinogen Proteins Starch Lipid 1-Lencylglycylglycine Phosphoric acid monoesters Acetyl choline ethylthiurate
High molecular weight { S = 7 Beta-1 globulins (lipid-poor) { S = 20	2.0 1.0	III-0 III-0		Iron and Copper
Iodoprotein‡		IV-6 IV-4		
Thyrotropic hormone‡		IV-6 IV-6	4.9	
Glycoproteins { Alpha- glyco-pseudoglobulin Alpha- mucoid globulin	0.5 0.5	IV-6 IV-6	4.9	
Lipoproteins { Beta-1 75 per cent lipid-containing protein Alpha-1 25 per cent lipid-containing protein	5.0 5.0	III-0 IV 0	5.6 5.2	Estrol carotenoids and other steroids Steroids
Blue-green pigment alpha globulin		IV-2		
Bilirubin-containing alpha-1 globulin‡	0.05	IV-1	4.7	Diazo reaction
Albumin crystallized with mercury		V	4.9	Mercury decanol
Albumin crystallized with decanol	0.0	V	4.9	Fatty acids bile salts many dyes and drugs

\*Adapted from Cohn<sup>18</sup>

†When purified chemical components have been separated from fractions they have not been given new fraction numbers. In that case the fraction number refers to the starting material for the separation of the component

‡These components represent but small proportions of the fraction and subfraction and their properties cannot therefore be deduced from those of the concentrates in which they have been separated

§These components have not been tested for since revision of the fractionation process

\*Albumin binds more bilirubin than the bilirubin pigment globulin in Fraction V 1 and more iodine than has been found in Fraction IV-6

has been found in Fractions I, II plus III and IV-1<sup>181-189</sup> Its nature is still unknown, since no electrophoretic or chemical difference can be detected between normal and hemophilic plasma or fractions but it is distinct from fibrinogen persisting after all clotting ability has been destroyed<sup>175</sup> With potent preparations 400 mg of Fraction I in a 20-cc solution given intravenously has controlled hemophilic bleeding especially if used with fibrin foam and thrombin locally. Dutch workers have obtained similar results using a fibrinogen solution prepared by ether precipitation<sup>180</sup>

per pound of body weight) or modify the disease (dose 0.02 to 0.025 cc per pound), giving a permanent protection. Equally satisfying results follow the prophylactic use of gamma globulin in epidemic hepatitis, especially if this substance is administered more than six days before onset of symptoms as shown by the groups of Stokes<sup>109, 110, 183</sup> and Paul.<sup>111</sup> Dosage varies from 10 cc per adult to 0.15 cc per pound of body weight in children. Unfortunately, it seems ineffective against homologous serum hepatitis<sup>111, 115</sup> despite earlier encouraging work<sup>112</sup>

The evidence on this point remains conflicting, however

Ordinary gamma globulin is ineffective against mumps. When prepared from mumps convalescent plasma, it is useful in preventing orchitis in adult males<sup>183, 187</sup>. Although gamma globulin has been reported to protect against chickenpox,<sup>188</sup> controlled studies have not confirmed this.<sup>189</sup>

Tremendous doses (20 to 100 cc intramuscularly) were ineffective in treating 56 poliomyelitis patients in a New York epidemic when compared with 55 alternate controls.<sup>190</sup> The extremely low attack rate of poliomyelitis has prevented any adequate trial of prophylaxis, very large groups would have to be inoculated to provide statistical data.

Adams and Smith<sup>191</sup> divided students at the University of Minnesota into two similar groups on

The possible origin of gamma globulin<sup>196</sup> from lymphocyte cytoplasm regulated by the pituitary-adrenal secretion and adrenal cortical activity has not been definitely established.<sup>197</sup>

**Isoagglutinins (Fraction III-I)** If plasma from Group A and B donors is pooled separately, anti-A and anti-B isoagglutinins of high titer and specificity can be obtained.<sup>198</sup> This, however, provides only small amounts of anti-A because of the low percentage of Group B donors encountered. Melin<sup>199</sup> overcame this difficulty by ingeniously combining blood from "O" and "B" donors in such proportion that the anti-B agglutinin of the "O" plasma is quantitatively removed by the "B" cells, leaving an adequate supply of potent anti-A material. Because the fractionation method concentrates agglutinins five to eight times it has also been

TABLE 3 Estimates of the Dimensions of Certain Plasma Proteins and Suggested Blood Substitutes \*

SUBSTANCE	MOLECULAR WEIGHT	DIMENSIONS OF ELLIPSOIDAL MODEL		INTRINSIC VISCOSITY
		LENGTH	DIAMETER	
	molecules	angstrom units	angstrom units	H <sub>2</sub> O
Serum albumin (human)	69 000 0	150 0	38 0	4.2
Alpha <sub>2</sub> -globulin (Fraction IV-1)	200 000 0	300 0	50 0	6.6
Beta <sub>2</sub> -globulin (Fraction IV-7)	90 000 0	190 0	37 0	5.5
Beta <sub>1</sub> -globulin (Fraction III-0)	1 300 000 0	185 0	185 0	4.1
Gamma globulin (Fraction II)	156 000 0	235 0	44 0	6.0
Fibrinogen (human)	400 000 0	700 0	38 0	25.0
Serum albumin (bovine)	69 000 0	150 0	38 0	4.2
Hemoglobin (human)	68 000 0	36 0†	64 0†	3.8
Globin (human)	34 000 0	118 0	28 0	7.0
Gelatin unodegraded	46 000 0	330 0	17 0	47.0
P 20 type	36 000 0	260 0	17 0	36.0
P 180 type	19 000 0	140 0	17 0	18.0
Isinglass (degraded)	29 000 0	240 0	16 0	24.0
Glutamic acid polypeptide	15 000 0	260 0	11 0	24.0
Glucose	180 0	9.5	6.5	4.0
Chloride ion	35.5	3.6	3.6	—
Sodium ion	23.0	1.9	1.9	—
Erythrocyte (human)	—	24 000 0	86 000 0	4

\*Adapted from Jacoway and Oncley,<sup>191</sup> Oncley, Scatchard and Brown<sup>192</sup> and Cohn.<sup>193</sup>

†From x-ray studies indicating that the hemoglobin molecule is a platelet having the approximate dimensions 36 x 64 x 48 angstrom units.

the basis of previous history of colds. The group receiving 6 cc of gamma globulin in October and 4 cc monthly for six months reported 77 colds (10 severe) as opposed to 132 (28 severe) in the controls. This has not been confirmed as yet.

Because of the grave effects on the fetus of maternal rubella in the first trimester as originally reported by Gregg,<sup>192</sup> gamma-globulin prophylaxis should be considered. No satisfactory series has been reported.<sup>183</sup>

All injections of gamma globulin must be given intramuscularly because of the occasional presence of a depressor substance<sup>189</sup> in some preparations. Although marked anticomplementary activity by gamma globulin has been observed in vitro,<sup>193</sup> none has been demonstrated in vivo.<sup>194</sup> A better preparation may result from the work of Deutsch et al.<sup>195</sup> showing that peptic digestion cleaves the gamma globulin molecule without diminishing antibody activity, thus improving absorption and effecting further concentration.

possible to prepare potent anti-Rh typing serum from pools of poorly immunized Rh— persons with a titer too low for ordinary use.<sup>198, 200</sup>

**Iron-binding globulin (Fraction IV-7)** After Holmberg and Laurell's<sup>201</sup> demonstration that serum iron is transported by an iron-binding protein that is normally one third saturated, Schade and Caroline<sup>202</sup> located this activity in Fraction IV-3,4 (later refractionated as IV-7), where it was identified<sup>203, 204</sup> as a  $\beta_1$  pseudoglobulin of 90,000 molecular weight, binding 2 molecules of iron per molecule of globulin (0.38 to 1.25 gamma of Fe<sup>++</sup> per milligram of globulin). Clinical investigation by Wintrobe et al.<sup>205</sup> and Rath and Finch<sup>206</sup> confirmed the ability of this fraction to transport iron. The latter's figures on 20 normal persons and 86 patients check closely with Laurell's<sup>207</sup> results: a normal serum iron-binding capacity of 314 microgm per 100 cc with normal iron content of 102 microgm per 100 cc, compared with Laurell's capacity of 315 microgm per 100 cc, 34 per cent saturated. The capacity

is unaffected by amount of iron intake. In iron-deficiency anemias the serum iron is decreased, and the unsaturated and total binding capacity increased. All decrease in anemias of infection. In hemochromatosis the percentage of saturation rises considerably. Studying 25 newborn infants and their mothers, Laurell<sup>207</sup> was able to show that the iron-binding protein did not pass through the placenta freely whereas the iron did (mothers, serum-iron 80 microgm per 100 cc and total binding capacity 446 microgm per 100 cc, newborn infants serum iron, 146 microgm per 100 cc and total binding capacity, 226 microgm per 100 cc). Apparently, copper is bound in the same fashion by this protein.<sup>204</sup>

**Miscellaneous.** After Szego and Roberts<sup>208</sup> demonstrated that two thirds of the total circulating estrogen in normal, pregnant or gonadotropin-injected cows, rabbits and women was closely associated with a plasma protein fraction, they were able to locate most of this activity in the 75-percent-lipid-containing  $\beta_1$  "X" protein of Fraction III-0.<sup>209</sup> The plasmin that Christensen<sup>210</sup> considers responsible for fibrinolysis\* is found in Fraction III-3. The choline activity of serum occurs in Fraction IV-6.<sup>212</sup>

\*Possible mechanism: plasminogen + streptokinase = plasmin that is inactive as long as neutralized by antiplasmin.<sup>211</sup>

(To be concluded)

## REFERENCES

1. Diamond L. K. Rh factor. *New Eng J Med* (in press)
2. Loch R. F. Plasma proteins in health and disease. *New Eng J Med* 224:980-987 1941
3. Janeway C. A. War medicine, with special emphasis on use of blood substitutes. *New Eng J Med* 225:571-581 1941
4. *Idem*. Plasma proteins: their importance in clinical medicine and surgery. *New Eng J Med* 229:151-156 and 779-785 1943
5. Metcalf J. and Stare, F. J. Physiologic and clinical significance of plasma proteins and protein metabolites. *New Eng J Med* 236:26-35 and 68-75 1947
6. Gnat, G. M. Methods of preservation of whole blood. In *Advances in Military Medicine*, 2 vol. Vol. 1. Boston: Atlantic-Little Brown 1948. Pp 462-472.
7. Richards D. W. Jr. Fine, J. Long C. N. H. Shock. In *Advances in Military Medicine*, 2 vol. Vol. 1. Boston: Atlantic-Little Brown 1948. Pp 335-363
8. Freeman N. E. Newer concepts of pathologic physiology of shock: peripheral circulatory collapse. *S Clin North America* 26:1319-1329 1946
9. Cohn E. J. History of plasma fractionation. In *Advances in Military Medicine*, 2 vol. Vol. 1. Boston: Atlantic-Little Brown 1948. Pp 364-443
10. *Idem*. Chemical specificity of interaction of diverse human plasma proteins. *Blood* 3:471-483 1948
11. White, C. S. and Weinstein J. J. *Blood Derivatives and Substitutes*. 454 pp. Baltimore: Williams & Wilkins 1947
12. Mulford, D. J. Derivatives of blood plasma. *Ann Rev Physiol* 9:327-356 1947
13. Brand E. and Edsall J. T. Chemistry of proteins and amino acids. *Ann Rev Biochem* 16:223-272 1947
14. Janeway, C. A. and Oncley J. L. Blood substitutes. In *Advances in Military Medicine*, 2 vol. Vol. 1. Boston: Atlantic-Little Brown 1948. Pp 444-461
15. Kremen A. J. Problem of parenteral nitrogen administration in surgical patients with special consideration of preoperative preparation and of means of effecting favorable nitrogen balance. *Surgery* 23:92-153 1948
16. Elman R. *Parenteral Alimentation in Surgery, With special reference to proteins and amino acids*. 284 pp. New York: Paul B. Hoeber Inc. 1947
17. Raydon I. S. Protein deficiency in surgical patients. *S Clin North America* 26:1306-1318 1946
18. Lutscher J. A. Jr. Biological and medical applications of electrophoresis. *Physiol Rev* 27:621-642 1947
19. Levine P. and Katzin E. M. Survey of blood transfusion in America. *J A M A* 110:1243-1248 1938
20. Gibson J. G. 2nd et al. Measurement of post-transfusion survival of preserved stored human erythrocytes by means of two isotopes of radioactive iron. *J Clin Investigation* 26:704-714 1947
21. Gibson J. G. 2nd, Evans R. D. Anh J. C. Sack T., and Peacock, W. C. Post-transfusion survival of preserved human erythrocytes stored as whole blood or in resuspension after removal of plasma by means of two isotopes of radioactive iron. *J Clin Investigation* 26:715-728 1947
22. Gibson J. G. 2nd, Peacock W. C., Evans R. D. Sack T. and Aub J. C. Rate of post transfusion loss of non viable stored human erythrocytes and reutilization of hemoglobin derived radioactive iron. *J Clin Investigation* 26:730-746 1947
23. Gibson J. G. 2nd, Sack T., Evans R. D. and Peacock W. C. Effect of varying temperatures on post-transfusion survival of whole blood during depot storage and after transportation by land and air. *J Clin Investigation* 26:747-755 1947
24. Osborne D. E. and Denstedt O. F. Estimation of cell survival after transfusion by selective agglutination. *J Clin Investigation* 26:655-666 1947
25. Parpart A. K., Lorenz, P. B., Parpart E. R. and Chase A. M. Osmotic resistance (fragility) of human red blood cells. *J Clin Investigation* 26:636-640 1947
26. Parpart A. K., Grege J. R., Lorenz, P. B., Parpart E. R. and Chase A. M. Whole blood preservation: problem of general physiology in vitro analysis of problem of blood storage. *J Clin Investigation* 26:641-654 1947
27. Rapoport, S. Changes of erythrocytes in stored blood. *J Clin Investigation* 26:591-635 1947
28. Ross J. F., Finch C. A., Peacock W. C. and Sammons M. E. In vitro preservation of post-transfusion survival of stored blood. *J Clin Investigation* 26:687-703 1947
29. Strumia M. M., Blake A. D. and Wicks W. A. Preservation of whole blood. *J Clin Investigation* 26:667-671 1947
30. *Idem*. Preservation of erythrocytes left over from plasma preparation. *J Clin Investigation* 26:672-677 1947
31. Strumia M. M., Blake A. D. and McGraw I. J., Jr. Acid citrate dextrose solution with low water volume and low dextrose concentration. *J Clin Investigation* 26:678-685 1947
32. Loutit J. F. and Molihon P. L. Advantages of disodium-citrate-glucose mixture as blood preservative. *Brit M J* 2:744 1945
33. Stewart J. D. Wound shock. *J A M A* 133:216-219 1947
34. Seligman A. M., Frank H. A. and Fine J. Traumatic shock. XIV. Successful treatment of hemorrhagic shock by vital perfusion of liver in dogs irreversible to transfusion. *J Clin Investigation* 26:530-535 1947
35. Glasser O. and Page I. H. Intra arterial transfusion in treatment of experimental hemorrhagic shock. *Cleveland Clin Quart* 14:121-125 1947
36. Lefebvre F. La transfusion et l'auto-transfusion oxygénée dans le traitement des asphyxies électrocutées, noyades et intoxication par l'oxyde de carbone. *Presse med* 54:633 1946
37. Iokhved, B. I. Intracardiac blood transfusion. *Am Rev Soviet Med* 3:116-119 1945
38. Kay E. P. and Hacker V. D. Treatment of shock by aortic transfusion during thoracic operations. *J A M A* 134:604 1947
39. Appelqvist, O., and Holsti O. Bloodtransfusions in treatment of rheumatoid arthritis. *Svensk red Wehrsch* 77:977-980 1947
40. Barni I. New treatment of rheumatoid arthritis. *Brit M J* 2:252, 1947
41. Wallerstein H. Treatment of severe erythroblastosis by simultaneous removal and replacement of blood of newborn infant. *Science* 103:555 1946
42. *Idem*. Substitution transfusion: new treatment for severe erythroblastosis fetalis. *Am J Dis Child* 73:19-35 1947
43. Wiener A. S., Wexler I. B. and Grundfast, T. H. Therapy of erythroblastosis fetalis with exchange transfusion. *Bull New York Acad. Med* 23:207-220 1947
44. Witekisky E., Anderson G. W. and Heide, A. Demonstration of Rh antibody in breast milk. *Proc Soc Exptl Biol & Med* 49:179-183 1942
45. Cathie, I. A. B. Breast feeding in erythroblastosis foetalis. *Brit M J* 2:650 1947
46. Stonham F. V. Useful pump for blood transfusion. *M J Australia* 1:115 1947
47. Wood D. A. and Black M. B. Further notes on pathology of acute epidemic hepatitis and homologous serum jaundice. *Am J Clin Path* 16:746-751 1947
48. Bruyn H. B. Homologous serum hepatitis following transfusion in infant. *J Pediatr* 31:60-69 1947
49. Dassen R. and Alvarez, G. H. La ictericia tardia post transfusion de sangre o de plasma. *Presse med argent* 33:1271-1274 1946
50. Sparling N., Shone J. and Vaughan J. Incidence incubation period and symptomatology of homologous serum jaundice. *Brit M J* 2:407-412 1946
51. Fischer W. J. H. Jr. and York C. L. Quartan malaria occurring subsequent to blood transfusion: report of case. *New Eng J Med* 235:411-413 1946
52. Coggeshall L. T. Danger of transmitting malaria by transfusion. *J A M A* 133:12-8 1947
53. Rogers K. B. Quartan malaria transmitted by blood transfusion: report of case. *Lancet* 2:688 1947

- 54 Morgan A D and Lumb G Fatal use of dangerous universal donor *Lancet* 2 866-868 1946
- 55 American National Red Cross *American Red Cross Blood Donor Service during World War II Its organization and operation* 99 pp Washington D C American Red Cross 1946
- 56 Snyder H E Replacement of blood in management of wounds *J A M A* 133 219-223 1947
- 57 Brown H R, Jr Distribution and use of human whole blood in Pacific war *U S Nav Med Bull* 47 396-420 1947
- 58 Witelsky E Klendshoj N C and Swanson P Preparation and transfusion of safe universal blood *J A M A* 116 2654-2656 1941
- 59 Muirhead E E, Small A B and McBride R B Peritoneal irrigation for uremia following incompatible blood transfusion *Arch Surg* 54 374-381 1947
- 60 Koff W J and Berk H T J Artificial kidney dialyzer with great area. *Acta med Scandinav* 117 121-134 1944
- 61 Koff W J, and Van Noordwijk J *The Artificial Kidney* 92 pp Kampen Holland J H Kok N V 1946
- 62 Murray G De'orme E and Thomas N Development of artificial kidney *Arch Surg* 55 505-522 1947
- 63 Frank H A Seligman A M and Fire J Treatment of uremia after acute renal failure by peritoneal irrigation *J A M A* 130 703-705 1946
- 64 Hustin A and Remy R Influence du sexe des 'donneurs' et de recepteurs sur la fréquence et la gravité des incidents survenant au cours des transfusions sanguines *Presse med* 54 728 1946
- 65 Danis P G Eto J K and Sennott J S Preparation and use of concentrated red blood cell transfusions in infancy *J Pediat* 28 449-452 1946
- 66 Murray C K and Shaar C M Red blood cell paste in treatment of ulcers and chronically infected wounds *J A M A* 125 779-782 1944
- 67 Braccato V Sull'azione delle polveri di sangue di globuli rossi e di plasma nei processi di guarigione delle ferite *Rassegna in ternat clin e terap* 27 87-94 1947
- 68 Foreign Letters Paris new method of hematotherapy *J A M A* 135 176 1947
- 69 Hamilton P B Farr L E Hiller A and Van Slyke D D Preparation of hemoglobin solutions for intravenous infusion *J Exper Med* 86 455-463 1947
- 70 Farr L E Hiller A and Van Slyke D D Preparation of dried hemoglobin without loss of activity *J Exper Med* 86 465-475 1947
- 71 Hamilton P B Hiller A and Van Slyke D D Renal effects of hemoglobin infusions in dogs in hemorrhagic shock *J Exper Med* 86 477-487 1947
- 72 Lalich J J Influence of injections of homologous hemoglobin on kidneys of normal and dehydrated animals *J Exper Med* 86 153-158 1947
- 73 Harrison H E Bunting H Ordway N K and Albinck W S Pathogenesis of renal injury produced in dog by hemoglobin or methemoglobin *J Exper Med* 86 339-356 1947
- 74 Struma M M, Chornock F W Blake A D and Karr W G Use of modified globin from human erythrocytes as plasma substitute preliminary report *Am J M Sc* 209 436-442 1945
- 75 Struma M M Blake A D Jr and Cornman H D Diuretic effect of globin in chronic glomerulonephritis *J A M A* 131 1033-1035 1946
- 76 Struma M M Blake A D Reider H C and Chornock F W Use of modified globin from human erythrocytes in hypoproteinemia *Am J M Sc* 211 51-61 1946
- 77 Rohsheit-Robbins F S Miller L L Alling E L and Whipple G H Plasma substitutes human and animal globin related to production of hemoglobin and plasma protein dog hemoglobin utilization improved by methionine but not by isoleucine *J Exper Med* 83 355-371 1946
- 78 Ashby W Span of life of red blood cell resume *Blood* 3 486-500 1948
- 79 Hawkins W B and Whipple G H Life cycle of red blood cells *Am J Physiol* 122 418-427 1928
- 80 Shemin D and Rittenberg D Biological utilization of glycine for synthesis of protoporphyrin of hemoglobin *J Biol Chem* 166 621-625 1946
- 81 *Idem* Studies on formation of heme and on average lifetime of human red cell *Federation Proc* 5 153 1946
- 82 London I M Shemin D and Rittenberg D Study of hemoglobin metabolism in man with aid of isotope technique *J Clin Investigation* 27 547 1948 (abstr)
- 83 Nizet A Nouvelles recherches sur la physiopathologie des hémazues IV Durée de vie des hémazues chez l'homme normal étude a partir de la reticulocytose *Acta med Scandinav* 127 565-569 1947
- 84 Hederstedt S Erythrocyte transfusions as method in studies on blood destruction blood volume and peritoneal resorption *Acta chir Scand* 95 (Supp. 128) 1-141 1947
- 85 Knisely M H Bloch E H Eliot T S and Warner L Sludged blood *Science* 106 431-440 1947
- 86 Blood sludge Photographic essay *Life* 24 49-59 (May 31) 1948
- 87 Knisely M H Stratman-Thomas W K, Eliot T S and Bloch E H Knowledge malaria in monkeys (motion picture) *J Nat Malaria Soc* 4 285-300 1945
- 88 Foreign Letters Italy National Association of blood donors *J A M A* 134 478, 1947
- 89 Foreign Letters London blood transfusion *J A M A* 134 104 1947
- 90 Anderson H D Plasma program Michigan Department of Health *Proc Conf State & Prov Health Author North America* 59-60 122 125 1944-45
- 91 Moore L D Edsall G and Getting V A Massachusetts blood and blood derivatives program *J A M A* 135 548-552 1947
- 92 Red Cross blood bank program *J A M A* 133 482, 1947 *Ibid* 134 172, 377 882 1035 and 1189 1947 *Ibid* 135 584, 651 653 and 1018, 1947
- 93 Greaves R I N *The Preservation of Proteins by Drying and Special Reference to the Production of Dried Human Serum and Plasma for Transfusion* Med Res Coun Spec Rep Ser No. 258 54 pp London His Majesty's Stationery Office 1946
- 94 Ward G R Transfusion of plasma *Brit M J* 1 301, 1918
- 95 Filatov A and Kartashevskij N G Die Transfusion von menschlichem Blutplasma als blutstillendes Mittel *Zentralbl J Clin* 62 441-445 1935
- 96 Findlay G M and MacCallum F O Note on acute hepatitis and yellow fever immunization *Tr Roy Soc Trop Med & Hyg* 31 297-303, 1937
- 97 MacNalty A S *On the State of Public Health Annual report of the chief medical officer of the Ministry of Health for the year 1937* 235 pp London His Majesty's Stationery Office 1938
- 98 Findlay G M and MacCallum F O Hepatitis and jaundice associated with immunization against certain virus diseases. *Proc Roy Soc Med* 31 799-805 1938
- 99 Soper F L and Smith H H Yellow fever vaccination with cultivated virus and immune and hyperimmune serum *Am J Trop Med* 18 111-134 1938
- 100 Sartwell P E Infectious hepatitis in relation to blood transfusion. *Bull U S Army Med Dept* 7 50-100 1947
- 101 Scheinberg I H Kinney T D and Janeway C A Homologous serum jaundice *J A M A* 134 841-848 1947
- 102 Brightman I J and Korns R F Homologous serum jaundice in recipients of pooled plasma *J A M A* 135 268-272 1947
- 103 Roenthal L T Homologous serum hepatitis in civilian hospital *Gastroenterology* 9 28-31 1947
- 104 Grossman C M and Saward E W Homologous serum jaundice following administration of commercial pooled plasma report of eight cases including one fatality *New Eng J Med* 234 181-183 1946
- 105 Ginsberg H S Homologous serum hepatitis following transfusion *Arch Int Med* 79 555-569 1947
- 106 Wolf A M Mason J Fitzpatrick W J Schwartz S O and Levinson S O Ultraviolet irradiation of human plasma to control homologous serum jaundice *J A M A* 133 175 1947
- 107 Oliphant J W Jaundice following administration of human serum. *Bull New York Acad Med* 20 429-445 1944
- 108 Gellis S S et al Inactivation of virus of homologous serum hepatitis in solutions of normal human serum albumin by means of heat *J Clin Investigation* 27 239-244 1948
- 109 Stokes J Jr and Neefe J R Prevention and attenuation of infectious hepatitis by gamma globulin preliminary note *J A M A* 127 144 1945
- 110 Gellis S S et al Use of human immune serum globulin (gamma globulin) in infectious (epidemic) hepatitis in Mediterranean Theater of Operations studies on prophylaxis in two epidemics of infectious hepatitis *J A M A* 128 1042 1945
- 111 Havens W P Jr and Paul J R Prevention of infectious hepatitis with gamma globulin *J A M A* 129 270-272 1945
- 112 Wilbur D L Therapeutic agents in liver disease review of medicinal agents *J A M A* 134 598-603 1947
- 113 Grossman E B Stewart S G and Stokes J Jr Post transfusion hepatitis in battle casualties and study of its prophylaxis by means of human immune serum globulin *J A M A* 129 991-994 1945
- 114 Robinson R W Hamblin W N Fleming R S and Queen F B Failure of immune serum globulin to prevent or modify course of infectious hepatitis homologous serum type *Proc Am Federation Clin Research* 2 93-95 1945
- 115 Duncan G G et al Evaluation of immune serum globulin as prophylactic agent against homologous serum hepatitis *Am J M Sc* 213 53-57 1947
- 116 Neefe J R Gellis S S and Stokes J Jr Homologous serum hepatitis and infectious (epidemic) hepatitis studies in volunteers bearing on immunological and other characteristics of etiologic agents *Am J Med* 1 3-22 1946
- 117 Gault R L Field studies relating to immunity in infectious hepatitis and homologous serum jaundice *Am J Pub Health* 37 400-405 1947
- 118 Paul J R and Havens W P Jr Recent advances in study of infectious hepatitis and serum (syringe transmitted) jaundice *Tr A Am Physicians* 59 133-141 1946
- 119 Truelove S C and Hogben L Documentary study of jaundice associated with syphilis treatment and blood transfusion *Brit J Social Med* 1 18-32 1947
- 120 Committee on Blood and Blood Derivatives of the American Red Cross Report on incidence of homologous serum jaundice following use of surplus dried plasma *J A M A* 135 714 1947
- 121 Lozner E L Lemish S Campbell A S and Newhouse L R Preservation of normal human plasma in liquid state V Clinical Preservation of normal human plasma in liquid state V Clinical, chemical and physicochemical studies during three years of storage at room temperature *Blood* 1 459-471 1946

122. Prober T F. Loss of virulence of *Treponema pallidum* during processing of dried blood serum. *Pub Health Rep* 62:1199-1202 1947
123. McNally W D. Is chemically preserved plasma safe? *Illness* 11:91-118 1947
124. Leamon W G Jr. Prolonged use of mercupurin in congestive cardiac failure: report of case receiving 437 injections over period of five years autopsy. *Proc Am Federation Clin Research* 2:25 1945
125. Cleland G. Traumatic pulmonary oedema treated with concentrated plasma. *Lancet* 2:667-670 1946
126. Fearnley G R. Ascites following infective hepatitis: case treated with concentrated plasma. *Lancet* 1:137-139 1947
127. Cohn E. J. Properties and functions of plasma proteins with consideration of methods for their separation and purification. *Chem Rev* 28:395-417 1941
128. *Idem*. Plasma proteins: their properties and functions. *Tr & Stud Coll Physicians Philadelphia* 10:149-162 1942.
129. *Idem*. Blood, blood derivatives and blood substitutes. *Proc Am Philos Soc* 88:159-173 1944
130. *Idem*. Blood proteins and their therapeutic value. *Science* 101:51-56 1945
131. *Idem*. Blood and blood derivatives. *Smithsonian Inst Ann Rep* (1945) pp 413-440 1946
132. *Idem*. Chemical separation and clinical appraisal of components of blood. *Medicine* 24:533-538 1945
133. *Idem*. Blood: brief survey of its chemical components and of their natural functions and clinical uses. *Blood* 1:9 1946
134. *Idem*. Separation of blood into fractions of therapeutic value. *Ann Int Med* 26:341-353 1947
135. Cohn E. J. Chemical, physiological and immunological properties and clinical uses of blood derivatives. *Experientia* 3:125-136 1947
136. Chemical, clinical and immunological studies on products of human plasma fractionation: I to VIII. *J Clin Investigation* 23:417-405 1944
137. Janeway C. A. Clinical experiences with purified human serum albumin. *Bull New Eng J Med* 6:112 1944
138. *Idem*. Clinical use of products of human plasma fractionation: albumin in shock and hypoproteinemia, gamma globulin in measles. *J A M A* 126:674-680 1944
139. *Idem*. Clinical uses of products of human plasma fractionation: Circumferential. *J Clin Invest* 23:675-691 1946
140. *Idem*. Clinical use of products of human plasma fractionation: New York State. *J Med* 47:1357-1362 1947
141. Hardy W B. Colloidal solutions: globulins. *J Physiol* 33:251-257 1903
142. Mellanby J. Globulin. *J Physiol* 33:353-377 1905
143. Oscey J L, Scatchard G and Brown A. Physical-chemical characteristics of certain of proteins of normal human plasma. *J Physiol & Colloid Chem* 51:184-198 1947
144. Cohn E. J. Personal communication
145. Bering E. A. Jr. Development of fibrin foam as hemostatic agent and for use in conjunction with human thrombin. *J Clin Investigation* 23:586-590 1944
146. Bailey O T and Ingraham F D. Use of fibrin foam as hemostatic agent in neurosurgery: clinical and pathological studies. *J Clin Investigation* 23:591-596 1944
147. Bailey O T, Ingraham F D, Swenson O, Lowrey J J and Bering E. A. Jr. Human fibrin foam with thrombin as hemostatic agent in general surgery: experimental studies and clinical use. *Surgery* 18:347-369 1945
148. Fallon J and Crockery W F. Plasma fractions — fibrin foam, thrombin and fraction No. 1 — in general surgery. *Surg Gynec & Obst* 84:361-368 1947
149. Baker G S and Smith C Jr. Bacteriostasis and hemostasis by use of fibrin foam and penicillin. *Mil Surgeon* 101:208-210 1947
150. Kepl M F and Ahlquist R E. Use of fibrin foam in bronchial stump closure. *Am J Med* 4:787 1948 (abstr)
151. Quirby W C. Hemostasis by thrombin and fibrin foam in suprapubic prostatectomy: analysis of 40 cases. *New Eng J Med* 235:603-612 1946
152. Yackel E. C. and Kenyon W O. Oxidation of cellulose by nitrogen dioxide. *J Am Chem Soc* 64:121-127 1942
153. Frantz A K. New absorbable hemostatic agents. *Bull New York Acad Med* 22:102-110 1946
154. Correll J T and Wise E. C. Certain properties of new physiologically absorbable sponge. *Proc Soc Exper Biol & Med* 58:233-237 1945
155. Jenkins H P, Janda R and Clarke J. Clinical and experimental observations on use of gelatin sponges or foam. *Surgery* 20:124-132 1946
156. Leibi R L and Prerence H R. Surgical investigation of new absorbable sponge derived from gelatin for use in hemostasis. *J Neurosurg* 2:43-45 1945
157. Fischer E. F. Gelatin foam in neurosurgery: further uses. *J Neurosurg* 4:97-104 1947
158. Jenkins H P and Janda R. Studies on use of gelatin sponge or foam as hemostatic agent in experimental liver resections and injuries to large vein. *Ann Surg* 124:952-961 1946
159. Hanlon C R. Observations on use of gelatin sponge in closure of experimentally produced defects of bronchus. *Surg Gynec & Obst* 86:531-538 1948
160. Guralnick W C. Absorbable gelatin sponge and thrombin in oral surgery. *Am J Orthodont* 32:792-794 1946
161. Schenck H P. Use of products of fibrinogen and thrombin in otolaryngology. *California & West Med* 63:10 1945
162. MacDonald S A and Matthews W H. Gelfoam in experimental kidney wounds. *J Urol* 57:802-811 1947
163. MacDonald S A and Powell R E. Gelfoam hemostasis in prostatic surgery. *J Urol* 57:812-815 1947
164. Heckel N J and Waller J I. Use of gelfoam in transurethral resection. *J Urol* 57:828 1947
165. Buchman J and Blair J E. Use of absorbable substance to obliterate bone cavities and as hemostatic agents in operative procedures on bones and joints. *J Bone & Joint Surg* 29:650-658 1947
166. Olwin I H and Wahl F J. Effect of absorbable sponge material on activity of thrombin. *Surg Gynec & Obst* 86:203-212 1948
167. Ferry J D and Morrison P R. Fibrin clots, fibrin films and fibrinogen plastics. *J Clin Investigation* 23:566-572 1944
168. Bailey O T and Ingraham F D. Fibrin films in neurosurgery with special reference to their use in repair of dural defects and in prevention of meningocerebral adhesions. *J Clin Investigation* 23:597-600 1944
169. Bailey O T and Ford R. Fibrinogen plastics: tissue reaction induced by series of fibrinogen plastics implanted in abdominal wall of guinea pigs. *Arch Path* 42:53-54 1946
170. Ferry J D and Morrison P R. Fibrin film and other products from human plasma. *Indust & Engin Chem (Indust Ed)* 38:1217-1221 1946
171. *Idem*. Preparation and properties of serum and plasma proteins VIII. Conversion of human fibrinogen to fibrin under various conditions. *J Am Chem Soc* 69:888-900 1947
172. *Idem*. Preparation and properties of serum and plasma proteins IX. Human fibrin in form of elastic film. *J Am Chem Soc* 69:400-409 1947
173. Ferry J D, Singer M, Morrison P R, Putsche J D and Kutz R. L. Preparation and properties of serum and plasma proteins X. Modification of physical and chemical properties of fibrin film by heat treatment. *J Am Chem Soc* 69:403-416 1947
174. Morrison P R and Singer M. Persistence of fibrin film in tissue and its modification by heat treatment. *J Clin Investigation* 26:929-935 1947
175. Swenson O and Gross R E. Absorbable fibrin tubes for vein anastomoses. *Surgery* 22:137-143 1947
176. Dees J E. Use of fibrinogen coagulum in pyelolithotomy. *J Urol* 56:271-283 1946
177. Lewis J H et al. Coagulation defect in hemophilia: in vitro and in vivo comparison of normal and hemophilic whole blood plasma and derived plasma protein fractions. *J Clin Investigation* 25:810-873 1946
178. Lewis J H, Souier J P and Taylor F H L. Coagulation defect in hemophilia: effect in vitro and in vivo on coagulation time in hemophilia of prothrombin and fibrinogen free normal plasma and its derived protein fractions. *J Clin Investigation* 25:876-879 1946
179. Minot G R and Taylor F H L. Hemophilia: clinical use of anti-hemophilic globulin. *Ann Int Med* 26:363-367 1947
180. van Creveld, S and Mastenbroek, G G A. Plasma fractions in hemophilia. *Nederl tijdschr geneesk* 91:1303-1312 1941
181. Eanders J F. Concentrations of certain antibodies in globulin fractions derived from human blood plasma. *J Clin Investigation* 23:510-520 1944
182. Stokes J Jr, Mans E. P and Gellis S S. Use of concentrated normal human serum gamma globulin (human immune serum globulin) in prophylaxis and treatment of measles. *J Clin Investigation* 23:531-540 1944
183. Stokes J Jr. Use of gamma globulin from large pools of adult blood plasma in certain infectious diseases. *Ann Int Med* 26:353-362 1947
184. Janeway C. A. Use of concentrated human serum gamma globulin in prevention and attenuation of measles. *Bull New York Acad Med* 21:202-222 1945
185. Greenberg M, Frant S and Rutstein D D. Gamma globulin and parental globulin: comparison of their effectiveness in prevention and modification of measles. *J A M A* 126:944-947 1944
186. Anderson S G and Ket W M. Use of gamma globulin in prophylaxis of measles. *N J J Med* 2:196 1946
187. Berenberg W. Gamma globulin as prophylactic and therapeutic agent in communicable disease. *Milbank Mem Fund Quart* 25:119-127 1947
188. Funkhouser W L. Use of serum gamma globulin antibodies to control chicken pox in convalescent hospital for children. *J Pediatr* 32:257-259 1948
189. Janeway C. A. Personal communication
190. Bahlke A. M. and Perkins I E. Treatment of preperitoneal poliomyelitis with gamma globulin. *J A M A* 129:1146-1150 1945
191. Adams J M and Smith N. Clinical trial of gamma globulin in prevention of common respiratory diseases. *Proc Soc Exper Biol & Med* 63:446-449 1946
192. Gregg N M. Congenital cataract following German measles in mother. *Tr Ophth Soc Australia* (1941) 3:35-46 1942
193. Davis B D, Kabat, E A, Harris A., and Moore D H. Anti-complementary activity of serum gamma globulin. *J Immunol* 49:225-232 1944
194. Waring G W Jr and Weinstein L. Effect of gamma globulin on circulating human complement. *Science* 105:474 1947
195. Deutsch H F., Petermann M L and Williams J W. Biophysical studies of blood plasma proteins. II. Fibrin digestion and recovery of human gamma globulin. *J Biol Chem* 164:93-107 1946

- 54 Morgan A D and Lumb G Fatal use of dangerous universal donor *Lancet* 2 866-868 1946
- 55 American National Red Cross *American Red Cross Blood Donor Service during World War II Its organization and operation* 99 pp Washington D C American Red Cross 1946
- 56 Snyder H E. Replacement of blood in management of wounds *J A M A* 133 219-223, 1947
- 57 Brown H R., Jr. Distribution and use of human whole blood in Pacific war *U S Nav M Bull* 47 396-420 1947
- 58 Witebsky E Klendshoj N C and Swanson P Preparation and transfusion of safe universal blood *J A M A* 116 2654-2656 1941
- 59 Muirhead E E., Small A B and McBride R. B Peritoneal irrigation for uremia following incompatible blood transfusion *Arch Surg* 54 374-381 1947
- 60 Kolff W J, and Berk, H T J Artificial kidney dialyzer with great area *Acta med Scandinav* 117 121-134 1944
- 61 Kolff W J and Van Noordwijk J *The Artificial Kidney* 92 pp Kampen Holland J H Kok N V 1946
- 62 Murray G De'orme E and Thomas N Development of artificial kidney *Arch Surg* 55 505-522 1947
- 63 Frank H A Seligman A M and Fire J Treatment of uremia after acute renal failure by peritoneal irrigation *J A M A* 130 703-705 1946
- 64 Hustin A and Remy R Influence du sexe des "donneurs" et de "recepteurs" sur la fréquence et la gravité des incidents survenant au cours des transfusions sanguines *Presse med* 54 728, 1946
- 65 Denis P G Eto J K and Sennott J S Preparation and use of concentrated red blood cell transfusions in infancy *J Pediatr* 28 449-452 1946
- 66 Murray C K and Shaar C M Red blood cell paste in treatment of ulcers and chronically infected wounds *J A M A* 125 779-782 1944
- 67 Braccato V Sull'azione delle polveri di sangue di globuli rossi e di plasma nei processi di guarigione delle ferite *Rassegna internaz clin e terap* 27 87-94 1947
- 68 Foreign Letters Paris new method of hematotherapy *J A M A* 135 176 1947
- 69 Hamilton P B Farr L E Hiller A and Van Slyke D D Preparation of hemoglobin solutions for intravenous infusion *J Exper Med* 86 455-463 1947
- 70 Farr L E Hiller A and Van Slyke D D Preparation of dried hemoglobin without loss of activity *J Exper Med* 86 465-475 1947
- 71 Hamilton P B Hiller, A, and Van Slyke D D Renal effects of hemoglobin infusions in dogs in hemorrhagic shock *J Exper Med* 86 477-487 1947
- 72 Lalich, J J Influence of injections of homologous hemoglobin on kidneys of normal and dehydrated animals *J Exper Med* 86 153-158 1947
- 73 Harrison H E Bunting H Ordway N K and Albrink W S Pathogenesis of renal injury produced in dog by hemoglobin or methemoglobin *J Exper Med* 86 339-356 1947
- 74 Strumia M M, Chornock F W Blake A D and Karr W G Use of modified globin from human erythrocytes as plasma substitute preliminary report. *Am J M Sc* 209 436-442 1945
- 75 Strumia M M Blake A D Jr and Cornman H D Diuretic effect of globin in chronic glomerulonephritis *J A M A* 131 1033-1035 1946
- 76 Strumia M M Blake A D Reider H C and Chornock F W Use of "modified globin" from human erythrocytes in hypoproteinemia *Am J M Sc* 211 51-61 1946
- 77 Robscheit-Robbins F S Miller L L Alling E L and Whipple G H Plasma substitutes human and animal globin related to production of hemoglobin and plasma protein dog hemoglobin utilization improved by methionine but not by isoleucine *J Exper Med* 83 355-371 1946
- 78 Ashby, W Span of life of red blood cell resume *Blood* 3 486-500 1948
- 79 Hawkins W B and Whipple G H Life cycle of red blood cells *Am J Physiol* 122 418-427 1928
- 80 Shemin D and Rittenberg D Biological utilization of glycine for synthesis of protoporphyrin of hemoglobin *J Biol Chem* 166 621-625 1946
- 81 Idem Studies on formation of beme and on average lifetime of human red cell *Federation Proc* 5 153 1946
- 82 London I M Shemin D, and Rittenberg D Study of hemoglobin metabolism in man with aid of isotope technique *J Clin Investigation* 27 547 1948 (abstr)
- 83 Nizet, A Nouvelles recherches sur la physiopathologie des hématies IV. Durée de vie des hématies chez l'homme normal étudiée à partir de la reticulocytose *Acta med Scandinav* 127 565-569 1947
- 84 Hederstedt S Elliptocyte transfusions as method in studies on blood destruction blood volume and peritoneal resorption *Acta chir Scand* 95 (Supp. 128) 1-141 1947
- 85 Knisely M H Bloch, E H Eliot, T S and Warner L Sludged blood *Science* 106 431-440 1947
- 86 Blood sludge Photographic essay *Life* 24 49-59 (May 31) 1948
- 87 Knisely M H., Stratman-Thomas W K Eliot T S and Bloch E. H Knowless malaria in monkeys (motion picture) *J Nat Malaria Soc* 4 285-00 1945
- 88 Foreign Letters Italy National Association of blood donors *J A M A* 134 478, 1947
- 89 Foreign Letters London blood transfusion *J A M A* 134 204, 1947
- 90 Anderson H D Plasma program Michigan Department of Health *Proc Conf State & Prov Health Author North America* 59 60-117 125 1944-45
- 91 Moore L D, Edsall G and Getting, V A Massschnietts blood and blood derivatives program *J A M A* 135 548-552, 1947
- 92 Red Cross blood bank program *J A M A* 133 482, 1947 *Rd* 134 172 377 882 1035 and 1189 1947 *Ibid* 135 584 651 653 and 1018 1947
- 93 Greaves R I N *The Preservation of Proteins by Drying and Special Reference to the Production of Dried Human Serum and Plasma for Transfusion* Med Res Coun Spec Rep Ser No. 258 54 pp London His Majesty's Stationery Office 1946
- 94 Ward G R. Transfusion of plasma *Br M J* 1 301 1918.
- 95 Filatov A and Kartasevskij N G Die Transfusion von menschlichem Blutplasma als blutstillendes Mittel. *Zentralbl f Chir* 62 441-445 1935
- 96 Findlay G M and MacCallum, F O Note on acute hepatitis and yellow fever immunization *Tr Roy Soc Trop Med & Hyg* 31 297-303 1937
- 97 MacNalty A S *On the State of Public Health Annual report of the chief medical officer of the Ministry of Health for the year 1935* 235 pp London His Majesty's Stationery Office 1938
- 98 Findlay G M and MacCallum F O Hepatitis and jaundice associated with immunization against certain virus diseases *Proc Roy Soc Med* 31 799-805 1938
- 99 Soper F L and Smith H H Yellow fever vaccination with cultivated virus and immune and hyperimmune serum. *Am J Trop Med* 18 111-134 1938
- 100 Sartwell P E Infectious hepatitis in relation to blood transfusion. *Bull U S Army M Dept* 7 40-100 1947
- 101 Scheinberg I H Kinney T D and Janeway C. A. Homologous serum jaundice *J A M A* 134 841-848 1947
- 102 Brightman I J and Korns R F Homologous serum jaundice in recipients of pooled plasma *J A M A* 135 268-272 1947
- 103 Rosenthal L T Homologous serum hepatitis in civilian hospital. *Gastroenterology* 9 28 31 1947
- 104 Grossman C M and Seward E. W Homologous serum jaundice following administration of commercial pooled plasma report of eight cases including one fatality *New Eng J Med* 234 181-183 1946
- 105 Ginsberg H S Homologous serum hepatitis following transfusion *Arch Int Med* 79 555-569 1947
- 106 Wolf A M Mason J Fitzpatrick W J Schwartz, S O and Levinson S O Ultraviolet irradiation of human plasma to control homologous serum jaundice *J A M A* 135 175 177 1947
- 107 Oliphant J W Jaundice following administration of human serum. *Bull New York Acad Med* 20 429-445 1944
- 108 Gellis S S et al Inactivation of virus of homologous serum hepatitis in solutions of normal human serum albumin by means of heat *J Clin Investigation* 27 239-244 1948
- 109 Stokes J Jr and Neefe J R Prevention and attenuation of infectious hepatitis by gamma globulin preliminary note. *J A M A* 127 144 1945
- 110 Gellis S S et al Use of human immune serum globulin (gamma globulin) in infectious (epidemic) hepatitis in Mediterranean Theater of Operations studies on prophylaxis in two epidemics of infectious hepatitis *J A M A* 128 1032 1945
- 111 Havens W P Jr and Paul J R. Prevention of infectious hepatitis with gamma globulin *J A M A* 129 270-272 1945
- 112 Wilbur D L Therapeutic agents in liver disease review of medicinal agents *J A M A* 134 598-603 1947
- 113 Grossman E B Stewart S G and Stokes J Jr Post transfusion hepatitis in battle casualties and study of its prophylaxis by means of human immune serum globulin *J A M A* 129 991-994 1945
- 114 Robinson R W Hamblin W N Fleming R S and Queen F B Failure of immune serum globulin to prevent or modify course of infectious hepatitis homologous serum type *Proc Am. Federation Clin Research* 2 93 95 1945
- 115 Duncan G G et al Evaluation of immune serum globulin as prophylactic agent against homologous serum hepatitis *Am J M Sc* 213 53-57 1947
- 116 Neefe J R Gellis S S and Stokes J Jr Homologous serum hepatitis and infectious (epidemic) hepatitis studies in volunteers bearing on immunological and other characteristics of etiologic agents *Am J Med* 13 22 1946
- 117 Gauld R L Field studies relating to immunity in infectious hepatitis and homologous serum jaundice *Am J Pub Health* 37 400-405 1947
- 118 Paul, J R and Havens W P Jr. Recent advances in study of infectious hepatitis and serum (syndrome transmitted) jaundice *Tr Am Physicians* 59 133-141 1946.
- 119 Truelove S C and Hogben L Documentary study of jaundice associated with syphilis treatment and blood transfusion *Brit. J Social Med* 1 18-32 1947
- 120 Committee on Blood and Blood Derivatives of the American Red Cross Report on incidence of homologous serum jaundice following use of surplus dried plasma *J A M A* 135 714 1947
- 121 Lozner E L Lemish S Campbell A S and Newhouser L R Chemical preservation of normal human plasma in liquid state V Clinical chemical and physicochemical studies during three years of storage at room temperature *Blood* 1 459-471 1946

There is no definite statement that it was ever present.

We have to explain the presence of this mass in the left lower abdomen. That location is the graveyard of all gynecologic diagnoses. It is very difficult to make a diagnosis of a lesion in the left lower quadrant because of the presence of the sigmoid. That is where we "come a cropper" so many times. The patient was operated on for dysmenorrhea, and endometriosis was said to have been found. Apparently it was an external form of endometriosis. There is no mention of involvement of the ovary and nothing is said about what was done at the original operation. I do not know whether the tube and ovary were removed and showed evidence of endometriosis.

DR TRACY B. MALLORY: They were not removed. The surgeon reported that there was peritoneal endometriosis but did only a routine appendectomy.

DR PARSONS: There was a family history of tuberculosis. The chest films were normal. To go along with the possibility of tuberculosis of the tube is the fact that at one time the white-cell count was 3000, although it was said to have been associated with the taking of anacin tablets. It is interesting that every now and then one finds a patient who has a leukopenia at the time of her period. Possibly this was associated with the anacin tablets, on the other hand, she may have had a marked fall in the white-cell count at the time of the period. The fact that she had normal chest films does not necessarily rule out tuberculosis of the tube. The thing that is most likely to rule it out is the subsequent operation. The left tube and ovary and a follicular cyst of the right ovary were removed, and no mention of tuberculosis was made at that time. Unilateral tuberculosis is unlikely. Do we have any note of the pathology at the time of the removal of the left tube and ovary at the second operation?

DR MALLORY: In addition to the fibroid and the follicular cyst mentioned there was a ruptured corpus hemorrhagicum, but no endometriosis could be identified. The tube showed no evidence of tuberculosis.

DR PARSONS: That has some bearing on the rest of the picture. There is one other pathologic entity that closely simulates tuberculosis of the tube. Air insufflation was done followed by a salpingogram. In a number of cases in this hospital I have been grossly fooled. Lipiodol injected into the tube and uterus has produced a granulomatous type of lesion within the tube, and when these lesions develop on the outside of the tube they closely simulate tuberculosis. I do not believe one can distinguish it grossly, and it is very difficult for the pathologist to tell whether this lesion is tuberculosis of the tube or whether it is a granuloma associated with foreign-body reaction to the lipiodol. So that is a possibility.

Endometriosis was mentioned at the original operation and the patient was subsequently given testosterone therapy for dysmenorrhea, with partial relief. One would expect no more than partial relief from testosterone with the type of endometriosis that is external. If the testosterone inhibits the pituitary gland and thereby affects the uterine musculature, partial relief from the dysmenorrhea might occur. I assume that is why she was given it.

I think we have been, in the past, a little bit too ready to take out ovaries in association with endometriosis in younger girls. I think it is possible to be more conservative. The endometriosis can be resected out of the ovary and a fair amount of normal tissue left. However, it is difficult to tell grossly whether one is dealing with a corpus hemorrhagicum or a chocolate cyst due to endometriosis. There is one factor about the diagnosis of endometriosis that puzzles me. With endometriosis the tubes are invariably open and yet in the tests for sterility, the air did not pass readily and the lipiodol subsequently given met a block. The record does not say that there was block, it simply says "complete filling," but when the x-ray film was taken twenty-four hours later it failed to show passage of lipiodol in the peritoneal cavity. Three years before when she came into the hospital this tube must have been open. It is not invariable, but in 276 out of 283 cases of endometriosis that Sampson\* has reported, the tubes were open.

I think the adhesions present in the pelvis at the time of the second operation may well be explained by the presence of endometriosis, but again one would expect that to be ovarian. Adhesions do not occur with external implants on the peritoneum as in ovarian endometriosis.

Everything is "rigged" against pregnancy in this patient, and yet that is what I think she had. In the first place, the air insufflation is said to have shown a block in the only tube that she had. After lipiodol injection no droplets were seen in the peritoneal cavity when the film was taken subsequently. Nevertheless, she came in complaining of pain in the lower back, crampy pain in both lower quadrants associated with nausea, and a brownish vaginal discharge. I interpret this as a delayed period. She was said to have had a period that was normal in all respects two days before entry, but it is possible of course that this was not a normal period at all. I would assume death of the ovum within the tube and consequent bleeding, which might closely simulate a normal period. She had had some brownish vaginal discharge and some crampy lower abdominal pain. On examination the cervix was said to be tender on motion, and an ill defined mass could be felt in the right lower quadrant. The left tube and ovary had been removed. One interesting fact is that definite pulsations were felt in the right uterine artery. We do

\*Sampson J. A. Peritoneal endometriosis due to menstrual dissemination of endometrial tissue into peritoneal cavity. *Tr. Am. Gynec. Soc.* 52: 171-215, 1927.

- 196 Dougherty, T F., and White, A. Evaluation of alterations produced in lymphoid tissue by pituitary adrenal cortical secretion. *J Lab & Clin Med* 32 584-605 1947
- 197 Eisen, H N., Mayer M M., Moore D H., Tarr R. R., and Stoerk H C. Failure of adrenal cortical activity to influence circulating antibodies and gamma globulin. *Proc Soc Exper Biol & Med* 65 301-306 1947
- 198 Oncley, J L., Melin M., Cameron J W., Richert, D A., and Diamond, L. K. Methods for preparation of anti A, anti-B and anti-Rh isoagglutinin reagents. *Ann New York Acad Sc* 46 899-914 1946
- 199 Melin M. Chemical, clinical, and immunological studies on products of human plasma fractionation: preparation of anti A isoagglutinin from mixed blood of groups O and B. *J Clin Investigation* 24 662-670 1945
- 200 Cameron J W. and Diamond L K. Chemical clinical and immunological studies on products of human plasma fractionation: serum albumin as diluent for Rh typing reagents. *J Clin Investigation* 24 793-801 1945
- 201 Holmberg C G. and Laurell C B. Studies on capacity of serum to bind iron: contribution of knowledge of regulation mechanism of serum iron. *Acta physiol Scandinav* 10 307-319, 1945
- 202 Schade A L. and Caroline L. Iron binding component in human blood plasma. *Science* 104 340 1946
- 203 Sargenor, D M., Koechlin B A. and Strong L E. Chemical clinical and immunological studies on products of human plasma fractionation. XXXVII. Metal combining globulin of human plasma. *J Clin Investigation* (in press)
- 204 Koechlin, B A. Unpublished data.
- 205 Cartwright G E., Black, P., Wintrobe M M. Chemical clinical and immunological studies on products of human plasma fractionation. XXXIX. Anemia of infection: studies on iron binding capacity of serum. *J Clin Investigation* (in press)
- 206 Rath C E. Jr. and Finch C A. Chemical clinical and immunological studies on products of human plasma fractionation. XXXVIII. Serum iron transport — measurement of iron binding capacity of serum in man. *J Clin Investigation* (in press)
- 207 Laurell, C B. Studies on transportation and metabolism of iron in body, with special reference to iron binding component in human plasma. *Acta physiol Scandinav* 14 (supp 46) 1 129 1947
- 208 Szego C M. and Roberts S. Nature of circulating estrogen. *Proc Soc Exper Biol & Med* 61 161 164 1946
- 209 Roberts S., and Szego C M. Nature of circulating estrogen: Epprotein-bound estrogen in human plasma. *Endocrinology* 39 183 187 1947
- 210 Christensen L R. Activation of plasminogen by chloroform. *J Gen Physiol* 30 149-157 1946
- 211 McFarlane, R. G., and Pilling, J. Observations on fibrinolysis: plasminogen, plasmin and antiplasmin content of human blood. *Lancet* 2 562-565, 1946
- 212 Sargenor, D M., Strong L E., Taylor H L. and Gordoo, R. S. Jr. Unpublished data.

## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

EDITH E. PARRIS, *Assistant Editor*

### CASE 34411

#### PRESENTATION OF CASE

**First admission.** A twenty-eight-year-old married nulliparous housewife entered the hospital complaining of pain in the left lower abdomen.

She had had dysmenorrhea for several years. In the past she had had an appendectomy and uterine suspension, at which time endometriosis was found. There was a family history of tuberculosis, but the patient's chest films were consistently normal. Recently during her periods she had taken large numbers of anacin tablets and on one occasion the white-cell count fell to 3000. Examination revealed a small cervix and a large uterus, which was thought to contain a large fibroid. An operation was performed and a fibroid, 5 by 5 by 4 cm., was removed. Also removed were the left tube and ovary and a follicle cyst of the right ovary. Many adhesions were present in the peritoneal cavity.

**Second admission** (three years later). Following operation the patient was placed on testosterone therapy for severe dysmenorrhea. She had marked but not complete relief. She had extensive studies for sterility. Another fibroid appeared to be grow-

ing in the uterus. Air insufflation at 200 mm. of mercury produced no shoulder pain. Six months before admission a salpingogram showed complete filling of the right tube and of the proximal stump of the left. There was no escape of lipiodol into the peritoneal cavity.

For two and a half weeks before admission the patient complained of pain low in the back and crampy pain in both lower quadrants of the abdomen, associated with some nausea and a brownish vaginal discharge. Her period, which was three weeks late, commenced two days before admission and was normal in all respects. She stated that she had had delayed periods, brown discharge and similar pain with periods before, but the pain had not been quite so severe. There were no gastrointestinal, genitourinary or cardiorespiratory symptoms, or breast changes.

Physical examination revealed slight tenderness deep in the right lower quadrant, and on pelvic examination the cervix was firm, smooth, and somewhat tender on motion. The uterus was enlarged, apparently with a fibroid. There was a tender, ill defined mass in the right vault, and the pulsations of the right uterine artery were noticeably increased.

The temperature was 99.8°F. (Urine was taken for an Aschheim-Zondek test before admission, but the animals died before the reaction could be read.)

The day after admission an operation was performed.

#### DIFFERENTIAL DIAGNOSIS

**DR. LANGDON PARSONS.** One thing that intrigues me is the inaccuracy of pelvic examination at various times. First, the large uterus was thought to contain a large fibroid, at another time the fibroid appeared to be growing in the uterus, then the uterus was enlarged, apparently with a fibroid.

Physical examination disclosed a round area of swelling 10 cm in diameter in the left paravertebral region at the level of the lower part of the thorax. There was considerable tenderness to percussion, with diminution of breath sounds and tactile and vocal fremitus over this area. There was tenderness of the spleen on deep palpation. The liver edge was palpated one fingerbreadth below the costal margin in the epigastrium and was firm and nontender.

The temperature was 100.8°F, the pulse 94, and the respirations 20. The blood pressure was 98 systolic, 65 diastolic.

Examination of the blood revealed a hemoglobin of 9.8 gm and a white-cell count of 16,000, with 88 per cent neutrophils. Urinalysis gave a specific gravity of 1.018 and was negative for sugar, albumin and bile. A tuberculin test in a dilution of 1:10,000 was negative.

X-ray examination showed that the process in the left-lower-lung field had increased somewhat and was considerably larger than it had been originally. It was difficult to be certain whether it was primarily within the lung or pleura, but it seemed more likely that the bulk of the disease was in the lung. There was also soft-tissue thickening along the left paravertebral margin of the lower vertebrae, which was perhaps slightly more than at the time of previous study. The lumbar spine was not definitely abnormal.

An operation was performed on the fifth hospital day.

#### DIFFERENTIAL DIAGNOSIS

DR HELEN S. PITTMAN: I understand that the only x-ray film available is the one taken in the Out-Patient Department one week before admission. Is that correct?

DR JAMES J. MCCORT: Yes.

DR PITTMAN: So that we are missing an outside film taken twelve months before admission — said to be normal — and the Out-Patient Department film taken two weeks after, which was reported to show an area of pneumonitis in the posterior basilar segment of the left lower lobe and possibly a small amount of fluid in the left costophrenic sinus. Then we have the next one taken a week before admission. May we see that, Dr. McCort?

DR MCCORT: The area of pneumonitis described is present in the posterior basal segment of the left lower lobe. This segment also shows partial col-

lapse, and the left leaf of the diaphragm is elevated. A small amount of fluid is present in the left costophrenic sinus. The paravertebral thickening may be caused by a small amount of fluid in the left inferoposterior costomediastinal space. Soft-tissue thickening over the left lateral margin of the chest wall can be seen, and the normal, clear-cut outline of the subcutaneous fat line is lost on that side. The lung fields are otherwise clear. The heart and vessels are normal.

DR PITTMAN: The upper edge of the liver is down a little bit, perhaps one fingerbreadth. It does not necessarily indicate increased size, does it?

DR MCCORT: No.

DR PITTMAN: We are missing the first film taken on admission to the Out-Patient Department and the one taken in the house that shows this process reported in the left-lower-lung field to have increased somewhat and to be considerably larger than in the first film. It is difficult to be certain whether the process is primary in the lung or pleura, but more likely it is in the lung. The soft-tissue thickening along the paravertebral margin is perhaps slightly more marked.

I am having trouble discussing this case because I can make only one thing out of it and I think it is dangerous to have only one idea as soon as one reads a protocol. One should, I suppose, always think of a neoplasm. And this time I would think of neoplasm to exclude it. It does not seem to me that this is the history of neoplasm or that the x-ray films suggest any of the common features of neoplasm. And I am throwing neoplasm out now permanently.

The next thing in the history, which I suppose should get a moment of attention, is the story that the pain at the onset was in the right upper quadrant and was "gnawing," although it was unrelated to breathing or eating. A "gnawing" pain always makes one think of ulcer, but I am throwing that out because it seems to me that the idea that the chest process was anything secondary to the stomach is perfectly fantastic. I always remember a case of empyema that I saw many years ago when I was a house officer that was secondary to perforated ulcer, but I cannot make such a diagnosis fit here at all.

Then we come down, it seems to me, to infection. Infection has to be broken down into three groups: tuberculosis, the more common bacterial infections and the nonbacterial infections. This woman apparently had an acute onset. It was in

not know how often such pulsations are felt with ectopic pregnancy. As I say, everything has conspired against pregnancy. The fact that there were no breast changes is against pregnancy. She had had one follicular cyst, which required removal. This could have been another cyst with infarction, but I am inclined to think that it was an ectopic pregnancy.

DR. JOE V. MEIGS: I did the second and third operations. When I operated the first time the tube and ovary on the left side were included in a mass with a large fibroid, which I removed. The consensus at that time was that it was necessary to remove the left tube and ovary as well as the fibroid. I thought that it was endometriosis and took a suspicious area for biopsy, but according to the report that was sent back I was wrong, although I still thought that she had some. She had a good tube and ovary on the right side. Her husband's sperm count was 60,000,000, which Dr. Ingersoll thought was at the lower edge of normal. We would classify such a patient with a fibroid and endometriosis in the low fertility group and would not expect her to become pregnant. When the recent episode developed she thought that she was miscarrying and Dr. Morris, who went to see her, was of the same opinion. We found the uterus enlarged, with many intramural fibroids, and decided to do a hysterectomy.

#### CLINICAL DIAGNOSIS

Endometriosis  
Ectopic pregnancy?

#### DR. PARSONS'S DIAGNOSIS

Ectopic pregnancy

#### ANATOMICAL DIAGNOSES

*Tubal pregnancy*  
Endometriosis of peritoneal surface of uterus

#### PATHOLOGICAL DISCUSSION

DR. MALLORY: The sections from the tube did show recognizable chorionic villi. There was a very marked decidual reaction in the endometrium of the uterus. At the previous operation we failed to find the endometriosis that Dr. Meigs expected,

in spite of the fact that we examined many sections. On this occasion he sent the specimen over with the familiar safety pins in it, and on cutting our sections from those areas we found the endometriosis.

#### CASE 34412

##### PRESENTATION OF CASE

A thirty-four-year-old housewife entered the hospital complaining of pain in the left chest.

Five months prior to admission the patient had had a "cold," with a temperature of 101 and 103°F at night, without chills. The episode was associated with "gnawing" pain in the right upper quadrant, unassociated with eating or breathing and of an intermittent character. She had received penicillin once and sulfadiazine. X-ray films of the chest were reported normal. Two weeks later pain developed in the left upper quadrant, aggravated by deep breathing and associated with a dry morning cough. The pain gradually became more severe and extended to include the left paravertebral area. She was seen in the Out-Patient Department. X-ray examination showed an area of pneumonitis present in the posterior basilar segment of the left lower lobe and possibly a small amount of fluid in the left costophrenic sinus. The remaining lung fields were clear. The heart and vessels appeared normal. A diagnosis of pneumonitis with residual involvement of the left lower lobe was made. About one and a half months before admission another x-ray examination in the Out-Patient Department showed that the left lower lobe was slightly smaller and more dense than on previous examination. The diaphragm was adherent to the chest wall posterolaterally adjacent to this area. There was possibly a small amount of fluid also present. About one week before admission the patient was again seen in the Out-Patient Department. The left-chest pain, which had disappeared some time after the last visit, had recurred, had become continuous, and was of a pleuritic nature. Since the reappearance of pain, she had run a mild fever and had complained of some insomnia because of pain. At this time there was slight swelling in the left paravertebral region. A history of a weight loss of about 15 pounds since the beginning of the illness was elicited.

DR F THOMAS GEPHART At operation this patient obviously had a fluctuant mass over the left lower chest posteriorly, and we had intended to drain the empyema at the same time. However, when we opened the lesion along the lower medial aspect, we encountered an estimated 100 to 200 cc of cloudy pus, which had no unpleasant odor. We examined the cavity and found no areas of denudation of the ribs or any apparent break into the pleural cavity. So we felt that it would be better to pack this loosely and wall it off before sticking a needle into the chest to try to locate further fluid intrapleurally. We took cultures and a small amount of tissue for study.

DR MALLORY Have you anything to add, Dr Miller?

DR CARROLL C MILLER The only thing that I might add is that in operating we were cautious, particularly because of the location next to the vertebral column, thinking that it might possibly represent cold abscess with origin in the spine and that it might entail subsequent orthopedic maneuvers or possibly contamination of the spinal canal during a drainage operation. But we were more or less forced into operating — this lesion suddenly became so much larger and more tender. The patient was put on chemotherapy. I think two days before operation was done, and the chart actually looked better. In considering the chart alone we might have chosen to wait. After we saw the increased size and the tenderness of the process, we went ahead. I would like to make a statement from the therapeutic and diagnostic point of view — namely, to remind any listeners and subsequent readers of the advisability of being prepared to drain such a process immediately after tapping. This is said, not in criticism of the way in which

the case was handled, because no pus was obtained, but so often we find that a diagnostic tap of the chest is done — maybe in the office or in the patient's bed — without preparation for operation. And we subsequently see a fulminating infection of the chest wall, which requires much more surgical treatment than if it had been immediately drained — by "immediately" I mean within a few hours.

DR ROBERT H BROWNING This patient was seen in the Out-Patient Department, and one thing that is not mentioned in the history was that she was acutely tender over the spine, over the ninth, tenth and eleventh thoracic vertebrae. A few days later when I saw her on the wards the tenderness had disappeared. I wonder if there was any evidence to indicate whether the thoracic spine was involved in the process either at operation or subsequently.

DR MALLORY The tissue removed for biopsy showed many clusters of actinomycetes. I cannot tell you the extent of the anatomic involvement, or whether or not there was empyema or splenic or spinal involvement.

DR GEPHART A barium enema and an intravenous pyelogram were normal.

DR MALLORY Is the patient still in the hospital?

DR GEPHART Yes, she is still in the hospital. She has been afebrile and feels much better. The chest-wall cavity is closing down, although it has been open.

DR PITTMAN What are you treating her with?

DR GEPHART We started on penicillin, but after discussing the case with Dr Kane we have taken several cultures and are trying to find out the sensitivity of this particular organism to various chemotherapeutic agents. At the present time we are also treating her with streptomycin.

the chest, and therefore we should think about tuberculosis. Also, the fact that pleural pain was a rather constant feature should make one think about tuberculosis. It seems to me, going back to two weeks after the onset when the pain moved from the right upper quadrant to the left upper quadrant and was aggravated by deep breathing and associated with morning cough, that the pain was pleural — pain of pleural irritation. The tuberculin test at 1:10,000 dilution was negative. There is no history of sputum at any time, and so none was available for examination. I do not believe that tuberculosis needs to be considered any further.

So far as the common bacterial infections in the chest are concerned, this case began with a "cold," which according to our information was associated with fever and I suppose the common things that go with so-called "colds," and then a morning cough. At that time, when she came to the Out-Patient Department, two weeks after the onset, she had what was interpreted as pneumonitis with residual involvement in the left lobe. The initial x-ray film was said to be entirely clear. Did she have a pneumonia that only partially resolved? Did she have an empyema secondary to that pneumonia? I do not believe she did, and that brings me down to the other group of nonbacterial infections. And of that group I thought immediately of actinomycosis, and I cannot get away from it. We think now that one does not have to suck a straw or anything of that sort to introduce actinomyces into the body. They are present about the teeth and in the mouths of healthy people, at least part of the time, and they go down into the chest and start off the process, which I understand usually starts in the bronchi. I do not know anything about that stage of the disease from personal experience — that is just what I read. This woman started with signs of infection, she then developed a cough, having had some pleural pain (granted, before she had anything in the nature of a cough), and when she first appeared for x-ray study, she had a process in the left-lower-lung field and probably in the pleura. That went on for a bit, and then the symptoms subsided, which is perfectly commonplace in a story of an infection with actinomycosis. She then had a recurrence, having meanwhile come in with signs of chronic infection, such as fever, loss of weight, a significant anemia (98 gm of hemoglobin) and a moderate leukocytosis (white-cell count of 16,000), with 88 per cent neutrophils. The

urine was entirely normal. When she came in the process in the chest had increased. She had a round area of swelling, 10 cm in diameter, on the left posteriorly at the level of the lower thoracic region. We know that actinomycosis invades the pleura, we know it invades the chest wall. She had a tender and palpable spleen, actinomycosis also invades the spleen, or one might have a tender area in the region of the spleen. One may have inflammation in the region above or below the diaphragm, with pleural involvement. So although I think she may have had disease in the spleen, I would not be surprised if she failed to show it. The only preoperative diagnosis that I can make is actinomycosis, and my assumption is that the operation performed was a needle biopsy of this area on the back of the chest or possibly exploration of it.

DR JACOB LERMAN: When this patient first came on the ward the striking thing about the physical findings was the swelling of the chest wall. The lower half of the wall posteriorly was swollen, which was a little unusual in the presence of signs of empyema and pneumonitis. It is not mentioned in the record, but a needle was inserted into the chest wall by the resident, who was unable to obtain fluid. On the following day the swelling of the chest wall increased considerably. We assumed that he got into an area of pus. The service thought that it was necessary to rule out the various types of common organisms that infect the pleura following pneumonia, and, in addition, the uncommon types, particularly pneumonia due to Friedländer's bacillus with empyema. We discussed the possibility of mycotic infections of the chest wall, resulting from empyema. Unfortunately, we did not obtain a culture from the needle so that we were unable to settle the problem until operation was performed.

#### CLINICAL DIAGNOSIS

Unresolved pneumonia, with empyema

#### DR PITTMAN'S DIAGNOSIS

Actinomycosis

#### ANATOMICAL DIAGNOSIS

*Actinomycosis of chest wall*

#### PATHOLOGICAL DISCUSSION

DR TRACY B MALLORY: Will you tell us the operative findings, Dr Gephart?

DR F THOMAS GEPHART At operation this patient obviously had a fluctuant mass over the left lower chest posteriorly, and we had intended to drain the empyema at the same time. However, when we opened the lesion along the lower medial aspect, we encountered an estimated 100 to 200 cc of cloudy pus, which had no unpleasant odor. We examined the cavity and found no areas of denudation of the ribs or any apparent break into the pleural cavity. So we felt that it would be better to pack this loosely and wall it off before sticking a needle into the chest to try to locate further fluid intrapleurally. We took cultures and a small amount of tissue for study.

DR MALLORY Have you anything to add, Dr Miller?

DR CARROLL C MILLER The only thing that I might add is that in operating we were cautious, particularly because of the location next to the vertebral column, thinking that it might possibly represent cold abscess with origin in the spine and that it might entail subsequent orthopedic maneuvers or possibly contamination of the spinal canal during a drainage operation. But we were more or less forced into operating — this lesion suddenly became so much larger and more tender. The patient was put on chemotherapy. I think two days before operation was done, and the chart actually looked better. In considering the chart alone we might have chosen to wait. After we saw the increased size and the tenderness of the process, we went ahead. I would like to make a statement from the therapeutic and diagnostic point of view — namely, to remind any listeners and subsequent readers of the advisability of being prepared to drain such a process immediately after tapping. This is said, not in criticism of the way in which

the case was handled, because no pus was obtained, but so often we find that a diagnostic tap of the chest is done — maybe in the office or in the patient's bed — without preparation for operation. And we subsequently see a fulminating infection of the chest wall which requires much more surgical treatment than if it had been immediately drained — by "immediately" I mean within a few hours.

DR ROBERT H BROWNING This patient was seen in the Out-Patient Department and one thing that is not mentioned in the history was that she was acutely tender over the spine over the ninth, tenth and eleventh thoracic vertebrae. A few days later when I saw her on the wards the tenderness had disappeared. I wonder if there was any evidence to indicate whether the thoracic spine was involved in the process either at operation or subsequently.

DR MALLORY The tissue removed for biopsy showed many clusters of actinomycetes. I cannot tell you the extent of the anatomic involvement, or whether or not there was empyema or splenic or spinal involvement.

DR GEPHART A barium enema and an intravenous pyelogram were normal.

DR MALLORY Is the patient still in the hospital?

DR GEPHART Yes, she is still in the hospital. She has been afebrile and feels much better. The chest-wall cavity is closing down, although it has been open.

DR PITTMAN What are you treating her with?

DR GEPHART We started on penicillin, but after discussing the case with Dr Kane we have taken several cultures and are trying to find out the sensitivity of this particular organism to various chemotherapeutic agents. At the present time we are also treating her with streptomycin.

# The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established 1828

Official Organ of

THE MASSACHUSETTS MEDICAL SOCIETY

and

THE NEW HAMPSHIRE MEDICAL SOCIETY

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND  
PUBLISHED WEEKLY UNDER THE JURISDICTION OF THE  
COMMITTEE ON PUBLICATIONS

James P. O'Hare M.D. Richard M. Smith, M.D. Chairman  
Oliver Cope M.D. Conrad Vessellhoeft M.D.  
John Fallon M.D.

Joseph Garland M.D., Editor

ASSOCIATE EDITORS

Thomas H. Linnaman M.D. Donald Mudro, M.D.  
Henry Jackson, Jr. M.D.

Clara D. Davies EXECUTIVE EDITOR

Robert O'Leary ASSISTANT EDITOR

EDITORIAL BOARD

C. Guy Lane M.D. Maxwell Finland M.D.  
Henry R. Vieta, M.D. James M. Faulkner M.D.  
Robert M. Green M.D. Carroll B. Larson, M.D.  
Dwight O'Hara M.D. Francis D. Moore M.D.  
Fletcher H. Colby, M.D. C. Stuart Welch M.D.  
Robert L. Goodale M.D. Vernon P. Williams M.D.  
Chester M. Jones M.D. Benjamin Castleman M.D.  
Harvey R. Morrison M.D. Hugh R. Leavell M.D.

SUBSCRIPTION TERMS \$7.00 per year in advance, postage paid for the  
United States (medical students \$4.00 per year) Canada \$8.00 per year  
(Boston funds) \$9.50 per year for all foreign countries belonging to the  
Postal Union

MATERIAL should be received not later than noon on Thursday three  
weeks before date of publication

THE JOURNAL does not hold itself responsible for statements made by any  
contributor

COMMUNICATIONS should be addressed to the *New England Journal of  
Medicine*, 8 Fenway, Boston 15, Massachusetts. Telephone KE 6-2094

NEW ENGLAND ADVERTISING REPRESENTATIVE, Edwin B. Tyler, 89 State  
Street, Boston, Massachusetts. Telephone LA 3-5516

## ELEVENTH HOUR

ON JUNE 20 Dr Paul R. Hawley, speaking before the presidents and other officers of the various state medical associations, warned them that the moment of reckoning was at hand, that the hour was about to strike after which it would be too late for the medical profession in this country to determine its own future course. There is a strong and growing demand for national health insurance on the part of many powerful and resolute groups in the nation, and already the point has been reached "when the medical profession has the choice only of making a reasonable effort to meet the requirements of these large groups of consumers of medical care, or of watching the private practice of medicine in this country being rapidly

strangled by either co-operative or Government medicine. No other alternatives are left."

This was a straightforward declaration by the chief executive officer of the Blue Cross and Blue Shield Commissions reiterating the important decision that faces medicine today. This decision is not whether there shall be effected an equitable distribution of medical care or whether a planned medical economy is desirable, but who shall bring about these changes.

Organized medicine, so-called (a name now changed to the noncommittal term "medical profession," a faint but fetid aroma having developed about the term "organized"), takes its steps always too reluctantly. It is the conservative bulwark of an ancient calling, and slow motion is almost implicit in its design, each year only those compromises with social reform being accepted that might have been considered progressive in the previous decade. Whether tardy approach is an utter necessity is another matter. Large bodies can sometimes move rapidly in the face of impending disaster.

This slowly moving body, however, is in the unfortunate predicament of being harassed by a confusion of committees and leagues and other groups, each, no doubt, completely worthy according to its principles, but whose insistence serves also to obscure the issue and to hide the light. They are the champions of private practice and a reformed status quo—the pillars of professional dignity; they are the advocates of universal and compulsory state medicine; they are, like General Hawley, the agents of a free system of prepaid medical care, delivered on an actuarial basis, which, today, might be considered as the middle lane of the road down which mankind is traveling.

In all justice the statement may be tentatively advanced and might still prove acceptable to a reasonable majority that this country is not yet ready for that compulsion of which there is already too much in the world. It must be remembered however, that a compulsory Government insurance plan received strong support in the deliberations of the Section on Medical Care of the recent National Health Assembly.

The profession of medicine is not on as sure a footing with its public as might be wished, it has

so far done less than it could and than it should have done to ensure reasonably adequate medical care to all the people. It must remember that some of the criticisms directed toward it in this respect are in a sense a basic compliment. They are an acknowledgment that the services of medicine are considered by the people to be equally indispensable with the various accepted public services and, indeed, the very freedoms that are cherished — pure water and sanitation, police and fire protection, education, freedom of speech and of worship and the privilege of representative government.

If the medical profession does not assume active leadership, however, in assuring adequate distribution of its services and that very shortly, its opportunity will be gone. It is the eleventh hour and there are many that still stand idle outside the vineyard.

### INTERNATIONAL HEALTH PROGRAMS

THE World Health Organization, now firmly established as a member agency of the United Nations, held its first World Health Assembly in Geneva in June and July 1948. As a major part of the constructive work of the Assembly, provisional agenda for various international programs were drawn up and approved.

The Committee on Programme placed malaria control first on the list of recommended activities in view of the high prevalence of the disease with hundreds of millions of cases and millions of deaths occurring each year. Next in order came maternal and child health, tuberculosis and venereal diseases. For further activities it was recommended that particular attention should be given to alcoholism, drug addiction and habit-forming drugs, hygiene of seafarers, influenza, nursing, nutrition, rural hygiene and schistosomiasis.

The proposed methods of attack under each major title are divided into specific procedures, the details of which are pertinent to that subject. These consist of a statement of the particular objectives to be sought, the development of a program of study, the provision of suitable assistance to governments and a program of action on the international plane.

So the world makes its slow progress, with men and nations of good will struggling for mutual bene-

fits in the shadow of still stronger destructive forces. As Sisyphus toiling with his stone in Hades could never quite reach the top of the hill, so mankind, constantly frustrated, still lives in constant hope that at some time all men and all nations may bend their efforts toward a common goal.

### COST OF THE COMMON COLD

AN ATTEMPT to arrive at a rough approximation of the cost to the American people of their common colds has been made by the statisticians of the Metropolitan Life Insurance Company,\* who came up with the appalling figure of well over \$1,000,000,000 a year. This figure was obtained by taking into account the data on incidence of the disease among wage earners, students and other special groups, according to the studies of many reliable investigators. The calculations ran somewhat as follows:

The average person suffers at least 2 colds a year or approximately 300 million annually for the entire country. The average duration of the simple cold is five days, giving a total of one and a half billion days of discomfort, decreased efficiency or disability. A conservative estimate of the time lost from work in this country is one day per employee per year, or more than sixty-million days lost in industry from this cause. Even at a low average of \$7 a day, the result in wages alone is more than \$420,000,000 annually.

The amount spent on medical care and drugs for the treatment of colds by the average family is impossible to arrive at, but it was assumed to be about \$10 a year, or a total of about \$400,000,000. No attempt was made to estimate the cost to employers resulting from the loss of production and disrupted routine, but it, too, must reach a considerable figure for the country as a whole.

These calculations led the Metropolitan's statisticians to arrive at the estimate of over \$1,000,000,000 a year as the cost of the common cold to the American people. Although the common cold is generally considered to be a minor illness, they concluded that any disease in which the cost runs to such astronomical figures must be rated high in the list of enemies of the public health.

\*Cost of common cold. *Statist. Bull. Metrof. Life Insur. Co.* 28 (No. 11) 6, 1947.

## LIFE INSURANCE MEDICAL RESEARCH FUND

THE Life Insurance Medical Research Fund, organized in 1945 by a group of United States and Canadian life-insurance companies, with Dr Francis R. Dieuaide as scientific director, has recently issued its third annual report. At the beginning of 1947 the Fund was contributing to the support of fifty-one research programs and nineteen research fellows. During the year this number was materially increased.

Present studies in which the Fund is interested are directed mainly toward the problems of heart disease, so important from the actuarial point of view, and are grouped under five general headings. These include studies on cellular metabolism of the heart and blood vessels, studies of the flow of blood, studies of kidney function and the development of hypertension, studies of the development of arteriosclerosis and studies of the causes of rheumatic fever.

Contributions by the life-insurance companies to research into the causes of premature death represent a sound investment on their part. Their profits are increased by human longevity, and, conversely, favorable results in the attainment of longevity should have their favorable effect on insurance premiums. It must still be borne in mind, however, lest universal longevity be achieved too rapidly, that the breadth of life may be more important than its length.

## MISCELLANY

### MEDICAL DIRECTOR OF LEVER BROTHERS COMPANY

The appointment of Dr. John J. Poutas, assistant medical director and chief of professional services in the New England office of the Veterans Administration, as medical director of Lever Brothers Company, Cambridge, has been announced.

## NOTICES

### SOUTH END MEDICAL CLUB

A meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, on Tuesday, October 19, at 12 noon. Dr. Paul G. Myerson will speak on the subject "New Trends in Psychiatric Treatment."

This meeting will mark the beginning of the twenty-second year for the South End Medical Club. Physicians are cordially invited to attend.

### NEW ENGLAND SOCIETY OF ANESTHESIOLOGISTS

A meeting of the New England Society of Anesthesiologists will be held in the Auditorium of Building A, Boston University School of Medicine, 80 East Concord Street, Boston,

on Monday, October 18, at 8 p.m. The scientific program will be presented by Dr. Donald E. Hale, Cleveland Clinic, Cleveland, Ohio, whose subject will be "Anesthesia for Neurosurgery. Use of hypotension."

Physicians and medical students are invited to attend.

### JOSEPH H. PRATT DIAGNOSTIC HOSPITAL

Bennet Street, Boston  
Lecture Hall, 9-10 a.m.

#### MEDICAL CONFERENCE PROGRAM

Friday, October 8 — Metabolic and Therapeutic Problems of Alkalosis. Dr. Charles H. Burnett.  
Wednesday, October 13 — Journal Review.  
Friday, October 15 — Renal Tuberculosis. Dr. Roger C. Graves.  
Wednesday, October 20 — Pediatric Clinicopathological Conference. Drs. James M. Baty and H. E. MacMahon.  
Friday, October 22 — Rice Diet. Some experimental and clinical observations. Dr. William B. Schwartz.  
Wednesday, October 27 — Some Problems in Clinical Cancer Research. Dr. Fred Homburger.  
Friday, October 29 — Some Special Features of Marked Mitral Stenosis. Dr. Edward F. Bland.

On Tuesday and Thursday mornings from 9 to 10 Dr. S. J. Thannhauser will give medical clinics on hospital cases. On the second and third Friday afternoons in October therapeutic conferences will be held from 2 to 4 with round table discussion. Dr. Robert P. McCombs, moderator, the speakers will be Dr. Somers H. Sturgis, whose subject will be "Sterility," and Dr. Fred Homburger, whose subject will be "Chemotherapy of Cancer." On the second and fourth Friday afternoons of each month Dr. Merrill Sosman will conduct x-ray conferences from 4 to 6. On Saturday mornings from 9 to 10 clinics will be given by Dr. William Dameshek. Medical rounds are conducted each weekday except Saturday by members of the staff from 12 to 1.

All exercises are open to the medical profession.

### NEW ENGLAND DIABETES ASSOCIATION

The fall meeting of the New England Diabetes Association will be held in the Cheever Amphitheater of the Boston City Hospital on Wednesday, October 20, at 8:00 p.m.

The speaker of the evening will be Dr. George W. Thorn, whose subject will be "Some Fundamental Endocrine Relations in Diabetes."

After the clinical program there will be an important business meeting of the Association to discuss future policies.

### SOCIETY MEETINGS AND CONFERENCES

#### CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, OCTOBER 14

##### FRIDAY, OCTOBER 15

\*9:00-10:00 a.m. Renal Tuberculosis. Dr. Roger C. Graves. Joseph H. Pratt Diagnostic Hospital.  
\*9:00 a.m.-12:00 p.m. Combined Medical and Surgical Staff Rounds. Peter Bent Brigham Hospital.  
\*12:00 p.m. X-Ray Conference. Margaret Jewett Hall. Mt. Auburn Hospital. Cambridge.

##### MONDAY, OCTOBER 18

\*8:00 p.m. New England Society of Anesthesiologists. Auditorium of Building A. Boston University School of Medicine.

##### TUESDAY, OCTOBER 19

\*12:00 p.m. South End Medical Club. Boston Tuberculosis Association. 554 Columbus Avenue, Boston.  
\*12:15-1:15 p.m. Clinicoradiogenetological Conference. Peter Bent Brigham Hospital.  
\*1:30-2:30 p.m. Pediatric Rounds. Brnham Memorial Hospital for Children. Massachusetts General Hospital.

##### WEDNESDAY, OCTOBER 20

\*9:00-10:00 a.m. Pediatric Clinicopathological Conference. Drs. James M. Baty and H. E. MacMahon. Joseph H. Pratt Diagnostic Hospital.  
\*11:00 a.m.-12:00 p.m. Medical Clinic. Amphitheater. Children's Hospital.  
\*12:00 p.m. Clinicopathological Conference (Children's Hospital). Amphitheater. Peter Bent Brigham Hospital.  
\*2:00-3:00 p.m. Combined Clinic by the Medical Surgical and Orthopedic Services. Amphitheater. Children's Hospital.

\*Open to the medical profession.

(Notices concluded on page xiii)

# NOTICES (Concluded from page 564)

- OCTOBER 1-MAY 20 Metropolitan State Hospital Page 413 issue of September 9
- OCTOBER 4-15 New York Academy of Medicine Page 492 issue of September 23
- OCTOBER 8-29 Joseph H. Pratt Diagnostic Hospital Medical Conference Program. Page 564
- OCTOBER 9 Suffolk District Medical Society Page 452 issue of September 16
- OCTOBER 12 Harvard Medical Society Page 530 issue of September 30
- OCTOBER 14 The Practical and Clinical Sides of the Management of the Rh Problem in Pregnancy Dr. William C. Moloney Pentucket Association of Physicians 8 30 p.m. Haverhill
- OCTOBER 15 American Trudeau Society Page 418 issue of September 9
- OCTOBER 18 New England Society of Anesthesiologists Page 564
- OCTOBER 18-22 American College of Surgeons Page 417 issue of September 9
- OCTOBER 19 South End Medical Club Page 564
- OCTOBER 20 New England Diabetes Association Page 564
- OCTOBER 20 New England Dermatological Society Page 530 issue of September 30
- OCTOBER 27 New England Obstetrical and Gynecological Society Annual Meeting Hotel Somerset, Boston
- OCTOBER 27 New England Pediatric Society Page 530 issue of September 30
- OCTOBER 31 and NOVEMBER 1 American Society for the Study of Arteriosclerosis Page 530 issue of September 30
- NOVEMBER 1-3 American Clinical and Climatological Association Page 582 issue of April 15
- NOVEMBER 3 and 4 Annual Meeting of National Committee for Mental Hygiene, Inc. Page 282 issue of August 12
- NOVEMBER 3-5 Seventh New England Postgraduate Assembly Copley Plaza Hotel Boston
- NOVEMBER 4-6 American Society of Anesthesiologists Page 418 issue of September 9
- NOVEMBER 8-12 American Public Health Association Page 420 issue of March 18
- NOVEMBER 10-13 Association of Military Surgeons of the United States Page 722 issue of May 13
- NOVEMBER 20-23 American Academy of Pediatrics Annual Meeting Chalfonte-Haddon Hall Hotel Atlantic City New Jersey
- NOVEMBER 30 Hampden District Medical Society Page 492 issue of September 23
- DECEMBER 2 Suffolk Censors Meeting Page 492, issue of September 23
- DECEMBER 7-9 Southern Surgical Association Annual Meeting Page 543 issue of April 8
- DECEMBER 9 and 10 New York State Society of Anesthesiologists Page 54 issue of July 1
- FEBRUARY 4 1949 American Board of Obstetrics and Gynecology L.C. Page 244 issue of August 5
- MARCH 25-APRIL 1 1949 American College of Physicians Page 158 issue of July 22
- MAY 16-19 1949 American Urological Association Biltmore Hotel Lancaster
- MAY 26-28 1949 American Gynecological Association Hotel Lorraine Madison Wisconsin
- NOVEMBER 11-17 1949 Third Inter American Congress of Radiology Page 158 issue of July 22

## DISTRICT MEDICAL SOCIETIES

### HAMPDEN

NOVEMBER 10 8:30 p.m. Academy of Medicine Springfield Care of the Breast. Dr. Grantley W. Taylor

### SUFFOLK

OCTOBER 9 Fall Dinner  
DECEMBER 2 Suffolk Censors Meeting

## PENICILLIN

by

DONALD G. ANDERSON and  
CHESTER S. KEEFER

## STREPTOMYCIN

by


CHESTER S. KEEFER and  
WILLIAM L. HEWITT

These two new books discuss the therapeutic value of penicillin and streptomycin and give the results of clinical investigations of 10 000 and 3000 cases respectively conducted by the Committee on Chemotherapy of the National Research Council

Each book contains approximately 500 pages \$7.00 each

J. W. EDWARDS

Ann Arbor, Michigan



**LABORATORY C&B REAGENTS**

Inorganic and Organic Chemicals  
Biological Stains • Solutions  
Chemical Indicators • Test Papers

*Distributed by*  
Physician and Laboratory Supply Houses

**The COLEMAN & BELL COMPANY, Inc.**  
MANUFACTURING CHEMISTS      NORWOOD OHIO U.S.A.

**COLEMAN & BELL** *Norwood, Ohio*

BAKER'S Combined Vitamins	BAKER'S Therapeutic Vitamins
5000 U.S.P. Units Vitamin A	12,500 U.S.P. Units Vitamin A
1000 U.S.P. Units Vitamin D	1000 U.S.P. Units Vitamin D
5 mg. B <sub>1</sub> Thiamin Chloride	10 mg. B <sub>1</sub> Thiamin Chloride
5 mg. B <sub>2</sub> Riboflavin	10 mg. B <sub>2</sub> Riboflavin
1 mg. B <sub>3</sub> Pyridoxine	2 mg. B <sub>3</sub> Pyridoxine
5 mg. Calcium Pantothenate	10 mg. Calcium Pantothenate
50 mg. Nicotinamide	75 mg. Nicotinamide
75 mg. Ascorbic Acid (Vit. C)	150 mg. Ascorbic Acid (Vit. C)
5.67 mg. Mixed Tocopherols (Vit. E)	5.67 mg. Mixed Tocopherols (Vit. E)
\$3.00 per Hundred	RETAIL PRICE \$6.50 per Hundred
Available to druggists through their wholesaler	
<b>Chester A. Baker Laboratories, Inc.</b> BOSTON MASS	

## CHARLES B. TOWNS HOSPITAL

Established 1901

### for ALCOHOLISM, NARCOTIC AND BARBITURATE ADDICTIONS exclusively

THE TOWNS TREATMENT is a medical and psychiatric procedure

Withdrawal of narcotics, either opiates or synthetics, is by gradual reduction and specific medication. After 47 years, this treatment is generally accepted as standard. Physicians and psychiatrists in residence. Trained nursing, physio- and hydrotherapy staff.

Patients are assured of complete privacy if desired

Length and cost of treatment are pre-determined

Advantageously situated facing Central Park. Solarium and recreation roof. Excellent cuisine and service.

*Letters are or Request*

W. D. SILEWORTH  
Medical Sup.

EDWARD B. TOWNS  
Director

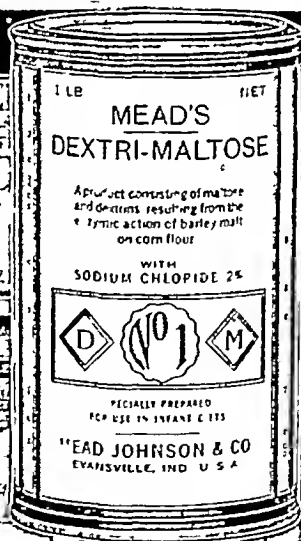
293 CENTRAL PARK WEST NEW YORK 24 N.Y. SCHUler 4-0770

*Member American Hospital Association  
Officially approved by the American Medical Association*

# BACKGROUND

The use of cow's milk, water and carbohydrate mixtures represents the one system of

infant feeding that consistently, for over three decades, has received universal pediatric



recognition. No carbohydrate employed in this system of infant feeding enjoys so rich and enduring a background of authoritative clinical experience as Dextri Maltose.

# The New England Journal of Medicine

Copyright 1948 by the Massachusetts Medical Society

Volume 239

OCTOBER 14, 1948

Number 16

## DISSEMINATED LUPUS ERYTHEMATOSUS OCCURRING AMONG STUDENT NURSES\*

L. FRED AYVAZIAN, M.D.,\* AND THEODORE L. BADGER, M.D.†

BOSTON

IN the course of a follow-up survey† on a group of 750 nurses who trained at a large municipal hospital between 1932 and 1946,<sup>1</sup> it was found that 3 of these girls had developed and succumbed to disseminated lupus erythematosus. These cases represent 23 per cent of the total mortality among the nurses, the disease being second only to tuberculosis as the major cause of death. The deaths in the entire group have numbered 13, and have been distributed as shown in Table 1.

The occurrence of lupus three times in this group is by itself a curious and unexpected finding, but its interpretation and significance are doubtful. These figures obviously cannot be compared to the causes of death in the general population of this age group and sex, since several artificial factors enter into the selection of this group to distort the pattern. A search for a factor common to the 3 cases, however, brought to light several circumstances that appear to have a direct bearing on the present-day concepts of the pathogenesis and etiology of the disease.

### ETIOLOGY OF DISSEMINATED LUPUS ERYTHEMATOSUS

Since the earliest reviews on the subject there has remained a group, mainly French, Austrian and Scandinavian, who consider the tubercle bacillus as the etiologic agent in lupus. The great volume of clinical and autopsy material, however, lends no support to this concept, and in this country at least it has been virtually discarded.<sup>2</sup>

A second group, consisting mainly of the British, have become convinced that the hemolytic streptococcus is most usually responsible for the disease. The evidence for this concept is reviewed below.

The etiology of lupus is less definitely stated in this country. Ginzler and Fox<sup>3</sup> (1940) state "There is a tendency at present to regard the disease as a peculiar response, in a constitutionally predisposed

person, to a variety of harmful agents." Multiple etiologic factors are in general considered to be instrumental. The varied etiologies postulated assume the form of tissue sensitization to and destruction by various bacteria or toxins, and are in agreement with Bloch's<sup>4</sup> dictum that "the type and course of the allergic reaction are independent of the nature of the antigen, but vary according to the localization of the antibody, that is, according to which organ reacts to the antigen." The streptococcus is again the organism most frequently

TABLE 1 Causes of Death Among 750 Nurses, 1932-1946

CAUSE OF DEATH	NO. OF CASES	PERCENTAGE OF DEATHS
Tuberculosis	4	30.7
Disseminated lupus erythematosus	3	23.0
Staphylococcal septicemia	1	7.7
Carcinoma	1	7.7
Accident and suicide	2	15.4
War casualty	2	15.4

incriminated, with the pneumococcus,<sup>5</sup> staphylococcus and even the gonococcus<sup>6</sup> receiving mention. Among nonbacterial agents, horse serum has received attention, as in the case of lupus described by Fox,<sup>7</sup> in which the disease followed the administration of prophylactic antitetanus serum. Throughout the entire pattern, hypersensitivity and allergy now receive major consideration.

In spite of these various speculations the etiology of lupus has remained unknown. It is of interest, however, to review the accumulating evidence supporting the concept that includes lupus among other diseases thought to be associated with allergy and hypersensitivity.<sup>2, 5-15</sup>

### Allergy or Hypersensitivity

The clinical and pathological features of the syndrome have been compared to the manifestations of serum sickness, and the correlation is frequently extremely suggestive. Indeed, lupus has been claimed by many to represent a prolonged, malignant form of serum sickness.<sup>7</sup>

The pathology of lupus has received critical consideration in several papers, and the findings are

\*Research fellow Harvard Medical School; research fellow and assistant in medicine, Thorndike Memorial Laboratory, Boston City Hospital.

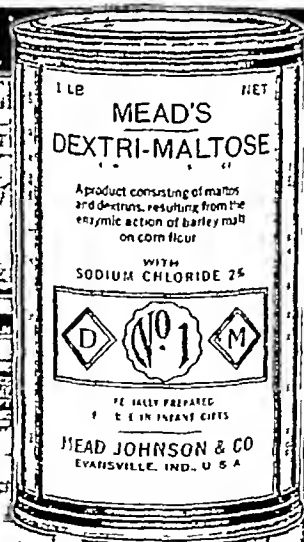
†Instructor in medicine, Harvard Medical School; junior visiting physician and chief of Thoracic Clinic, Boston City Hospital; consultant in cases of the lungs, Veterans Administration.

†This follow-up survey of tuberculosis in nurses was made possible through a grant from the National Tuberculosis Association.

# BACKGROUND

The use of cow's milk, water and carbohydrate mixtures represents the one system of

infant feeding that consistently, for over three decades, has received universal pediatric



recognition. No carbohydrate employed in this system of infant feeding enjoys so rich and enduring a background of authoritative clinical experience as Dextri Maltose.

fever and differing from that seen in other sulfonamide reactions. In addition to this observation, it is claimed by Barber as well as others in England<sup>30</sup> and this country<sup>31</sup> that treatment of lupus with the sulfonamides and, later, penicillin has met with dramatic results far superior to any other known therapy, although other reports list such therapy as a failure.<sup>32</sup>

It is further claimed that at least among the cases seen in England streptococcal septicemia is a usual form of death in fatal cases, and that evidence of tuberculosis is usually lacking at autopsy.<sup>29</sup> It is postulated by Barber that disseminated lupus erythematosus represents a nonspecific syndrome capable of being provoked by a variety of bacteria or toxins and that in England this agent is in most cases the hemolytic streptococcus, but that in other vicinities the tubercle bacillus may be of greater significance.

Working with a streptococcus isolated from patients with pemphigus, Welsh<sup>33</sup> was able to demonstrate that the serums from cases of lupus possessed antibodies against the organism. Although antistreptolysin titers are not usually measured in such cases, the titer has been shown to reach significant levels such as 1:640.<sup>34</sup> Denzer and Blumenthal,<sup>35</sup> testing the response to Dick toxin in a case of lupus, found it necessary to raise the dose to 120 units before a positive reaction was obtained. These authors state:

We do not know how to evaluate this finding. Dr Dick has advised us that it is unusual, that there are few people who failed to give a cutaneous reaction with such large doses of toxin.

### CASE REPORTS

All the cases of disseminated lupus in this series began insidiously with bizarre manifestations before the disease became clinically recognizable. Each case terminated fatally, and in each the diagnosis was confirmed at autopsy. In compiling the case summaries we gathered information from hospital records, clinic charts and files of the training-school office, and the final integrated summary appears to form a meaningful chronologic picture.

The first case presents a pattern in accord with the present-day concepts of the etiology of the disease, whereas the second and third cases are less convincing.

**CASE 1** J. S., an 18-year-old Negress, entered the training school in February, 1938. The history and physical examination were not remarkable at that time, and the tuberculin reaction was negative. In the fall of 1938 tests and inoculations were begun as follows: on October 1, 1938, Schick test (positive on October 5), on October 3, Dick test (positive on October 4), on October 10, 0.25 cc. of typhoid-paratyphoid vaccine (local erythema and fever and malaise for 24 hours); on October 17, 0.5 cc. of typhoid-paratyphoid vaccine (local erythema); on October 24, 0.75 cc. of typhoid-paratyphoid vaccine (local erythema), and on October 31, 1 cc. of typhoid-paratyphoid vaccine (local erythema).

On November 14 the patient received her first injection of 200 skin test doses (STD's) of scarlet-fever-streptococcus toxin with no ill results. One week later the second

injection of 2000 STD's was given and was followed by joint pains and fever. She remained in bed for 3 days at that time, but did not report to the health office. No mention of this appeared on her clinic chart. Nine days later she returned and received the third injection of 8000 STD's, after which she developed severe arthralgia in the fingers and knees and a sore throat. She was hospitalized for 5 days, during which a low-grade fever was found. Physical findings showed a red throat and a large area of hyperemia extending from the site of the injection on the left arm down the forearm midway to the wrist. Examination of the blood showed a red-cell count of 4,200,000 with a hemoglobin of 80 per cent, and a white-cell count of 7950. The blood Hinton reaction was negative. The urine was normal. She received aspirin with some improvement and was discharged on December 7, with the diagnosis of "Dick-toxin reaction."

She returned to the clinic on December 12, and her inoculations were continued in lower and more gradually increasing doses so that the series included a total of 10 instead of the usual 7 injections, and the highest amount given was 40,000 STD's rather than 80,000. These were presumably injected into the deltoid regions of both arms, alternating from left to right. Epinephrine usually accompanied these injections, as follows: December 12, 8000 STD; December 19, 12,500 STD (in addition to 0.4 cc. of epinephrine); December 27, 20,000 STD; January 4, 1939, 25,000 STD (in addition to 0.3 cc. of epinephrine); January 9, 32,000 STD (in addition to 0.4 cc. of epinephrine); January 16, 1939, 40,000 STD (in addition to 0.4 cc. of epinephrine); January 23, 1939, 40,000 STD (in addition to 0.4 cc. of epinephrine); January 30, 1 cc. of toxin-antitoxin (for diphtheria); February 6, 1 cc. of toxin-antitoxin; February 13, 1 cc. of toxin-antitoxin in addition to 0.4 cc. of epinephrine; and February 20, Dick test (negative).

The patient was re-admitted to the hospital for 12 days in April, 1939, with swelling and pain of the ankles and toes and tenderness of the joints of both hands, which she said had been constant since the Dick-toxin reactions 5 months earlier. An erythematous area with a pustule was present over the right deltoid, which still represented the site of the Dick-toxin injections. At this time urinalysis showed a +++ test for albumin. Examination of the blood demonstrated a red-cell count of 4,250,000 and a white-cell count of 8200. The blood Hinton reaction was negative. The joint pains subsided on aspirin therapy, and the patient was discharged with the diagnosis of "rheumatic arthritis."

Two weeks later the joint pains returned, and the patient developed chills and fever, sore throat and cough. She was re-admitted for 2 weeks 1 month later, at which time one of four Hinton tests was found to be positive, and heterophil antibodies were present up to a titer of 1:64. During this admission streptococcus vaccine was started in small doses but because of a severe reaction further injections were refused. The diagnoses after this admission were "rheumatoid arthritis and infectious mononucleosis."

During the summer months the joint pains became generalized and persistent, and profound weakness appeared. In September the patient first became aware of a skin eruption over her nose and both cheeks, and the saliva became foul. Examination in the Out-Patient Department in November showed no swelling or redness of the joints. The skin of the cheeks and bridge of the nose was purplish red, mottled and indurated, and some indurated lesions were also found on the upper lip. The lymph nodes were enlarged to visible size in the cervical, supraclavicular, axillary and inguinal regions and were soft and nontender. The spleen was enlarged to percussion and was palpable on deep inspiration. At this time examination of the blood showed a red-cell count of 3,180,000 with a hemoglobin of 67 per cent, and a white-cell count of 3650. The erythrocyte sedimentation rate was 36 mm. per hour. In addition to albumin, the urine showed occasional red blood cells, white blood cells and hyaline and finely granular casts.

Final admission to the hospital was on November 11 at the age of 19. The eruption had spread to include the anterior portion of the chest, and the patient complained of frequent chills and a temperature rising to 102°F. In addition to the anemia and leukopenia laboratory examination revealed three positive blood Hinton reactions and two positive gonococcus complement-fixation tests. Heterophil-antibody agglutinations were negative and tuberculin testing gave a negative result to a dilution of 1:100. On x-ray study

described as being entirely compatible with those of allergic or pathergic inflammation<sup>5, 6, 10, 12, 15</sup>. In particular, the work of Rich,<sup>15</sup> which has recently come to include lupus, lends support to this concept. According to Klemperer et al,<sup>10</sup> the common denominator of the pathology of the disease is the widespread fibrinoid degeneration of collagen, considered also to be the pathology of hypersensitivity and hyperergic inflammation, as in the Arthus phenomenon. The fatal outcome in the disease has been attributed to the pronounced necrotic components of these allergic processes,<sup>6</sup> localized in the experimental Arthus phenomenon but widespread in lupus.

Impressive also is the pathological finding in the kidneys of horses rendered hyperimmune to bacteria for the purpose of developing therapeutic antitoxin, on which typical wire-loop glomerular lesions were found.<sup>5, 11</sup> These lesions, described by Klemperer et al<sup>6</sup> as being a characteristic finding in lupus, have been found in only three situations in disseminated lupus, in eclampsia of pregnancy in the human being and in horses in which bacterial antiserum has been produced by repeated intravenous injections of live bacteria. Although the significance and specificity of this lesion is by no means clear, it is considered to be compatible with that of hyperergic inflammation.

The bizarre manifestations of the disease as it unfolds clinically have given rise to much speculation regarding its etiology. Stokes,<sup>8</sup> in 1932, described the victim of disseminated lupus erythematosus as "first and foremost an allergic person explosively and furiously responsive to his infection with a broken or inhibited leucocytic defense." The peculiarities in the behavior of the patient with lupus have long been noted, and their interpretations have stimulated controversy.

Therapy with certain agents, such as gold salts, x-rays, drugs, skin applications, vaccines and serums, is said to offer hope in some cases, but in others precipitates violent reactions and tragic results.<sup>16-18</sup> The intolerance to sunlight is well known and documented. The tuberculin reaction is most frequently negative in these cases, which may again represent an immunologic imbalance since the patients are almost invariably adult. In some cases reaction to tuberculin administered intracutaneously is explosive, and has been known to be fatal.<sup>19, 20</sup> The Wassermann reaction very frequently becomes positive during activity of the disease without evidence of syphilis being present,<sup>21</sup> again representing abnormal antibody content.

Hyperglobulinemia is a constant occurrence in lupus, as found by Coburn and Moore,<sup>22</sup> and the erythrocyte sedimentation rate rises to levels much higher than those usually seen in infections, achieving the ranges seen in multiple myeloma, lymphopathia venereum and other high globulin syndromes. Electrophoretic analysis of the plasma

fraction showed the gamma globulins to be elevated and the other globulins normal. This pattern is also found in hyperimmune horse serum, apparently representing antibody. The antibody for the Wassermann reaction is apparently also in this electrophoretic area.

Again illustrating the overwhelming antibody response elaborated in the lupus syndrome, Calender et al<sup>23, 24</sup> report their extensive investigation of a patient who received a series of transfusions and developed "a remarkable series of antibodies in her serum." They demonstrated that she had immunized herself against the bloods of eight different donors with the formation of one familiar and three new antibodies, thereby exhibiting an extraordinary sensitivity to antigenic differences with a remarkable liability to undergo isoimmunization.

The occurrence of the disease almost exclusively among female patients between puberty and the menopause appears to bear no relation to the sensitivity state. It is, however, suggested by many isolated observations that a hormonal factor is of some importance in this regard. For example, it has been shown that the Schwartzman phenomenon can most easily be induced in the pregnant laboratory animal.<sup>11</sup> French investigation has demonstrated that the duration of the anaphylactic state can be altered by the removal of the ovaries in the rabbit,<sup>25</sup> and a synergistic effect is suggested. It has been reported that in the occasional male patient developing lupus the urinary excretion of 17-ketosteroids is low, and the follicle-stimulating hormone high,<sup>26</sup> suggesting hypogonadism with increased estrogen-androgen ratio. Premenstrual exacerbation of the disease has been reported,<sup>26</sup> and improvement following natural or induced menopause has also been observed.<sup>26</sup> Treatment designed at reducing ovarian function has met with good results in some hands and failure in others.

### *Streptococcus*

The case for the streptococcus as one of the sources of the antigen in lupus has received consideration in this country as well as in England. This concept apparently gained favor during the early trial of prontosil in various disease states. It was observed by Barber<sup>27-29</sup> that the use of this new chemotherapeutic drug in lupus was followed in 70 per cent of the cases by such reactions as chills, fever, scarlatiniform eruption and a local aggravation of the lesions. In other diseases drug fever and reaction was not seen in greater frequency than 15 per cent. It was believed that the phenomenon in lupus represented a manifestation similar to the Herxheimer reaction in the treatment of syphilis — namely, a general constitutional response to the toxin and bacterial products resulting from a massive bacterial necrosis. The scarlatiniform rash was described as being typical of that of scarlet

fever and differing from that seen in other sulfonamide reactions. In addition to this observation, it is claimed by Barber as well as others in England<sup>30</sup> and this country<sup>31</sup> that treatment of lupus with the sulfonamides and, later, penicillin has met with dramatic results far superior to any other known therapy, although other reports list such therapy as a failure.<sup>32</sup>

It is further claimed that at least among the cases seen in England streptococcal septicemia is a usual form of death in fatal cases, and that evidence of tuberculosis is usually lacking at autopsy.<sup>29</sup> It is postulated by Barber that disseminated lupus erythematosus represents a nonspecific syndrome capable of being provoked by a variety of bacteria or toxins and that in England this agent is in most cases the hemolytic streptococcus, but that in other vicinities the tubercle bacillus may be of greater significance.

Working with a streptococcus isolated from patients with pemphigus, Welsh<sup>33</sup> was able to demonstrate that the serums from cases of lupus possessed antibodies against the organism. Although antistreptolysin titers are not usually measured in such cases, the titer has been shown to reach significant levels such as 1:640.<sup>34</sup> Denzer and Blumenthal,<sup>35</sup> testing the response to Dick toxin in a case of lupus, found it necessary to raise the dose to 120 units before a positive reaction was obtained. These authors state:

We do not know how to evaluate this finding. Dr Dick has advised us that it is unusual, that there are few people who failed to give a cutaneous reaction with such large doses of toxin.

### CASE REPORTS

All the cases of disseminated lupus in this series began insidiously with bizarre manifestations before the disease became clinically recognizable. Each case terminated fatally, and in each the diagnosis was confirmed at autopsy. In compiling the case summaries we gathered information from hospital records, clinic charts and files of the training-school office, and the final integrated summary appears to form a meaningful chronologic picture.

The first case presents a pattern in accord with the present-day concepts of the etiology of the disease, whereas the second and third cases are less convincing.

**CASE 1.** J. S., an 18-year-old Negro, entered the training school in February, 1938. The history and physical examination were not remarkable at that time and the tuberculin reaction was negative. In the fall of 1938 tests and inoculations were begun as follows: on October 1, 1938, Schick test (positive on October 5), on October 3, Dick test (positive on October 4), on October 10, 0.25 cc. of typhoid-paratyphoid vaccine (local erythema and fever and malaise for 24 hours), on October 17, 0.5 cc. of typhoid-paratyphoid vaccine (local erythema), on October 24, 0.75 cc. of typhoid-paratyphoid vaccine (local erythema), and on October 31, 1 cc. of typhoid-paratyphoid vaccine (local erythema). On November 14 the patient received her first injection of 100 skin test doses (STD's) of scarlet-fever-streptococcus toxin with no ill results. One week later the second

injection of 2000 STD's was given and was followed by joint pains and fever. She remained in bed for 3 days at that time, but did not report to the health office. No mention of this appeared on her clinic chart. Nine days later she returned and received the third injection of 8000 STD's, after which she developed severe arthralgia in the fingers and knees and a sore throat. She was hospitalized for 5 days, during which a low-grade fever was found. Physical findings showed a red throat and a large area of hyperemia extending from the site of the injection on the left arm down the forearm midway to the wrist. Examination of the blood showed a red-cell count of 4,200,000 with a hemoglobin of 80 per cent, and a white-cell count of 7950. The blood Hinton reaction was negative. The urine was normal. She received aspirin with some improvement and was discharged on December 7, with the diagnosis of "Dick-toxin reaction."

She returned to the clinic on December 12, and her inoculations were continued in lower and more gradually increasing doses so that the series included a total of 10 instead of the usual 7 injections, and the highest amount given was 40,000 STD's rather than 80,000. These were presumably injected into the deltoid regions of both arms, alternating from left to right. Epinephrine usually accompanied these injections, as follows: December 12, 8000 STD, December 19, 12,500 STD (in addition to 0.4 cc. of epinephrine), December 27, 20,000 STD, January 4, 1939, 25,000 STD (in addition to 0.3 cc. of epinephrine), January 9, 32,000 STD (in addition to 0.4 cc. of epinephrine), January 16, 1939, 40,000 STD (in addition to 0.4 cc. of epinephrine), January 23, 1939, 40,000 STD (in addition to 0.4 cc. of epinephrine), January 30, 1 cc. of toxin-antitoxin (for diptheria), February 6, 1 cc. of toxin-antitoxin, February 13, 1 cc. of toxin-antitoxin in addition to 0.4 cc. of epinephrine, and February 20, Dick test (negative).

The patient was re-admitted to the hospital for 12 days in April, 1939, with swelling and pain of the ankles and toes and tenderness of the joints of both hands, which she said had been constant since the Dick-toxin reactions 5 months earlier. An erythematous area with a pustule was present over the right deltoid, which still represented the site of the Dick-toxin injections. At this time urinalysis showed a +++ test for albumin. Examination of the blood demonstrated a red-cell count of 4,250,000 and a white-cell count of 8200. The blood Hinton reaction was negative. The joint pains subsided on aspirin therapy, and the patient was discharged with the diagnosis of "rheumatic arthritis."

Two weeks later the joint pains returned, and the patient developed chills and fever, sore throat and cough. She was re-admitted for 2 weeks 1 month later, at which time one of four Hinton tests was found to be positive, and heterophil antibodies were present up to a titer of 1:64. During this admission streptococcus vaccine was started in small doses but because of a severe reaction further injections were refused. The diagnoses after this admission were "rheumatoid arthritis and infectious mononucleosis."

During the summer months the joint pains became generalized and persistent, and profound weakness appeared. In September the patient first became aware of a skin eruption over her nose and both cheeks, and the saliva became foul. Examination in the Out-Patient Department in November showed no swelling or redness of the joints. The skin of the cheeks and bridge of the nose was purplish red, mottled and indurated, and some indurated lesions were also found on the upper lip. The lymph nodes were enlarged to visible size in the cervical, supraclavicular, axillary and inguinal regions, and were soft and nontender. The spleen was enlarged to percussion and was palpable on deep inspiration. At this time examination of the blood showed a red-cell count of 3,180,000 with a hemoglobin of 67 per cent, and a white-cell count of 3650. The erythrocyte sedimentation rate was 36 mm. per hour. In addition to albumin, the urine showed occasional red blood cells, white blood cells and bialine and finely granular casts.

Final admission to the hospital was on November 11 at the age of 19. The eruption had spread to include the anterior portion of the chest, and the patient complained of frequent chills and a temperature rising to 102°F. In addition to the anemia and leukopenia laboratory examination revealed three positive blood Hinton reactions and two positive gonococcus complement-fixation tests. Heterophil-antibody agglutinations were negative and tuberculin testing gave a negative result to a dilution of 1:100. On x-ray study

the lung fields remained clear. Clinically, the patient's condition deteriorated rapidly, with a persistently high fever, tachycardia, rising nonprotein nitrogen (to 67 mg per 100 cc) and the development of diarrhea. Petechiae developed terminally, and at this time blood culture was positive for *Staphylococcus aureus*. Electrocardiograms remained normal. The patient finally expired on November 20—1 year after the Dick-toxin reactions and the apparent onset of the disease.

Post-mortem examination confirmed the clinical diagnosis of lupus erythematosus disseminatus. In addition, the coronary arteries were said to show the changes of periarthritis. Other diagnoses were as follows: bilateral bronchopneumonia, mural bacterial endocarditis of the right auricle and ventricle due to *Staph. aureus*, focal abscesses of the myocardium, epicardium, pericardium and endocardium and kidneys.

CASE 2. E. P., an 18-year-old nurse, entered the training school in August, 1939, in good health. Physical examination at that time was negative, and she received the routine inoculations, which are listed in her clinic record as follows: on September 18, 0.25 cc of typhoid-paratyphoid vaccine was followed by local erythema and tenderness; on September 25, 0.5 cc of typhoid-paratyphoid vaccine resulted in a larger and severe local reaction, fever and chills; on October 2, 0.75 cc of typhoid-paratyphoid vaccine resulted in local reaction of the same severity; on October 9, 1 cc of typhoid-paratyphoid vaccine caused a small local reaction; on October 19, Dick and Schick tests were given (both were positive on October 20 and 23); on October 23, 500 STD; on October 30, 1000 STD; on November 6, 2000 STD; on November 13, 8000 STD; on November 20, 25,000 STD; on November 27, 40,000 STD and on December 4, 80,000 STD. scarlet-fever streptococcus toxin were administered\*; on November 13, a tuberculin test was positive; on December 15, 22 and 29, 1 cc of toxin-antitoxin (diphtheria) was given; on January 15 a Dick test was given (it was negative on January 17, 1940); on July 8, a Schick test was given, but the results were not read (the patient was away from school); and on September 6, another Schick test was given (this was negative on September 10).

No record of the patient's health is available until April, 1940, when she was admitted to the hospital for 1 week with chills, fever and headache. The temperature was 104°F, and she was found to have edema of the right orbital tissues and firm cervical lymph nodes. The hemoglobin was 71 per cent, and the white-cell count 7900; the urine was normal. A blood Hinton reaction was doubtful at that time, and an x-ray film of the chest was clear. After return of temperature to normal, she was discharged with the diagnosis of "grippe."

Early in 1940 she began to complain of pains in the feet, numbness of the toes and local erythema, and in May of that year she had plantar calluses excised, although her pains were not localized to these parts.

There is no record of the interval from May, 1940, to January, 1941, when she re-entered the hospital with coryza, cough and sore throat. The right orbit was again found to be inflamed, and the cervical lymph nodes were bilaterally enlarged. Examination of the urine was negative. Examination of the blood showed a hemoglobin of 78 per cent and a white-cell count of 8650. At that time the blood Hinton reaction was positive. She was discharged in 24 hours with the diagnoses of "grippe and conjunctivitis on the right." Because of the doubtful blood Hinton reaction in April, 1940, and the positive reaction in January, 1941, the patient was investigated for syphilis after discharge. She vigorously denied the possibility, and no evidence of the disease could be found. Because of ill health and mental turmoil, however, she finally submitted to a course of antisyphilitic therapy under the care of a private physician. The details of this period are not available.

In February, 1943, after graduation, she re-entered the hospital complaining of a cold with chills of 1 week's duration. The temperature was 105°F.

Physical examination showed an injected throat and a large right cervical lymph node and crepitant rales with bronchovesicular breath sounds at the left base posteriorly.

The urine was normal. Examination of the blood revealed a red-cell count of 3,330,000, with a hemoglobin of 67 per

cent, and a white-cell count varying from 18,100 to 4100. An x-ray film of the chest showed infiltration in the left lower lobe, which improved rapidly on sulfadiazine therapy. She was discharged in 4 days with the diagnoses of "atypical pneumonia and secondary anemia."

Her next admission to the hospital was in June, 1944. She complained of mild pharyngitis followed by pains in the fingers, left knee and right shoulder. She gave a history of pleuritic pain on three occasions 3 months earlier, stating that chest x-ray films taken at that time had been normal. Physical findings included large, nontender lymph nodes in the right cervical region and a systolic murmur at the cardiac apex.

The urine again was normal. Examination of the blood disclosed a red-cell count of 3,400,000, with a hemoglobin of 67 per cent, and a white-cell count between 6200 and 10,650. The erythrocyte sedimentation rate showed marked elevation in all tests. Gastric aspiration was negative for acid-fast organisms. X-ray examination of the lungs was interpreted as showing an area of clouding 1.5 cm in diameter, in the outer zone of the first right interspace, which was considered suspicious of tuberculosis. No bone changes could be identified in the hands. Four electrocardiograms were found to be within normal limits, but PR-interval changes rose to 0.20 second. The infiltration at the right apex cleared, and there was a rise of the hemoglobin to a peak of 75 per cent after liver and iron therapy. She received salicylate therapy and developed a rash. She was discharged in 11 days for rest at home, with a diagnosis of "acute rheumatic fever."

From that time on the patient was aware of a constant fever with occasional bleeding from the gums and palate, weakness and fatigability. She went to Florida in the winter of 1944, and after exposure to the sun she developed and maintained an erythematous, edematous rash over her face, neck and upper back. These areas ulcerated and desquamated over a period of 4 months. The rash gradually faded when she returned to the north, but in the winter of 1945, joint pains returned. In the spring of 1946 she again visited the South and again developed chills, fever, aggravation of the joint pains and return of the rash, which developed a purplish tinge. In July she again entered the hospital for 1 month, presenting a history of chills, with a temperature spiking to 104°F for 3 weeks. There were also severe generalized joint and muscle pains, excessive salivation and loss of head hair. She had been taking large amounts of aspirin since the last hospital discharge, without effect on the pains. Sensitivity to morphine and codeine had developed, with a reaction shown by vomiting and skin rash.

Physical examination in July, 1946, showed a butterfly rash over the face and anterior part of the chest, and a lymph node, 3.0 by 1.5 cm in diameter, in the right cervical region. The heart was enlarged, and a loud systolic apical murmur was described. Urine specimens showed occasional albuminuria, with the tests up to ++. Hemoglobin levels ranged between 27 per cent and 52 per cent, and the red-cell count between 1,400,000 and 1,700,000; the white-cell count was maintained between 3000 and 3900, and the blood Hinton test was positive. Cephalin flocculation was + + + +, and electrocardiograms were normal. X-ray examination of the lungs was negative, but a calcified lymph node was seen in the right cervical region. The temperature ranged to 104°F. Five transfusions of whole blood failed to effect significant improvement.

Final admission was on August 17. Chills, fever and joint pains continued at that time, and alopecia was well developed. Additional laboratory studies showed a rise in the icteric index to 35, a cold agglutinin blood titer of 1:640 and a positive blood Hinton test. Each attempt at blood transfusion brought violent reactions, with chills and temperature reaching over 107°F, so that it became necessary to prepare her for these transfusions with nembutal and epinephrine, as well as warming of the donor's blood. Temperatures remained irregular up to levels of 105°F and the patient finally developed convulsions and disorientation and died on September 4.

The findings at post-mortem examination were described as confirming the clinical diagnosis of lupus erythematosus disseminatus, and no evidence of active tuberculous infection was found.

CASE 3. M. S., an 18-year-old nurse, entered training in February, 1942. Her history at that time revealed that in

\*No statement about reactions to these inoculations was included in the clinic record.

childhood she had had a vesicular skin eruption and one episode of hives while in grammar school. She also reported profuse menstrual flow with severe dysmenorrhea, often associated with nausea and vomiting. Physical examination was negative, as was the tuberculin reaction. She received the following tests and inoculations:

On March 2, 0.5 cc. of typhoid vaccine was followed by a large area of local erythema with discharge. On March 9, 1 cc. of typhoid vaccine was given, and the arm was stiff and painful for 2 days. On March 16, 1 cc. of typhoid vaccine was given. On March 23, Dick and Schick tests were given — they were negative on March 24 and 27, and on March 30, the tuberculin test was negative.

Three months later while at the seashore, she fell asleep on the beach and suffered a severe sunburn. When this subsided it left two small erythematous areas symmetrically placed at the outer end of each eyebrow. These slowly enlarged and spread over the nose and cheeks, preserving a remarkable symmetry. She left the training school at this time, but in September she sought admission to another training school. At that time a "facial acne" was described, and a systolic cardiac murmur was reported over the entire precordium. The Schick test was again negative.

In August, skin lesions had also appeared over the right forearm and over the lumbar spine. By December, the facial lesion had spread around the eye to the cheeks and over the bridge of the nose still preserving symmetry. In January 1943, she developed an upper respiratory infection with diarrhea, for which she was hospitalized for 2 days. Two months later she became aware of profound anorexia and loss of energy. In May diarrhea returned, this time with sore throat and severe headaches. Physical examination showed congestion of the eyelids, nasal mucosa and throat.

Examination of the blood revealed a red-cell count of 2,910,000, with 60 per cent hemoglobin, which fell to 46 per cent in 2 days, and a white-cell count of 27,000. The blood smear showed the presence of small nucleated red blood cells. The urine contained a few red blood cells and white cells per high-power field, and a trace of albumin.

On May 6, she was hospitalized complaining of swelling of the entire face and puffiness of the eyes, fever and sore throat with bleeding from the nose and mouth. There was some cough, associated with substernal pain. Small ulcerated lesions on the fingertips had been noticed for several weeks.

Physical examination showed a temperature of 105.2°F, a pulse of 146 per minute and respirations of 36 per minute. In addition to the eruption symmetrically located over the nose, cheeks, temples and ears, eroded and bleeding lesions were found on the lips, hard palate, fingertips and toes. The face was puffy and swollen and examination of the heart showed a rapid rate with gallop rhythm and a systolic murmur along the left sternal border and base.

Examination of the urine disclosed a ++ test for albumin, and the sediment contained 1 to 10 white cells per high-power field. The red-cell count was 2,980,000, with a hemoglobin of 10 gm., and the white-cell count 4050. The total protein was 5.01 gm per 100 cc., with an albumin-globulin ratio of 2.7:2.3. Throat cultures on two occasions yielded beta-hemolytic streptococci, but the blood culture was negative. Electrocardiograms and x-ray films of the chest were not remarkable.

The temperature ranged between 103 and 105°F, and the patient's course was rapidly downhill. She died on May 9, after an episode of pulmonary edema.

Post-mortem examination confirmed the diagnosis of disseminated lupus erythematosus in addition to bilateral pneumonia and fatty degeneration of the liver.

## DISCUSSION

Considering the current speculations regarding the etiology of lupus, it may be of interest that an allergen can be traced as a possible causative factor in each of the cases presented above. The circumstances preceding the onset of the disease in Case 1 indicate a close association between the reactions to the streptococcus toxin and the disease state itself. Indeed, the metamorphosis from one to the other is such a direct and continuous process that it is impossible to outline the termination of the reactions

to the toxin and the earliest symptoms of the disseminated disease. Although the patient reacted with severe manifestations to the scarlet-fever streptococcus-toxin injections, the entire series was completed. The rash that appeared on her arm at the site of the inoculation persisted for a year up to the time of death, gradually transforming into the lesions of lupus. The facial lesion became a later manifestation. The joint pains and malaise associated with the reactions never fully subsided and slowly merged into the florid process of disseminated lupus.

In Case 2 no such definite correlation could be demonstrated. If, however, the change in the blood Hinton reaction can be accepted as an early serologic alteration of disseminated lupus, it can be seen that this occurred shortly after a series of inoculations had been completed.

In Case 3 the typhoid vaccination might be considered an associated allergen. It was after exposure to sunlight less than three months later, however, that the cutaneous manifestations of lupus first appeared. Fourteen months after the injections the patient died of lupus, having progressed rapidly through the final stages of the disease.

It is conceivable that an antigen was supplied in the form of a bacterial product in all 3 cases, and in 2 it may have been the streptococcal toxin. This is entirely compatible with the multiple or variable nonspecific sensitivity concept of the pathogenesis of lupus as a disease of allergy or adaptation.

The local and systemic reactions to the Dick toxin may be severe in 10 to 15 per cent of cases.<sup>36</sup> These are characterized by headache, fever, nausea, vomiting, abdominal distress, sore throat and scarlatinal rashes.<sup>36-38</sup> Local reactions of purplish mottled and dusky-red erythematous areas<sup>39</sup> which may achieve some chronicity at times, have been described. Muscle and joint pains are apparently less frequently seen, but according to Healer<sup>40</sup> occur in about 3 per cent of young adults immunized. He demonstrated that the arthralgia in 5 subjects was not produced by the protein contained in the broth used in the preparation of the toxin and that it was absent when the toxin was destroyed by heat. According to Toomer<sup>38</sup> the person reacting with arthritis is "never desensitized by repeated injections of scarlet fever toxin to the point where he may not have reactions following subsequent increased injections of the toxin."

If such reactions possess a denominator in common with the so-called diseases of allergy and hypersensitivity, it seems possible that there is a point at which the systemic effect of the antigen-antibody reaction becomes irreversible and the disease progresses even if the antigen is removed. Although the situation outlined above is unusual and artificial, it is conceivable that in other cases a constantly present or frequently recurring obscure infection can render the patient sensitive and from that point on supply a bacterial antigen to initiate a series of bodily reac-

tions similar to those supplied by the injections in these 3 cases

The facts of the cases as presented herein obviously justify no conclusion regarding the etiology of disseminated lupus erythematosus. Can there be an association between the pathogenesis of the disease and allergenic factors?

### SUMMARY

The etiologic speculations regarding disseminated lupus erythematosus as listed in the literature are reviewed. There is a trend at present to include this disease among others thought to be associated with allergy and hypersensitivity, although the evidence for this is indirect.

Three cases of disseminated lupus occurring among student nurses are presented. In 1 the apparent onset of the process coincided with Dick toxin reactions. In the others such a direct correlation was not present, but the disease followed similar inoculations by several months.

The possibility that an allergen was present in each of these cases is suggested.

### REFERENCES

- 1 Badger T L and Ayzarian L F. Unpublished data.
- 2 Keil H. Relationship between lupus erythematosus and tuberculosis: critical review based on observations at necropsy. *Arch Dermat & Syph* 28:765-779, 1933.
- 3 Ginzler A, M and Fox T T. Disseminated lupus erythematosus: cutaneous manifestation of systemic disease (Lilman Sachs). *Arch Int Med* 65:26-50, 1940.
- 4 Bloch B. Role of idiosyncrasy and allergy in dermatology. *Arch Dermat & Syph* 19:175-197, 1929.
- 5 Baehr G, Kemperer P and Schiffrin A. Diffuse disease of peripheral circulation (usually associated with lupus erythematosus and endocarditis). *Tr A Am Physicians* 60:139-155, 1935.
- 6 Teilum G. Pathogenetic studies on lupus erythematosus disseminatus and related diseases. *Acta med Scandinav* 123:126-142, 1946.
- 7 Fox R A. Disseminated lupus erythematosus—allegic disease? *Arch Path* 36:311-315, 1943.
- 8 Stokes J H. Discussion of Madden J F. Acute disseminated lupus erythematosus. *Arch Dermat & Syph* 25:854-875, 1932.
- 9 Rose E, and Pillsbury D M. Acute disseminated lupus erythematosus—systemic disease. *Ann Int Med* 12:951-963, 1939.
- 10 Klemperer P, Pollack A D and Baehr G. Pathology of disseminated lupus erythematosus. *Arch. Path.* 32:569-631, 1941.
- 11 Sullians A. W. Lupus erythematosus. *M Clin North America* 26:29-46, 1942.
- 12 Klemperer P, Pollack A D and Baehr G. Diffuse collagen disease: acute disseminated lupus erythematosus and diffuse scleroderma. *J A M A* 119:331, 1942.
- 13 Foldes J. Acute systemic lupus erythematosus. *Am J Clin Path* 16:160-173, 1946.
- 14 Feinberg S M. Allergy: trends and their implications. *Ann. Int. Med* 27:723-732, 1947.
- 15 Rich A R and Gregory J E. Experimental anaphylactic lesions of coronary arteries of "sclerotic" type commonly associated with rheumatic fever and lupus erythematosus disseminatus. *Bull. Johns Hopkins Hosp* 81:312-324, 1947.
- 16 Keil H. Conception of lupus erythematosus and its morphologic variants with particular reference to "systemic" lupus erythematosus. *Arch Dermat & Syph* 36:729-757, 1937.
- 17 O'Leary P A. Prognosis and treatment of lupus erythematosus. *Proc Staff Meet., Mayo Clin* 15:686-688, 1940.
- 18 Cluxton H. E. Jr, and Krause L. A. M. Acute lupus erythematosus disseminatus. *Ann Int Med* 24:843-872, 1943.
- 19 Ravogli A. Lupus erythematosus diffusum unfortunately treated with tuberculin. *J Cusan Dis* 33:266-272, 1915.
- 20 Rose E, and Goldberg L. C. Visceral lesions of acute disseminated lupus erythematosus. *M Clin North America* 19:333-346, 1935.
- 21 Sompayrae L and Hailey H E. Lupus erythematosus with false positive Kahn reactions. *Arch. Dermat & Syph* 49:335, 1944.
- 22 Coburn A F and Moore D H. Plasma proteins in disseminated lupus erythematosus. *Bull. Johns Hopkins Hosp* 73:196-221, 1943.
- 23 Callender S, Race R. R. and Paykoc Z V. Hypersensitivity to transfused blood. *Brit M J* 2:83, 1945.
- 24 Callender S T, and Race R. R. Serological and genetical study of multiple antibodies formed in response to blood transfusion by patient with lupus erythematosus diffusum. *Ann. Eugenics* 13:102-117, 1946.
- 25 Vallery-Radot, P. Manrice G, and Holtzer, A. Contribution à l'étude de l'influence des hormones génitales féminelles sur la sensibilité anaphylactique de la lapine. *Compt rend Soc de biol* 137:334, 1943.
- 26 Stokes J H, Beerman H, and Ingraham, N R. Jr. "Lupus erythematosus" concept: attempt at integration. *Am J M Sc* 207:540-549, 1944.
- 27 Barber H W. Facial carbuncle treated with protosil album: personal experience with note upon its effect in lupus erythematosus. *Lancet* 2:668-670, 1938.
- 28 *Idem*. Lupus erythematosus: effects of sulphonamides. *Lancet* 1:583-586, 1940.
- 29 *Idem*. Effects of sulphonamide compounds upon lupus erythematosus. *Brit J Dermat & Syph* 53:1, 1941.
- 30 Glynn-Hughes, F and Spence A M. Sulphonamide therapy in lupus erythematosus. *Brit M J* 2:741, 1940.
- 31 Strakosch E A. Acute lupus erythematosus disseminatus treated with penicillin: report of case. *Arch. Dermat & Syph* 54:197-199, 1946.
- 32 Johnson, J B, and Mazique E. C. Disseminated lupus erythematosus unsuccessfully treated with penicillin, roentgen ray castration and serum albumin. *Ann Int Med* 25:859-862, 1946.
- 33 Welsh A L. Studies on specificity of streptococci isolated from patients with pemphigus. *Proc Staff Meet., Mayo Clin.* 9:369-373, 1934.
- 34 Ginzler, A, and Fox T T. Disseminated lupus erythematosus in youth with some interesting findings. *Arch. Path.* 26:916-919, 1935.
- 35 Denzer, B S and Blumenthal S. Acute erythematosus disseminatus. *Am J Dis Child* 53:525-540, 1937.
- 36 Anderson G W. Present status of scarlet fever prevention. *New Eng J Med* 213:203-208, 1935.
- 37 Glazier, M. M. Active immunization against scarlet fever. *New Eng J Med* 233:204-206, 1945.
- 38 Toomey J A. Scarlet fever immunization. *Ann. Int. Med* 15:959-973, 1941.
- 39 Melnick T. Prevention of scarlet fever: methods to minimize reactions following inoculations of Dick scarlet fever toxin. *Arch. Pediat* 50:158-172, 1933.
- 40 Healey C E. Cause of joint pain occurring during active immunization with scarlet fever streptococcus toxin. *J A M A* 108:618-630, 1937.

## NECROTIC LESIONS OF THE LEG IN ARTERIOSCLEROSIS\*

EDWARD A. EDWARDS, M.D. †

BOSTON

IT IS commonly known that necrosis can occur in the toes or feet in the presence of arteriosclerosis. It is the purpose of this paper to indicate that necrosis may likewise start more proximally in the leg, and that the lesion is of grave import and deserves painstaking treatment. The disorder may arise spontaneously as an infarction of the skin and subcutaneous tissue. In other cases the necrosis follows local trauma or infection.

## CLINICAL VARIETIES

*Infarction of the Skin*

In this category may be placed cases in which there is the sudden appearance of a blue-red area on the leg, which quickly turns black. This is followed in a few days by sloughing and ulceration. The limb shows evidence of high-grade arteriosclerosis, with ischemia of long standing. Such lesions are presumably the result of spontaneous thrombosis in small arteriosclerotic arteries, though the exact mode of genesis is not proved. Small lesions of this type resemble those described by Hines and Farber<sup>1</sup> as "hypertensive-ischemic" ulcers. These writers believe that the local ischemia is due to the arteriosclerosis of hypertension. The mechanism of the necrosis is probably the same as that responsible for many such lesions in the toes. Skin necrosis due to local arterial thrombosis is rare, but may be seen in other parts of the body, such as the trunk and the upper extremities.

The infarct and resultant ulceration may be small or large, single or multiple. Its course is to some extent related to the size of the necrotic zone and the location. Small ulcers tend to heal, the larger ones, with the aid of superimposed infection, tend to go on to massive gangrene. A proximal level is somewhat more conducive to healing than a more distal one.

The following cases are representative of those in this group.

**CASE 1** H. R., a 74-year-old man, was seen at the Massachusetts Soldiers' Hospital. He presented three ulcers of the left upper leg of 4 weeks' duration. The lesions had first appeared as painful isolated red spots, which had turned black in 2 days, and had then begun to ulcerate. There was a history of claudication of 10 years' duration, but with no apparent recent change in circulatory status.

Physical examination disclosed three separate ulcers, each about 1.5 cm in diameter (Fig. 1). The edges were irregular with gray sloughing sides and base and the lesion was surrounded by a narrow red areola. The limb was moderately

ischemic. The femoral pulsation was of fair quality, but there was no pulsation below this level. The vascular status of the right limb was similar to that of the involved side.

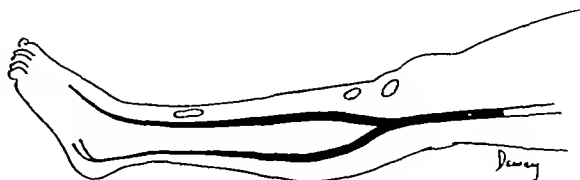


FIGURE 1 Spontaneous Small Areas of Necrosis in Case 1. There is occlusion of the popliteal and both tibial arteries.

The blood pressure in the arm was 160/110. There were signs of arteriosclerotic heart disease, but no overt failure.

Treatment consisted of the daily application of wet dressings of tyrothricin solution (0.5 mg per cubic centimeter). The ulcers improved rapidly and healed in 4 weeks.

**CASE 2** E. LeP., a 57-year-old man, was seen at the Massachusetts Soldiers' Hospital for ulceration of the leg of 2 weeks' duration. The involved area had initially turned black and painful and had then broken down. Diabetes was known to have been present for 6 years. It was well controlled by diet and the taking of 15 units of protamine insulin daily.

Physical examination disclosed a slough, 4 cm in diameter, over the lower lateral aspect of the left leg (Fig. 2). There

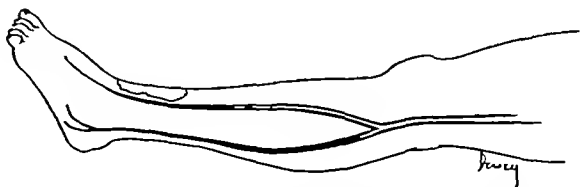


FIGURE 2 Extensive Spontaneous Ulceration in Case 2. There are patent popliteal, narrowed anterior tibial and occluded posterior tibial arteries.

was evidence of mild infection about the involved area. Pulsations of good quality were felt over the femoral and popliteal areas. There was a faintly perceptible pulsation in the dorsalis pedis artery but none in the posterior tibial artery. Oscillometric examination disclosed moderate reduction in pulse expansion and pressure in the upper calf, but great reduction at the level of the ankle. The foot blanched moderately on elevation. The right lower leg showed a similar vascular status.

Treatment consisted of local dressings of tyrothricin solution and parenteral administration of penicillin. The slough had not separated after 6 weeks of this treatment, and infection about the edges of the ulcer was increasing. A lumbar sympathectomy was advised but refused until 5 weeks later. Sympathectomy was performed and induced a marked increase in blood flow. The slough separated in a week, and the ulcer healed 3 weeks after the operation.

\*From the Department of Surgery, Tufts College Medical School. This study was aided by a grant from the Charlton Research Fund, Tufts College Medical School.

†Instructor in surgery, Tufts College Medical School; clinical associate in anatomy, Harvard Medical School; consultant in peripheral vascular disease, Joseph H. Pratt Diagnostic Hospital.

**CASE 3** A. H. P., a 77-year-old man, was referred by Dr. Tracey Roberson, of Ware, Massachusetts, for extensive necrosis of the right leg. Ten days earlier a painful, small, black area had appeared on the lateral aspect of the lower third of the leg. It had increased rapidly in size and appeared to be progressing. Varicose veins had been present for many years, but had not given rise to symptoms. The patient had had a severe coronary thrombosis 7 years and a cerebral vascular accident 2 years before the present illness.

Physical examination showed a black, necrotic zone of irregular outline, 100 by 85 cm, at the junction of the middle and lower thirds of the right leg, mainly on the lateral surface, but encircling about two thirds of the circumference of the leg (Fig. 3). About the ulcer was a red zone of irregu-

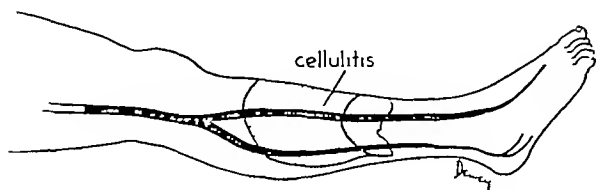


FIGURE 3 Extensive Spontaneous Ulceration with Secondary Infection in Case 3

There is old occlusion of the popliteal and both tibial arteries

lar outline, but no great tenderness or swelling. The foot was cold and dry. There was pronounced blanching on elevation. The femoral pulsation was of good quality, but no pulsation was made out below this level. The oscillometer showed a minimal pulsation below the knee, with no pulsation whatsoever at the ankle. There were a few varices in the calf. The vascular status of the left limb was similar to that of the right.

After a few days' observation it was evident that the ulceration was deep and that infection presented a real threat. Amputation was advised. The patient refused, went home and died from spreading sepsis in 6 weeks.

#### Necrosis Secondary to Trauma or Infection

As in the spontaneous variety, the necrosis following local injury or infection resembles that commonly seen in the toes. The precipitating incident does not need to be severe to set off an advancing necrosis in an arteriosclerotic limb.

Varicose ulcer affords the commonest example of superficial infection of the leg in arteriosclerotic patients. The tissues withstand this chronic form of infection rather well. The ulcers may commonly exist intermittently for many years in the presence of arteriosclerosis without giving rise to gangrene. The lesions will usually heal if the varices are treated by ordinary means. However, one should avoid operative procedures in the lower parts of the leg.<sup>2</sup> Rarely, as in Case 4, necrosis advances outward from a varicose ulcer. The precipitation of the necrosis apparently depends upon a superimposed trauma, an episode of acute varicose thrombophlebitis, the acquisition of a more virulent bacterial flora or further degradation of the arteries by advancing atherosclerosis or arterial thrombosis.

It is important to recognize that trauma and infection can, by themselves, initiate arterial thrombosis (as in Case 6). This reduces further the

limited blood supply, and the necrosis of the limb can extend more easily.

**CASE 4** R. F., a 74-year-old woman, was referred by Dr. Maurice W. Tolman, of Boston. The patient had had varicose veins for about 40 years and varicose ulcers intermittently for 15 years. After having been healed for some months, the ulceration of the right leg had recurred 4 months before the present observations. It was more painful than usual and had enlarged progressively. For 1 month there had been much pain in the calf and foot, and during the past 5 days the foot had become pale and cyanotic.

Physical examination showed multiple foul-smelling ulcerations in the lower two thirds of the right leg (Fig. 4). The deeper parts of the ulcers totaled about 90 square cm. Here the skin and subcutaneous tissues were black and surrounded by additional superficial ulceration. Culture of the ulcers showed hemolytic *Staphylococcus aureus* predominating, with *Staph. albus*, anhemolytic streptococci, diphtheroids and rare coliform bacteria. The small veins in the dorsum of the foot were prominent, and some did not empty after elevation. Several other areas of static blood pigment were

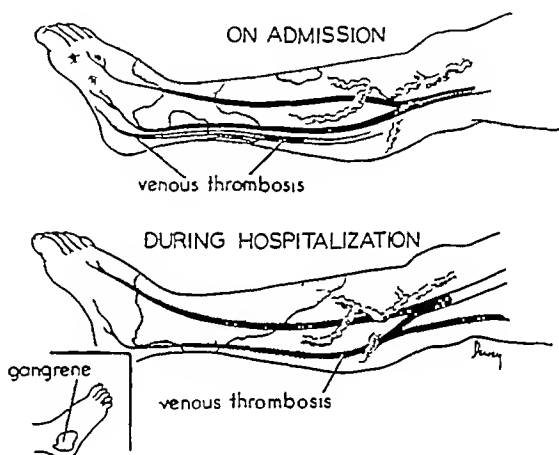


FIGURE 4 Necrosis Extending from Varicose Ulceration in Case 4

On admission there is old occlusion of the popliteal and both tibial arteries and early, deep venous thrombosis and blood pigment in the tissues of the dorsum of the foot. During hospitalization, there is extension of necrosis, extension of venous thrombosis and gangrene of the heel.

seen on the dorsum. The foot and toes showed a general cyanotic tinge, which slowly changed to a blanching after elevation. There was deep tenderness of the foot and calf. No pulsation was made out below the femoral level. The oscillometer likewise revealed no pulse expansion from the upper calf down.

It was apparent that the necrosis of this ischemic limb was complicated by spreading sepsis and deep venous thrombosis of the leg and foot. Thrombosis was also suspected in the finer skin vessels of the dorsum of the foot, and in the deep arteries of the leg and foot.

The patient was given penicillin and sulfadiazine, as well as heparin in Pitkin's menstruum. Dicumarol was soon substituted for the heparin. Wet dressings of tyrothricin solution were applied to the leg. The superficial ulcerations showed a tendency to heal, but it became evident that the slough had extended to the deep fascia in several places. In spite of the chemotherapy, intermittent fever continued. A large zone of gangrene appeared on the heel.

A low thigh amputation was advised and performed. The femoral vein was free of thrombus but there was thrombosis in a large vein in the posterior compartment of the thigh. Microscopical examination showed capillary thrombosis in the superficial tissues of the ulcer (Fig. 5).<sup>3</sup> The popliteal

<sup>3</sup>In my opinion such thrombosis may extend to the veins of the extremity inducing extensive thrombophlebitis.

artery was almost completely occluded, mainly by extensive atheroma, with further narrowing due to hemorrhage within the atheroma. The popliteal vein showed thrombosis. Unfortunately, sections were not made of the vessels of the leg or foot, leaving unproved the clinical impression of thrombosis in the arteries and veins of these parts.

Dicumarol was given postoperatively, but the prothrombin time was not consistently maintained at low levels. The



FIGURE 5 Tissues in Case 4

The upper photomicrograph of the edge of ulceration shows extensive purulent inflammation, with thrombosis of the small vessels in the ulcer bed and extensive proliferative phlebitis without thrombosis in a subcutaneous vein (hematoxylin and eosin stain,  $\times 50$ ). The lower photomicrograph shows the popliteal vessels. The vein on the right shows a completely occluding thrombus. The artery on the left shows extensive atheroma, the narrowed lumen being further reduced by hemorrhage within the atheroma at H (Verhoeff's elastic tissue stain,  $\times 15$ ).

stump and the buttock swelled considerably, suggesting an upward progression of the thrombosis to the common iliac vein. A small slough of the wound edges occurred and required 8 weeks to heal.

After discharge from the hospital, the patient complained of severe phantom pain. On three occasions a deep abscess formed in the stump end and drained spontaneously through

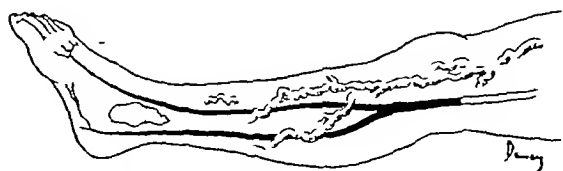


FIGURE 6 Necrosis Following Trauma in Case 5

There is old occlusion of the popliteal and both tibial arteries. Arteries are present.

the scar. A roentgenogram will be taken to determine whether osteomyelitis of the femur is present.

CASE 5 J McC, a 58-year-old man, was seen at the Avascular Clinic of the Boston Dispensary for an ulcer of the right lower leg. Four weeks earlier he had bruised this

area on a hand truck, and the ulcer had formed in a few days. Varicose veins had been present for 5 years, dating back to a deep thrombophlebitis after compound fracture of the leg. Ulceration had never previously been present.

Physical examination showed an ulcer, 4 cm in diameter, on the medial surface of the right lower leg (Fig 6). It was surrounded by a wide inflammatory zone. Beyond the involved area, the skin was atrophic, dry and shiny. The foot blanched markedly on elevation. The femoral pulsations were of good quality, but there were no pulsations below this level. The oscillogram showed a barely perceptible pulse expansion from the upper calf downward. Large varices were present.

A right lumbar sympathectomy and a division of the saphenous vein in the groin were carried out. The ulcer showed immediate improvement but required 3 months to heal. During most of this time, however, the patient was ambulatory and at work.

CASE 6 E W, a 74-year-old woman, was referred by Dr. Paul Hecht, of Braintree, Massachusetts, for ulceration of the right leg. One week earlier, while working in her garden, she had been stung on the leg by an insect. A virulent cellulitis developed, involving the entire leg and associated with chills and high fever. The patient was extremely ill, but improved after large doses of penicillin and sulfadiazine given

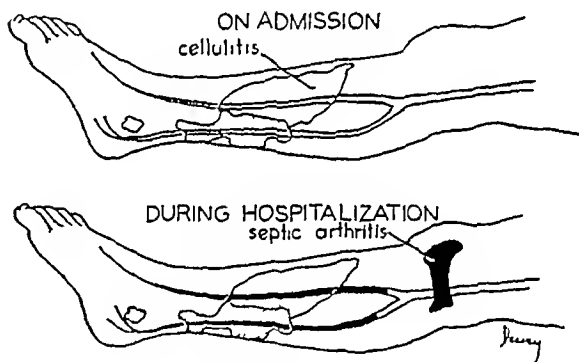


FIGURE 7 Necrosis and Secondary Arterial Thrombosis Following Infection in Case 6

On admission, the major arteries were patent. During hospitalization, thrombosis developed in the tibial arteries, and the knee joint became infected.

orally. Extensive slough of the skin developed, and it was evident that the cellulitis was continuing deeply, though its superficial spread had been halted.

Physical examination disclosed the patient to be in good general condition. Extensive deep slough and cellulitis were present on the medial surface of the right leg, in areas from the ankle to the knee (Fig 7). The dorsalis pedis and posterior tibial pulsations were present and only slightly reduced in volume. The foot showed no evidence of diminished blood flow. Culture of the lesion showed *Bacillus subtilis* predominating, with a hemolytic *Staph aureus* and a nonhemolytic *Staph albus*.

It was hoped that with increased doses of sulfadiazine and parenterally administered penicillin, ultimate separation of the slough and a satisfactory base for skin graft might be obtained. In spite of adequate chemotherapy a low fever continued. On the 5th day, after hospitalization the knee joint appeared distended with fluid, though not tender. The pedal pulses were no longer palpable, and the foot was ischemic.

Amputation was advised and performed above the femoral condyles. The popliteal artery and vein were patent. The knee joint was found distended with pus, and the ampu-

tation was therefore left open. Five days later a secondary suture was done. Healing was satisfactory.

Microscopical examination showed extensive arteriosclerosis in the popliteal, anterior and posterior tibial and in the peroneal arteries (Fig. 8). It was confirmed that acute

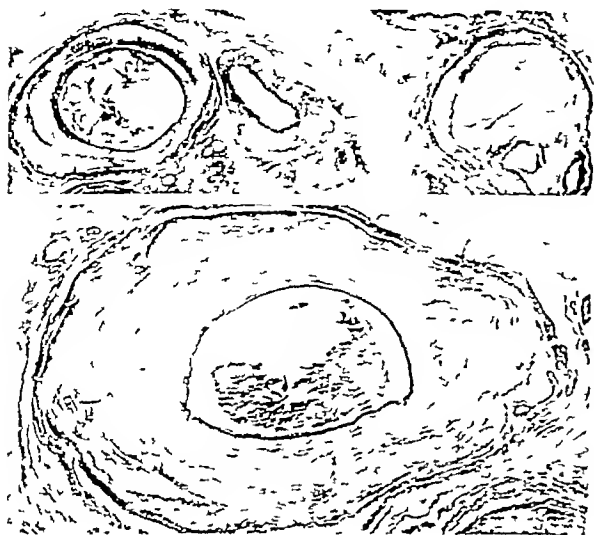


FIGURE 8 *Tissues in Case 6*

The upper photomicrograph of the posterior tibial artery on the left shows atherosclerosis with acute thrombosis, and the peroneal artery on the right is occluded by an old atheroma (Verhoeff's elastic tissue stain,  $\times 20$ ). The lower photomicrograph of the anterior tibial artery shows extensive atherosclerosis with acute thrombosis (Verhoeff's elastic tissue stain,  $\times 50$ ). In both sections the apparent incompleteness of thrombosis is due to an artifact.

thrombosis had taken place in the anterior and posterior tibial arteries.

### CLINICAL MANAGEMENT

In many respects the management of patients with necrosis is the same whether the lesion is located on the leg or on more distal parts. It is clear that the presence of infection and thrombosis must be kept in mind constantly. The advanced age of the patient and the presence of marked arteriosclerosis favor these pathologic processes. The tissues limit infection poorly, so that cellulitis and extension of the necrosis are common, and septicemia is a constant threat.

Thrombosis is encountered in a variety of vessels. Microscopical examination of the necrotic areas often reveals red agglutination thrombi in the surface capillaries. These may sometimes be followed into the subcutaneous veins and arteries. The process is often purulent and suggests a basis for septicemia. Thrombosis of the large deep veins is common, as noted by Veal<sup>3</sup> in gangrene from any cause. This process is usually bland at the popliteal level and aids in limiting the purulent phlebitis of the finer vessels. Organization is slowed in old age, especially in the presence of ischemia. Pul-

monary embolism may therefore be expected with unusual frequency. Thrombosis of the major arteries may likewise occur in the course of the illness, further limiting blood flow.

Except for small spontaneous ulcerations, necrosis of the leg in the presence of arteriosclerosis calls for treatment in a hospital. If ischemia is pronounced, and the necrosis is widespread and deep, immediate amputation appears most logical. Acute spreading infection is likewise an indication for amputation, but an attempt should first be made to control the infection by appropriate and intensive chemotherapy.

One of three types of amputation may be used: guillotine amputation at a low level followed by definitive closed amputation in the thigh, immediate amputation at the high level but with delayed suture, and high amputation with primary suture. Division of both femoral veins should accompany the amputation. My preference is for a division above the termination of the deep femoral vein, but below the circumflex femoral veins.<sup>4</sup> Dicumarol may be given instead, but only if the amputation wound is closed.

Conservative management may be chosen in the hope that the necrosis has not extended deeply, and that the infection will prove controllable. General chemotherapy is of prime importance. Local applications should be bland. In my experience, wet dressings are superior to greasy ones. Tyrothricin solution (0.5 mg. per cubic centimeter) appears to have some advantage over other materials. If venous thrombosis is present, a bilateral division of the femoral veins should be done. If thrombosis is not evident, dicumarol or heparin should be given as prophylaxis.

An increase in blood flow by lumbar sympathectomy may be extremely helpful, but the operation is only occasionally applicable. Sympathectomy should be considered only if there appears to be a good chance of saving the leg. A favorable effect may not be obtained in the very old patient with extensive arteriosclerosis. As a general rule, a good skin-temperature response after spinal anesthesia should be obtained before sympathectomy is performed in patients over fifty-five. This rule should be abrogated if the limb is in jeopardy.

Varices should be treated by high division of the saphenous vein.

In favorable cases these conservative measures may induce healing of the necrotic area. In others, a granulating area may be obtained, which can be skin-grafted, preferably with "pin-point" grafts. It is conceivable that débridement of the necrotic area may occasionally be used as a preliminary to skin grafting.

An opinion regarding the probable outcome of the conservative treatment should be made as soon as possible, generally in seven to ten days. Conservative treatment should be abandoned, and ampu-

tation performed, if it is evident that infection cannot otherwise be controlled, or if the necrosis increases

### CONCLUSIONS

Necrotic lesions on the leg in the presence of arteriosclerosis carry the same possibilities of loss of the limb, or of death, as lesions on the toes or foot

The patients are usually advanced in age, and the arteriosclerosis is severe

The lesions may arise spontaneously from thrombosis of arteries supplying the skin, with resultant infarction. In others, necrosis follows trauma or infection of the leg

The prognosis is poor because of infection and secondary thrombosis—the infection is apt to be difficult to control, and the thrombosis, which is extremely common, involves fine cutaneous and subcutaneous vessels in the necrotic area, the deep veins and occasionally the major arteries of the leg

Amputation is necessary for extensive necrosis, infection incompletely controlled or new areas of necrosis

Conservative treatment may be tried, but should be abandoned unless a good response is obtained promptly. Adequate and appropriate chemotherapy is necessary. Prophylactic use of anticoagulants may be indicated. Venous thrombosis calls for division of the femoral veins or for anticoagulant therapy. Lumbar sympathectomy is occasionally helpful in obtaining healing.

372 Marlborough Street

### REFERENCES

- 1 Hines E. A., Jr. and Farber E. M. Ulcer of leg due to arteriosclerosis and ischemia occurring in presence of hypertensive disease (hypertensive ischemic ulcers) preliminary report. *Proc Staff Meet Mayo Clin* 21 337-346 1946
- 2 Edwards E. A. Diseases of veins in middle and old age. *Am Practitioner* 2 143 150 1947
- 3 Veal J. R. High ligation of femoral vein in amputation of lower extremities, preliminary report based on twenty-eight amputations of thigh. *J A M A* 114 1616-1619 1940
- 4 Edwards E. A. and Robuck J. D. Jr. Applied anatomy of femoral vein and its tributaries. *Surg Gynec & Obst* 85 547 557 1947

## ANION EXCHANGE RESINS IN THE TREATMENT OF HEARTBURN DURING PREGNANCY

S. CHARLES KASDON, M.D.\*

BOSTON

**H** EARTBURN during pregnancy, an annoying symptom with little if any significance in mortality or serious morbidity statistics, is nevertheless distressing to the patient who suffers from it and to the physician who bears the brunt of the complaints. Rodway and Shelley<sup>1</sup> reported this symptom in 66 out of 100 pregnant women, and the experience of most obstetricians tends to corroborate this incidence. The modern theory for the etiology of heartburn states that the regurgitation of gastric contents into the distal esophagus distends the sensitive neural endings of the esophagus. The distention is further enhanced by intermittent spasm of the cardiac sphincter and causes the symptom. Prostagmin has been administered in accordance with this theory of etiology and has afforded satisfactory relief from pyrosis during pregnancy.<sup>2-4</sup> It is rational therapy since prostagmin has been shown clinically and experimentally to increase isoperistaltic contractions in the gastrointestinal tract.<sup>5-7</sup> It is somewhat disconcerting, therefore, to find that anion exchange resins,<sup>†</sup> admittedly an empiric, unphysiologic therapeutic agent for heartburn during pregnancy, offer quali-

tative and statistical relief as good as that obtained with cholinergic substances.

### GASTRIC PHYSIOLOGY DURING PREGNANCY

Williams<sup>4</sup> has reviewed the changes in the stomach and its physiology during pregnancy. The normal vertical position of the stomach is altered as the gestation progresses, so that near term the fundus is found under the left leaf of the diaphragm. The greater curvature is forced nearer the cardiac sphincter by a 45° dextrorotation of the axis of the stomach. As the gastric motility decreases and the emptying time increases<sup>8</sup> the tendency to regurgitation by means of reverse waves of peristalsis increases. The increase in atony of the stomach concomitant with advancing gestation involves the cardiac end of both the esophagus and the stomach, resulting in a reflux of gastric contents into the lower esophagus. Gastric acidity decreases with advancing gestation up to the last month before delivery, when it begins to rise again.<sup>9</sup> This fact appears incompatible with the relief afforded from the alkali therapy reported so widely.<sup>10-14</sup> On the basis of the decreased gastric acidity in late gestation hydrochloric acid has been used for heartburn,<sup>10, 15</sup> with relief reported in 76 per cent of 45 patients treated.<sup>12</sup> Experimental distention of the lower esophagus, irrespective of the type of fluid or mechanical agent used, has been demon-

\*Junior assistant surgeon, Department of Gynecology, Boston Dispensary, consultant in gynecology, Joseph H. Pratt Diagnostic Hospital.

†The anion exchange resin used was marketed as resinate (700 mesh) by the National Drug Company, Philadelphia, Pennsylvania. Chemically it is a polyethylene-polyamino methylene substituted resin of diphenylol dimethyl methane and formaldehyde in basic form.

strated to cause all the symptoms of heartburn<sup>4, 16-19</sup> On this basis the modern "neuromuscular theory" of heartburn has been postulated. After secondary intermittent spasm of the cardiac sphincter the normal esophageal wave of peristalsis distends the lower esophagus with its sensitive neural endings. Heartburn results and can be completely relieved by a cholinergic drug in 81 per cent of a total of 43 patients reported<sup>2-4</sup>.

The reported failure to relieve the heartburn in 19 per cent of these pregnant patients may be due in part to the presence of unsuspected diaphrag-

TABLE 1 Data in Pregnant Patients Administered Anion Exchange Resins for Heartburn

CASE No.	AGE	PARITY	DURATION OF HEARTBURN*	DEGREE OF HEARTBURN	RELIEF
	yr		wk		
1	32	I	32	Severe	Complete
2	24	II	30	Moderate	Complete
3	28	I	33	Moderate	Complete
4	29	I	32	Moderate	Complete
5	33	I	26	Severe	Complete
6	40	II	24	Moderate	Complete
7	21	II	20	Severe	Complete
8	32	IV	22	Moderate	Complete
9	23	I	28	Severe	Complete
10	29	I	16	Moderate	None
11	26	I	30	Moderate	Complete
12	26	II	32	Moderate	Complete
13	27	I	26	Severe	Complete
14	23	I	30	Moderate	Complete
15	18	I	23	Moderate	Complete
16	28	I	14	Severe	Complete
17	30	I	22	Severe	Complete
18	30	II	34	Moderate	Complete
19	29	I	30	Moderate	Complete
20	28	III	18	Moderate	None
21	31	II	33	Severe	None
22	40	I	27	Severe	Complete
23	37	I	18	Moderate	Complete
24	30	II	32	Moderate	Complete
25	23	III	24	Moderate	Complete
26	22	I	36	Severe	Complete
27	24	I	32	Severe	Complete
28	25	II	12	Moderate	Complete
29	24	I	27	Moderate	Complete
30	33	III	20	Severe	Complete
31	29	II	27	Moderate	None
32	21	I	15	Moderate	Complete
33	28	II	31	Moderate	Complete
34	24	I	28	Moderate	Complete
35	27	I	19	Moderate	Complete

matic hernia, which Rigler and Eneboe<sup>20</sup> have demonstrated in 181 per cent of primiparas during the third trimester of pregnancy. They report the incidence of hiatus hernia in pregnancy as 12.8 per cent. This has been corroborated by Evans and Bouslog,<sup>21</sup> Dwyer<sup>22</sup> and Schnepf.<sup>23</sup>

It is of course true that the majority of patients with heartburn have obtained symptomatic relief by using alkalis such as sodium bicarbonate, aluminum hydroxide and block magnesia<sup>10, 11, 14</sup>. The widespread recourse to alkalis attests to the efficacy of this symptomatic treatment, but reports limit relief obtained by alkalis to 50 per cent of these cases of heartburn<sup>12, 13</sup>. Roth<sup>3</sup> believes that the "effect of these alkalis must be largely psychic," and it must be agreed that in view of the hypo-secretion of acid that is present late in pregnancy and the equivocal results reported, this may be true.

## EXPERIMENTAL STUDY

Anion exchange resins were suggested in the management of heartburn in pregnancy for several reasons. They are biologically practically inactive, have no effect on the acid-base balance of the blood, do not cause constipation or diarrhea, have practically no significant toxicity<sup>24</sup> and serve to absorb and neutralize acids<sup>25</sup>. In addition, there is an absence of phosphate ion removal, lack of acid rebound, no chloride removal and effective pepsin inactivation<sup>26</sup>. They were found valuable in the relief of pain associated with peptic ulcer even though the progress of the ulcer was reported to be uncertain<sup>27</sup>.

A total of 35 private obstetric patients with sufficient heartburn of pregnancy to require medication were offered anion exchange resins in 0.25 gm gelatin capsules for relief of symptoms. The usual dose was two capsules repeated in one hour as necessary. More than two doses were rarely required, and relief was obtained in 31 out of 35 patients who received the medication (Table 1). As a rule the patients reported the disappearance of the epigastric and precordial burning within ten minutes of the time the two capsules of resin were taken. It is remarkable that although most women required medication three or four times a week, more than 40 per cent of those who obtained relief from the medication remained free from symptoms for seven to ten days. All these patients were treated before the last month of gestation since it has been reported that 75 per cent of untreated patients experience spontaneous remission of heartburn in the last month of pregnancy.<sup>1</sup> This factor has been all too frequently ignored in the evaluation of therapy for heartburn in pregnancy.

The average age of the patients in this group was 26.7 years, and it is of interest that 5 of the primiparas were over 30 years old. Twenty-one were primigravidas, 10 secundigravidas, 3 tertigravidas and 1 a quartigravida. The onset of heartburn occurred in the second trimester in 14 and in the last trimester in 21 cases. Only patients who voluntarily reported moderate (23 cases) or severe (12 cases) heartburn were included in this study. Relief was rapid and effective, and only those who reported unequivocal and complete relief from the heartburn were recorded as such. All patients who reported something less than complete relief are recorded as failures.

A group of 16 patients who obtained relief from the heartburn with the resin were given prostigmin bromide in 15-mg tablets for subsequent attacks, and the relief was identical with that obtained with resin. The 4 who failed to report relief of heartburn after resin medication were also offered prostigmin bromide tablets, with no improvement in their complaints.

## DISCUSSION

The relief of heartburn during pregnancy can be accomplished with variable but almost equal success by both unphysiologic empiric medication and definitive therapy based upon the modern theory of etiology. The administration of anion exchange resins orally for the relief of annoying heartburn in pregnancy has resulted in rapid relief of this symptom in 88 per cent of treated cases. This salutary result is at least comparable to that reported with prostigmin. Cholinergic drugs have been used to excellent advantage in heartburn of pregnancy in accordance with the neuromuscular-dysfunction theory now accepted by most physiologists. Yet this therapy appears to be no more effective qualitatively or statistically than anion exchange resins. This consideration suggests that there is still much to be explained in the etiologic picture of heartburn during pregnancy. The reports of relief obtained from the administration of yeast, thiamine chloride and nicotinic acid<sup>28</sup> and miscellaneous medication<sup>1, 15, 19, 29, 30</sup> merely add to the confusion. Between 8 and 20 per cent of the failures to obtain relief with any medication may be attributed to the presence of an occult diaphragmatic hernia that is reduced spontaneously post partum.

The fact that 88 per cent of the patients treated for heartburn with resin obtained complete relief makes it very unlikely that the mechanism was psychogenic. Rather, Bartlakowski<sup>31</sup> has reported that 70 per cent of esophagi studied microscopically showed islands of gastric-secreting mucosa in the distal segment. It is suggested that these gastric glands secrete sufficient acid and pepsin locally to complement that derived from the reflux of gastric juice and sufficient to discharge the sensory nerve endings of the lower esophagus, which have been primed by mechanical distention demonstrated to be present. The pepsin-inactivating role of the anion exchange resins employed in this study may play an undetermined part in the effectiveness of this medication. The resin is recommended because of its value in control of heartburn during pregnancy, its freedom from toxicity and its economy.

## SUMMARY

The etiology of heartburn in pregnancy, present in approximately two thirds of pregnant women, is believed to be a neuromuscular dysfunction of the esophagus and stomach.

Thirty-one out of 35 pregnant women with heartburn obtained complete relief from oral administration of anion exchange resins administered before the last month of gestation.

This unexpected result with an admittedly irrational, unphysiologic agent suggests that the modern theory of the etiology of heartburn has some undetermined defects.

## REFERENCES

- 1 Rodway H E and Shelley U. Heartburn in pregnancy. *J Obst & Gynec Brit Emp* 42:107-114 1935
- 2 Wiley H M. Etiology and treatment of heartburn of pregnancy. *Am J Obst & Gynec* 51:221-224 1946
- 3 Roth D B. Heartburn in pregnancy. *J M Soc New Jersey* 43:456 1946
- 4 Williams N H. Variable significance of heartburn. *Am J Obst & Gynec* 42:814-820 1941
- 5 Aeschlimann J A. and Reinert M. Pharmacological action of some analogues of physostigmine. *J Pharmacol & Exper Therap* 43:413-444 1931
- 6 Tractenberg I and Oliver W. Use of prostigmin in abdominal and vaginal operations for relief of postoperative distention and urinary retention in series of 96 consecutive cases. *Am J Surg* 53:284-290 1941
- 7 Konifman W B. Control of postoperative atonic intestinal states with prostigmin. *Mil Surgeon* 93:187-190 1943
- 8 Hansen R. Zur Physiologie des Magens in der Schwangerschaft. *Zentralbl f Gynäk* 61:2305-2314 1937
- 9 Strauss M B and Castle W B. Studies of anemia in pregnancy. I. Gastric secretion in pregnancy and puerperium. *Am J M Sc* 184:655-673 1932
- 10 Bna, I. Wesen und Behandlung des Sodbrennens. *Therapeut d Geger* 69:51-55 1928
- 11 Porger O and Sternberg O. Klinische und experimentelle Studien über das Zustandekommen des Sodbrennens. *Wier Arch f inn Med* 18:379-386 1929
- 12 Rayner E B. Heartburn in pregnancy. *Brit M J* 2:970 1933
- 13 Alvarez W C. Heartburn. *Gastroenterology* 3:1-12, 1944
- 14 Davis C H. *Gynecology and Obstetrics*, 5 vol. Vol 1 Hagerstown Maryland W F Prior Co Inc. 1946 P 51
- 15 Mowry A E. Acid in heartburn and vomiting of pregnancy. *Canad M J* 38:378 1938
- 16 Jones C M and Richardson W. Observations on nature of 'heartburn'. *J Clin Investigation* 2:610 1926
- 17 Bárony T and Szemző G. Wird das Sodbrennen durch Hyperacidität verursacht? *Med Klin* 23:1451 1927
- 18 Lewin C. Zur Pathogenese und Therapie des Sodbrennens. *Therapie d Geger* 71:531-534 1930
- 19 Jones C M. *Digestive Tract Pair. Diagnosis and treatment experimental observations*. 152 pp. New York. MacMillan Co. 1938
- 20 Rigler L G and Eneboe J B. Incidence of hiatal hernia in pregnant women and its significance. *J Thoracic Surg* 4:262 1935
- 21 Evans J R. and Bouslog J S. Intractable heartburn of pregnancy. *Radiology* 34:550-555 1940
- 22 Dwyer, M F. Hernia of cardiac end of stomach through diaphragm. *Radiology* 28:315-324 1937
- 23 Schniepp K. H. Diaphragmatic hernia as cause of 'intractable heartburn' of pregnancy. *Am J Obst & Gynec* 46:142 146 1943
- 24 Segal H L, Hodge H, Watson J S, Jr and Scott, W J M. Polyamine formaldehyde resin. I. Its effect upon pH of acidified solutions and pH and pepsin of gastric juice in vitro. II. Its toxicity in rats preliminary feeding tests. *Gastroenterology* 4:484-496 1945
- 25 Kraemer, M. and Lehman D J. Treatment of peptic ulcer with anion exchange resins. preliminary report. *Gastroenterology* 6:202-204 1947
- 26 Martin G J and Wilkinson J. Neutralization of gastric acidity with anion exchange resins. *Gastroenterology* 6:315-323 1946
- 27 Spears M M and Pfeiffer M C. J. Anion exchange resin and peptic ulcer pain. *Gastroenterology* 8:191-198 1947
- 28 Hart, B F. Vitamin B in heartburn of pregnancy. *Am J Obst & Gynec* 45:120-122, 1945
- 29 Crämer. Über Sodbrennen und Gähnen. *Arch f Verdauungskr* 33:149-162 1924
- 30 Tuft, L., and Thomsen H. J. Fat and sugar intolerance as cause of gastrointestinal symptoms. *J A M A* 130:624-627 1946
- 31 Bartlakowski J. Über die Ursache des Sodbrennens. *Med Klin* 26:388 1930

strated to cause all the symptoms of heartburn<sup>4, 16-19</sup> On this basis the modern "neuromuscular theory" of heartburn has been postulated After secondary intermittent spasm of the cardiac sphincter the normal esophageal wave of peristalsis distends the lower esophagus with its sensitive neural endings Heartburn results and can be completely relieved by a cholinergic drug in 81 per cent of a total of 43 patients reported<sup>2-4</sup>

The reported failure to relieve the heartburn in 19 per cent of these pregnant patients may be due in part to the presence of unsuspected diaphrag-

TABLE 1 *Data in Pregnant Patients Administered Anion Exchange Resins for Heartburn*

CASE No	AGE yr	PARITY	DURATION OF HEARTBURN* wk	DEGREE OF HEARTBURN	RELIEF
1	32	I	32	Severe	Complete
2	24	II	30	Moderate	Complete
3	28	I	33	Moderate	Complete
4	29	I	32	Moderate	Complete
5	33	I	26	Severe	Complete
6	40	II	24	Moderate	Complete
7	21	II	20	Severe	Complete
8	32	IV	22	Moderate	Complete
9	23	I	28	Severe	Complete
10	29	I	16	Moderate	None
11	26	I	30	Moderate	Complete
12	26	II	32	Moderate	Complete
13	27	I	26	Severe	Complete
14	23	I	30	Moderate	Complete
15	18	I	23	Moderate	Complete
16	28	I	14	Severe	Complete
17	30	I	22	Severe	Complete
18	30	II	34	Moderate	Complete
19	29	I	30	Moderate	Complete
20	28	III	18	Moderate	None
21	31	III	33	Severe	None
22	40	I	27	Severe	Complete
23	37	I	18	Moderate	Complete
24	30	II	32	Moderate	Complete
25	23	III	24	Moderate	Complete
26	22	I	36	Severe	Complete
27	24	I	32	Severe	Complete
28	25	II	12	Moderate	Complete
29	24	I	27	Moderate	Complete
30	33	III	20	Severe	Complete
31	29	II	27	Moderate	None
32	21	I	15	Moderate	Complete
33	28	II	31	Moderate	Complete
34	24	I	28	Moderate	Complete
35	27	I	19	Moderate	Complete

matic hernia, which Rigler and Eneboe<sup>20</sup> have demonstrated in 181 per cent of primiparas during the third trimester of pregnancy They report the incidence of hiatus hernia in pregnancy as 12.8 per cent This has been corroborated by Evans and Bouslog,<sup>21</sup> Dwyer<sup>22</sup> and Schnepf<sup>23</sup>

It is of course true that the majority of patients with heartburn have obtained symptomatic relief by using alkalis such as sodium bicarbonate, aluminum hydroxide and block magnesia<sup>10, 11, 14</sup> The widespread recourse to alkalis attests to the efficacy of this symptomatic treatment, but reports limit relief obtained by alkalis to 50 per cent of these cases of heartburn<sup>12, 13</sup> Roth<sup>3</sup> believes that the "effect of these alkalis must be largely psychic," and it must be agreed that in view of the hypo-secretion of acid that is present late in pregnancy and the equivocal results reported, this may be true

## EXPERIMENTAL STUDY

Anion exchange resins were suggested in the management of heartburn in pregnancy for several reasons They are biologically practically inactive, have no effect on the acid-base balance of the blood, do not cause constipation or diarrhea, have practically no significant toxicity<sup>24</sup> and serve to absorb and neutralize acids<sup>25</sup> In addition, there is an absence of phosphate ion removal, lack of acid rebound, no chloride removal and effective pepsin inactivation<sup>26</sup> They were found valuable in the relief of pain associated with peptic ulcer even though the progress of the ulcer was reported to be uncertain<sup>27</sup>

A total of 35 private obstetric patients with sufficient heartburn of pregnancy to require medication were offered anion exchange resins in 0.25 gm gelatin capsules for relief of symptoms The usual dose was two capsules repeated in one hour as necessary More than two doses were rarely required, and relief was obtained in 31 out of 35 patients who received the medication (Table 1) As a rule the patients reported the disappearance of the epigastric and precordial burning within ten minutes of the time the two capsules of resin were taken It is remarkable that although most women required medication three or four times a week, more than 40 per cent of those who obtained relief from the medication remained free from symptoms for seven to ten days All these patients were treated before the last month of gestation since it has been reported that 75 per cent of untreated patients experience spontaneous remission of heartburn in the last month of pregnancy<sup>1</sup> This factor has been all too frequently ignored in the evaluation of therapy for heartburn in pregnancy

The average age of the patients in this group was 26.7 years, and it is of interest that 5 of the primiparas were over 30 years old Twenty-one were primigravidae, 10 secundigravidae, 3 tertigravidae and 1 a quartigravida The onset of heartburn occurred in the second trimester in 14 and in the last trimester in 21 cases Only patients who voluntarily reported moderate (23 cases) or severe (12 cases) heartburn were included in this study Relief was rapid and effective, and only those who reported unequivocal and complete relief from the heartburn were recorded as such All patients who reported something less than complete relief are recorded as failures

A group of 16 patients who obtained relief from the heartburn with the resin were given prostigmin bromide in 15-mg tablets for subsequent attack and the relief was identical with that obtained with resin The 4 who failed to report relief of heartburn after resin medication were also offered prostigmin bromide tablets, with no improvement in their complaints

## DISCUSSION

The relief of heartburn during pregnancy can be accomplished with variable but almost equal success by both unphysiologic empiric medication and definitive therapy based upon the modern theory of etiology. The administration of anion exchange resins orally for the relief of annoying heartburn in pregnancy has resulted in rapid relief of this symptom in 88 per cent of treated cases. This salutary result is at least comparable to that reported with prostigmin. Cholinergic drugs have been used to excellent advantage in heartburn of pregnancy in accordance with the neuromuscular-dysfunction theory now accepted by most physiologists. Yet this therapy appears to be no more effective qualitatively or statistically than anion exchange resins. This consideration suggests that there is still much to be explained in the etiologic picture of heartburn during pregnancy. The reports of relief obtained from the administration of yeast, thiamine chloride and nicotinic acid<sup>18</sup> and miscellaneous medication<sup>1, 18, 19, 20, 21</sup> merely add to the confusion. Between 8 and 20 per cent of the failures to obtain relief with any medication may be attributed to the presence of an occult diaphragmatic hernia that is reduced spontaneously post partum.

The fact that 88 per cent of the patients treated for heartburn with resin obtained complete relief makes it very unlikely that the mechanism was psychogenic. Rather, Bartakowski<sup>22</sup> has reported that 70 per cent of esophagi studied microscopically showed islands of gastric-secreting mucosa in the distal segment. It is suggested that these gastric glands secrete sufficient acid and pepsin locally to complement that derived from the reflux of gastric juice and sufficient to discharge the sensory nerve endings of the lower esophagus which have been primed by mechanical distention demonstrated to be present. The pepsin-inactivating role of the anion exchange resins employed in this study may play an undetermined part in the effectiveness of this medication. The resin is recommended because of its value in control of heartburn during pregnancy, its freedom from toxicity and its economy.

## SUMMARY

The etiology of heartburn in pregnancy, present in approximately two thirds of pregnant women, is believed to be a neuromuscular dysfunction of the esophagus and stomach.

Thirty-one out of 35 pregnant women with heartburn obtained complete relief from oral administration of anion exchange resins administered before the last month of gestation.

This unexpected result with an admittedly irrational unphysiologic agent suggests that the modern theory of the etiology of heartburn has some undetermined defects.

## REFERENCES

1. Rodway H. E., and Sheller U. Heartburn in pregnancy. *J. Obst. & Gynec. Brit. Emp.* 42:107-114 1935.
2. Wiley H. M. Etiology and treatment of heartburn of pregnancy. *Am. J. Obst. & Gynec.* 51:221-224 1946.
3. Roth D. B. Heartburn in pregnancy. *J. M. Soc. New York* 43:456 1946.
4. Williams N. H. Variable significance of heartburn. *Am. J. Obst. & Gynec.* 42:514-519 1941.
5. Aschlimann J. A., and Renner, M. Pharmacological action of some analogues of physostigmine. *J. Pharmacol. & Exper. Therap.* 43:415-444 1931.
6. Traenberg L., and Oliver W. Use of prostigmin in abdominal and vaginal operations for relief of postoperative distention and urinary retention in series of 30 consecutive cases. *Am. J. Surg.* 53:204-209 1941.
7. Kaufman, W. B. Control of postoperative anomic intestinal states with prostigmin. *Mil. Surg.* 93:187-190 1943.
8. Hirsch, R. Zur Physiologie des Magens in der Schwangerschaft. *Zeitschr. f. Gyn.* 61:206-214 1907.
9. Strauss M. B., and Castle, W. B. Studies of anemia in pregnancy. I. Gastric secretion in pregnancy and puerperium. *Am. J. M. Sc.* 184:555-57 1932.
10. Boas, L. Weizen und Behandlung des Sodbrennens. *Therap. u. Gyn.* 69:51-55 1926.
11. Porret O., and Sternberg O. Klinische und experimentelle Studien über das Zustandekommen des Sodbrennens. *Wien. Arch. f. inn. Med.* 18:372-386 1929.
12. Ravner E. B. Heartburn in pregnancy. *Brit. M. J.* 2:970 1936.
13. Alvarez, W. C. Heartburn. *Gastr. enter.* 13:3 1-12, 1944.
14. Davis, C. H. *Gynecology and Obstetrics*, 3 vol. Vol. 1 Hagerstown, Maryland W. F. Prior Co., Inc., 1946. P. 51.
15. Mowry A. E. Aid in heartburn and vomiting of pregnancy. *Clinics* 1:1 35:576 1936.
16. Jones C. M., and Richardson, W. Observations on nature of heartburn. *J. Clin. Investigation* 2:610 1925.
17. Berger, T., and Szekess G. Wird das Sodbrennen durch Hyperacrität verursacht? *Mon. Klin.* 23:1451 1927.
18. Lewin C. Zur Pathogenese und Therapie des Sodbrennens. *Therap. u. Gyn.* 71:57-5 4, 1930.
19. Jones C. M. *Digestive Tract Path. Diag. and treatment experimental* 1927. New York MacMillan Co., 1928.
20. Raper L. G., and Enchew, J. B. Incidence of hiatus hernia in pregnant women and its significance. *J. Obst. Surg.* 4:262-265 1935.
21. Evans I. R., and Bonnier I. S. Intractable heartburn of pregnancy. *Post. op.* 34:5 0-5 5 1940.
22. Dwyer M. F. Hernia of cardiac end of stomach through diaphragm. *Ann. Surg.* 25:15-24 1907.
23. Schenck K. H. Diaphragmatic hernia as cause of intractable heartburn of pregnancy. *Am. J. Obst. & Gynec.* 46:142-146 1943.
24. Segal, H. L., Dodge, H., Watson, J. S., Jr., and Stern, W. J. M. Polyanion-coupled hydroxy resin. I. Its effect upon pH of acidified solutions and pH and pepsin of gastric juice in vitro. II. Its removal in rats following feeding tests. *Gastroenterology* 4:454-460, 1945.
25. Kramer, M., and Lehman D. I. Treatment of peptic ulcer with anion exchange resins preliminary report. *Gastr. enter.* 13:8 202-204, 1947.
26. Martin G. J., and Wilkison, J. Neutralization of gastric acidity with anion exchange resins. *Gastr. enter.* 13:6-15 1946.
27. Sweeny M. M., and Pfaffler M. C. I. Anion exchange resin and postoperative pain. *Gastr. enter.* 13:8 191-198 1947.
28. Hart, B. F. Vitamin B in heartburn of pregnancy. *Am. J. Obst. & Gynec.* 45:120-122 1945.
29. Götter, C. Sodbrennen und Gähnen. *Arch. f. Verdauungsph.* 33:149 1924.
30. Tall, L., and Tannen, H. J. Fat and sugar intolerance as cause of frequent crampy stools. *J. A. M. A.* 130:524-527 1945.
31. Bartakowski J. Über die Ursache des Sodbrennens. *Wien. Arch. f. inn. Med.* 26:35 1909.

strated to cause all the symptoms of heartburn<sup>4, 16-19</sup> On this basis the modern "neuromuscular theory" of heartburn has been postulated After secondary intermittent spasm of the cardiac sphincter the normal esophageal wave of peristalsis distends the lower esophagus with its sensitive neural endings Heartburn results and can be completely relieved by a cholinergic drug in 81 per cent of a total of 43 patients reported<sup>2-4</sup>

The reported failure to relieve the heartburn in 19 per cent of these pregnant patients may be due in part to the presence of unsuspected diaphrag-

TABLE 1 *Data in Pregnant Patients Administered Anion Exchange Resins for Heartburn*

CASE No	AGE yr	PARITY	DURATION OF HEARTBURN wk	DEGREE OF HEARTBURN	RELIEF
1	32	I	32	Severe	Complete
2	24	II	30	Moderate	Complete
3	28	I	33	Moderate	Complete
4	29	I	32	Moderate	Complete
5	33	I	26	Severe	Complete
6	40	II	24	Moderate	Complete
7	21	II	20	Severe	Complete
8	32	IV	22	Moderate	Complete
9	23	I	28	Severe	Complete
10	29	I	16	Moderate	None
11	26	I	30	Moderate	Complete
12	26	II	32	Moderate	Complete
13	27	I	26	Severe	Complete
14	23	I	30	Moderate	Complete
15	18	I	23	Moderate	Complete
16	28	I	14	Severe	Complete
17	30	I	22	Severe	Complete
18	30	II	34	Moderate	Complete
19	29	I	30	Moderate	Complete
20	28	III	18	Moderate	None
21	31	II	33	Severe	None
22	40	I	27	Severe	Complete
23	37	I	18	Moderate	Complete
24	30	II	32	Moderate	Complete
25	23	III	24	Moderate	Complete
26	22	I	36	Severe	Complete
27	24	I	32	Severe	Complete
28	25	II	12	Moderate	Complete
29	24	I	27	Moderate	Complete
30	33	III	20	Severe	Complete
31	29	II	27	Moderate	None
32	21	I	15	Moderate	Complete
33	28	II	31	Moderate	Complete
34	24	I	28	Moderate	Complete
35	27	I	19	Moderate	Complete

matic hernia, which Rigler and Eneboe<sup>20</sup> have demonstrated in 181 per cent of primiparas during the third trimester of pregnancy They report the incidence of hiatus hernia in pregnancy as 128 per cent This has been corroborated by Evans and Bouslog,<sup>21</sup> Dwyer<sup>22</sup> and Schnepf<sup>23</sup>

It is of course true that the majority of patients with heartburn have obtained symptomatic relief by using alkalis such as sodium bicarbonate, aluminum hydroxide and block magnesia<sup>10, 11, 14</sup> The widespread recourse to alkalis attests to the efficacy of this symptomatic treatment, but reports limit relief obtained by alkalis to 50 per cent of these cases of heartburn<sup>12, 13</sup> Roth<sup>3</sup> believes that the "effect of these alkalis must be largely psychic," and it must be agreed that in view of the hypo-secretion of acid that is present late in pregnancy and the equivocal results reported, this may be true

## EXPERIMENTAL STUDY

Anion exchange resins were suggested in the management of heartburn in pregnancy for several reasons They are biologically practically inactive, have no effect on the acid-base balance of the blood do not cause constipation or diarrhea, have practically no significant toxicity<sup>24</sup> and serve to absorb and neutralize acids<sup>25</sup> In addition, there is an absence of phosphate ion removal, lack of acid rebound, no chloride removal and effective pepsin inactivation<sup>26</sup> They were found valuable in the relief of pain associated with peptic ulcer even though the progress of the ulcer was reported to be uncertain<sup>27</sup>

A total of 35 private obstetric patients with sufficient heartburn of pregnancy to require medication were offered anion exchange resins in 0.25-gm gelatin capsules for relief of symptoms The usual dose was two capsules repeated in one hour as necessary More than two doses were rarely required, and relief was obtained in 31 out of 35 patients who received the medication (Table 1) As a rule the patients reported the disappearance of the epigastric and precordial burning within ten minutes of the time the two capsules of resin were taken It is remarkable that although most women required medication three or four times a week, more than 40 per cent of those who obtained relief from the medication remained free from symptoms for seven to ten days All these patients were treated before the last month of gestation since it has been reported that 75 per cent of untreated patients experience spontaneous remission of heartburn in the last month of pregnancy<sup>1</sup> This factor has been all too frequently ignored in the evaluation of therapy for heartburn in pregnancy

The average age of the patients in this group was 26.7 years, and it is of interest that 5 of the primiparas were over 30 years old Twenty-one were primigravidae, 10 secundigravidae, 3 tertigravidae and 1 a quartigravida The onset of heartburn occurred in the second trimester in 14 and in the last trimester in 21 cases Only patients who voluntarily reported moderate (23 cases) or severe (12 cases) heartburn were included in this study Relief was rapid and effective, and only those who reported unequivocal and complete relief from the heartburn were recorded as such All patients who reported something less than complete relief are recorded as failures

A group of 16 patients who obtained relief from the heartburn with the resin were given prostigmin bromide in 15-mg tablets for subsequent attacks and the relief was identical with that obtained with resin The 4 who failed to report relief of heartburn after resin medication were also offered prostigmin bromide tablets, with no improvement in their complaints

it was desired to establish an aorta-pulmonary artery shunt for alleviation of the cyanotic state of tetralogy of Fallot, and when it was impossible directly to anastomose vessels of the aortic and the pulmonary systems by the Blalock or the Potts technic. One of these patients died twelve days after operation, largely from the effects of dicumarol therapy. A second died two days after operation from cardiac decompensation. The grafts in both cases were patent at post-mortem examination. In the 7 surviving patients the grafts are apparently carrying blood and have been in place from one to five months. Evidence that these grafts are patent can be adduced from the fact that all the children have continuous murmurs, which previously did not exist, and that the cyanotic states have been markedly improved.

In 3 additional patients, segments of preserved human aorta have been used as grafts during surgical correction of coarctation of the thoracic aorta. Although it is usually possible to excise a narrowed segment of aorta and directly anastomose the remaining ends, removal of the constricted areas from these 3 subjects left very long gaps in the aorta,

which precluded reuniting the remaining aortic ends. In each case a graft about 5 cm in length was employed, and in each case a lumen of full size was established for the aortic pathway. All 3 patients survived operation, they have had relief of the hypertension that preoperatively existed in the upper portions of their bodies, and they have now developed a greatly increased blood flow to the legs. These grafts have been in place only two or three months.

It is too soon to give any final evaluation of the technic of blood-vessel grafting in human cases. However, the early postoperative results are very encouraging, and they certainly warrant further trial and study when no other means are available for satisfactorily bridging a gap in a large vessel of the arterial system.

## REFERENCES

- 1 Gross R. E. and Harwitz, E. S. Unpublished data.
- 2 Gross R. E., Bill A. H. Jr., and Peirce E. C. 2nd. Methods for preservation and transplantation of arterial grafts. *Surg., Gynec & Obst.* (in press)
- 3 Peirce E. C. 2nd, Gross R. E., Bill A. H. Jr. and Merrill, K. Tissue culture evaluation of viability of refrigerated, stored, blood vessels which are used for grafting. *Ann. Surg.* (in press)

## MEDICAL PROGRESS

### BLOOD AND ITS DERIVATIVES (Concluded)\*

SAM T. GIBSON, M.D.

BOSTON

#### Albumin (Fraction I)<sup>†</sup>

**Shock.** As the product whose preparation was responsible for the initiation of the entire fractionation program,<sup>9, 11, 212-217</sup> albumin remains of first importance, but its use in the treatment of shock has become secondary. Tested successfully in civilian cases<sup>218-222</sup> of shock, it proved to be a satisfactory therapeutic agent under field conditions.<sup>11, 223, 224</sup> Unless extra fluid was given, however, dehydrated patients received less benefit from the concentrated material than normally hydrated patients did.<sup>214, 215, 221</sup> Various investigators have reported plasma-volume increases due to albumin of 8 to 18 cc per gram under different conditions. These are summarized in Table 4. Albumin uniformly produces a rise in right atrial pressure and usually causes the hematocrit to decrease. Its effect on cardiac output varies. For civilian use concentrated albumin is a convenient, easily transported, immediately available, stable, safe and effective agent for the emergency treatment of shock and is useful in accident rooms and ambulances and in doctors' bags.

**Hypoproteinemia.** Considerably less agreement exists regarding the action of albumin in chronic hypoproteinemia.<sup>216</sup> Single injections of 25 gm in

TABLE 4 Increase in Plasma Volume Following Albumin Administration

CONDITION TREATED	NO OF CASES	AVERAGE INCREASE IN PLASMA VOLUME cc/gm of injected albumin <sup>225</sup>
Calculated from osmotic pressure of albumin <sup>225</sup>	—	18.0
Experimental hemorrhage in normal man	1	17.7
Heyl <sup>226</sup>	11	17.4
Stead <sup>227</sup>	2	20.0
Normal man without hemorrhage <sup>228</sup>	17	12.9
Clinical shock receiving less than 400 cc. of saline solution in addition to albumin	48	12.5
Warren <sup>229</sup>	10	16.0
Stead <sup>227</sup>	10	17.7
Coombes <sup>230</sup>	6	11.1
Lowell <sup>231</sup>	20	12.0
Clinical shock receiving more than 400 cc. additional saline solution	27	15.6
Stead <sup>227</sup>	6	22.0
Coombes <sup>230</sup>	6	14.2
Lowell <sup>231</sup>	18	15.0

nephrotic patients, as shown by Luetscher<sup>226</sup> and Thorn et al.,<sup>227</sup> produce a rapid increase in plasma volume (25 to 30 per cent) a rise in colloid osmotic

\*From the Medical Clinic, Peter Bent Brigham Hospital and the Department of Medicine, Harvard Medical School.  
<sup>†</sup>Milton Research Fellow in Medicine, Harvard Medical School; assistant in medicine, Peter Bent Brigham Hospital.

## PRELIMINARY OBSERVATIONS ON THE USE OF HUMAN ARTERIAL GRAFTS IN THE TREATMENT OF CERTAIN CARDIOVASCULAR DEFECTS

ROBERT E. GROSS, M.D.,\* ELLIOTT S. HURWITT, M.D.,† ALEXANDER H. BILL, JR., M.D.,‡  
AND E. CONVERSE PEIRCE, 2ND, M.D.§

BOSTON

FOR many years surgeons have felt the need for some technical procedure that would help in bridging gaps of the arterial system when a large vessel has been destroyed by trauma or has become thrombosed because of degenerative disease or embolism, or when certain cardiovascular abnormalities require operative correction. Extensive investigations have been conducted to further the work of other experimenters and to determine the feasibility of transferring a segment of large artery from one animal to another of the same species. Full reports of these studies will be published elsewhere.<sup>1-3</sup>

In the laboratory for surgical research sections of abdominal aorta were removed from donor dogs and were subsequently used to replace sections of the abdominal aorta of recipient dogs. Sixty-three such grafts were made, employing mongrel dogs. The studies were made in three sets of observations: vessels were removed from donor animals and implanted within a few hours into recipient dogs; segments of aorta were frozen and kept for varying periods before being implanted; and arterial segments were preserved for varying periods by storage in special nutritive solutions just above freezing before being placed in recipient animals.

In the first set of studies, there were twenty-seven grafts. After removal, the aortic segments were kept moist and in a common, domestic refrigerator for periods varying from two to seventy-eight hours, and were then grafted into recipient dogs. These recipient animals were kept under observation for as long as a year. When the segments for the grafts had been kept for only a few hours, there was a very high probability of their survival in the recipient animals. When segments were kept for about six hours and then implanted, only about two thirds of the grafts survived and remained in satisfactory condition. When specimens of aorta were kept from eighteen to seventy-eight hours before being implanted into recipient animals, the vast majority of the dogs died from thrombosis in the grafts or from rupture at the suture lines.

In the second set of studies, blood vessels from the donor dogs were rapidly frozen to  $-72^{\circ}\text{C}$  and were stored at this temperature for periods varying from two to thirty-five days before being im-

planted into recipient dogs. Twelve such grafts were made. Three quarters of these dogs died within five to thirty days from hemorrhage at the suture lines. Two grafts became partially thrombosed. One animal was kept for six months, and at autopsy the graft showed moderate intimal sclerosis. These results led to the firm conviction that storage of vessels by freezing would not be a satisfactory method for preserving arterial grafts.

In the third set of studies, aortic segments were taken from donor dogs and stored in flasks, the vessel being just covered with an electrolyte solution, to which had been added glucose (1 per cent) and dog serum (10 per cent) and a buffer, as well as penicillin and streptomycin (giving a concentration of 50 units of each per cubic centimeter), and finally a phenol-red indicator so that changes in the reaction of the solution could be determined by inspection of the fluid in the flasks. Each flask with its solution containing a segment of vessel was stored in an icebox, the temperature of which did not range beyond 1 to  $4^{\circ}\text{C}$ . Tissue-culture studies on segments of vessels preserved in this way showed that vessels were viable for as long as thirty-five to forty days in most cases. Segments of vessel that had been stored in this manner for periods of from two to ninety-eight days were implanted into recipient dogs. Twenty-four such grafts were made and the recipient animals kept from four days to ten months. There were no deaths from dehiscence or thrombosis of any of the grafts. Three animals had minor thrombi at the lines of anastomosis. The grafts were known to be carrying blood for periods as long as ten months. These vessels were studied in the living dogs by aortagrams, and were carefully studied at autopsy after death or sacrifice of the animals. The experiments indicated that arteries can be stored satisfactorily by this method in the cold for slightly more than a month and can still be used for purposes of grafting.

With the above summarized information from the experimental laboratory, it was believed that the last described method of arterial preservation might be applicable for vessel grafting in human subjects. Segments of arteries obtained within a few hours from human beings who had died in automobile accidents were collected under aseptic conditions and stored for use whenever the need for an arterial graft might arise in a human patient. Nine such grafts were used to bridge gaps between the aortic system and the pulmonary artery when

\*Ladd Professor of Children's Surgery, Harvard Medical School, surgeon-in-chief, Children's Hospital.

†Research fellow in pathology, Children's Hospital.

‡Assistant resident surgeon, Children's Hospital.

§Research fellow in surgery, Harvard Medical School.

bumin diffuses into the lymph,\* remains in equilibrium with the blood, and is gradually decomposed into amino acids, which are incorporated into tissue or slowly excreted

Recently many data have accumulated that cast considerable doubt on the universal applicability of Starling's<sup>240</sup> hypothesis of edema formation and removal. Keys and his associates<sup>241</sup> produced classic starvation edema in 34 normal volunteers on a six months' European starvation diet (49 gm of protein per day). The total proteins dropped only 0.73 gm per 100 cc, and albumin-globulin ratios remained essentially unchanged with no evidence of cardiac or renal failure or thiamine deficiency. Govaerts<sup>242</sup> had independently observed the same conditions in 17 starving Belgians. Schemm<sup>243</sup> has pointed out for some time the ease of diuresis and loss of ascitic and pleural fluid in many cases on a high-fluid, low-sodium, 40-gm-protein diet when 140-gm-protein diets and plasma intravenously had failed to produce any effect. The absence of correlation between edema formation and albumin levels in nephrosis is also well known.<sup>244-246</sup> (Many have no edema with an albumin of less than 1 gm per 100 cc.) Ralli et al<sup>247</sup> and Labby and his co-workers,<sup>248, 249</sup> using intravenous liver extract, have more recently induced disappearance of ascites in chronic cirrhosis without changing the serum protein levels. It is not too surprising, then, to find albumin administration followed by diuresis with no change in serum proteins or to have albumin increase circulating proteins without mobilizing ascitic fluid.

Mankin and Lowell<sup>250</sup> sought to explain Patek's<sup>251</sup> failure to remove ascites mentioned above. In 10 patients with cirrhosis they measured the colloidal osmotic pressure of serum and ascitic fluid, ascitic fluid volume and intraperitoneal hydrostatic pressure and then varied each of these experimentally. Usually, equilibrium was quickly re-established between plasma and ascitic fluid after the transfer of a small amount of fluid between them. When the serum colloidal osmotic pressure was increased, however, there was a threefold increase in rate of transfer of albumin to the ascites, thereby preventing any osmotic removal of fluid by the blood. This seems to be further evidence that in many cases Starling's hypothesis has little to do with the persistence of cirrhotic ascites. Certainly, the rapid restoration of equilibrium makes it impossible in such cases to apply Donnan's equilibrium principle and Starling's hypothesis, which depend by definition on a "semipermeable membrane" impermeable to the protein. Inability to by-pass or circumvent the membrane is also implied. Perhaps patients with cirrhosis who have responded to albumin therapy established plasma-ascitic equilibrium more slowly or had portal pres-

sure lowered or peritoneal lymphatic drainage improved.

Blakemore<sup>251, 252</sup> reports that all 4 cirrhotic patients with ascites in whom he created a portacaval shunt for portal hypertension lost their ascites postoperatively, and 3 of these had a persistent postoperative *drop* in total protein and albumin levels. It is interesting that of the 93 cirrhotic patients in 5916 autopsies recently reviewed by Hoffman and Lisa<sup>253</sup> 87 per cent had objective ascites, and 90 per cent of these (78 per cent of the group) had evidence of portal hypertension and obstruction. Perhaps this is more important in cirrhotic ascitic formation than colloidal osmotic pressure changes are.

In nephrosis, fluid imbalance may be due to an entirely different mechanism. Luetscher<sup>254</sup> postulates an excessive tubular resorption of sodium as the basic difficulty possibly owing to a diminished glomerular filtration rate.<sup>†</sup> The injection of albumin raises the circulating protein concentration (even though ever so slightly) that draws water into the blood, increasing glomerular filtration rate and thereby diminishing the proportion of sodium resorbed and perhaps moving out some edema.<sup>‡</sup> Armstrong<sup>255</sup> tends to favor this explanation, calling it "isosmotic" addition of albumin (sustained increase in plasma volume without increase in edema-fluid osmotic pressure) as opposed to "isometric" (increased edema-fluid osmotic pressure without increased plasma volume), which fails to mobilize edema. Increased capillary permeability or restricted cardiac output may be responsible for the latter condition.<sup>246</sup>

If, on the other hand, one inclines to the theories<sup>259-261</sup> that protein normally passes the glomerulus and that proteinuria is a failure of the tubules to resorb protein rather than of the glomeruli to retain it, one must consider the possibility that the increased filtration and reabsorption of protein following an increase in serum protein might interfere with the simultaneous reabsorption of sodium. Smetana's<sup>262</sup> demonstration of dye-tagged protein resorption by normal mouse and rat tubules and Gunton and Burton's<sup>263</sup> measurement of normal proteinuria as 2 to 4 mg per 100 cc call for serious consideration of this theory.

Obviously much more work is necessary to improve understanding of the role albumin plays in edema and diuresis. Many studies are underway, and the known unpublished data far exceed the published information. Rumor brings no word of a solution, however.

**Binding.** In seeking an agent to improve the heat stability of albumin Luck and his asso-

\*Li and Reinhardt<sup>256</sup> report that the albumin content of normal rat thoracic-duct lymph is consistently much higher than that of rat cervical duct lymph or plasma.

†Schweppe and Freeman<sup>257</sup> find that the glomerular filtration rate is routinely depressed in hypoproteinemic plasmapheresed dogs. They did not report sodium studies. On the other hand, Emerson et al<sup>258</sup> find that the inulin glomerular filtration rate increased in some nephrotic cases.

‡All studies of renal function must be reviewed in relation to Cargill's<sup>259</sup> preliminary observation that renal blood flow measurements following albumin administration are one third higher when measured by renal vein catheterization than when done by indirect techniques.

pressure (10 to 20 per cent), a smaller increase in total circulating albumin than the amount injected, a slight rise in circulating globulin, an increase in proteinuria (chiefly albumin and alpha<sub>1</sub> globulin) and a slight rise in urine volume without change in chloride excretion or albumin or globulin clearance. Within 48 hours most effects have disappeared, and the albumin has left the circulating plasma without being quantitatively excreted in the urine. Doses of 50 gm given daily for two to thirty days to patients with chronic Bright's disease are reported by Thorn et al<sup>227</sup> to produce moderate diuresis best in patients with edema, low proteins, no nitrogen retention and normal blood pressure. This stops when albumin is withdrawn. Others<sup>228</sup> have observed, however, that after sixty to ninety days' treatment diuresis may continue to dryness. Perhaps a spontaneous diuresis was initiated. DeSanctis and Sullivan<sup>229</sup> have also reported a successful remission (six months) and rise in serum protein to normal in a four-and-a-half-year-old boy with nephrosis receiving 15 gm of albumin daily for sixty days, in addition to a low-sodium, high-protein diet. Similar responses were seen in 4 more nephrotic children still under treatment, 2 of whom lost their ascites on this regimen.

In cirrhosis equally confusing results have been observed. Five patients on low-salt, low-fat, high-protein, high-vitamin and high-liver diets were given 50 gm of albumin daily for one to ten days by Thorn et al<sup>230</sup>. An immediate diuresis was not maintained, and no remarkable effects on ascites were noted. Patek and his associates<sup>231</sup> report a similar failure in 3 patients with chronic cirrhosis treated thirteen to sixteen days. Apparently, the rate of transfer of albumin from plasma to ascitic fluid increased threefold during treatment.

The largest series of cases of albumin-treated cirrhosis followed the longest time was recently published by Kunkel et al<sup>232</sup>. Using doses of 4 to 80 units (100 to 2000 gm) of concentrated albumin, they treated 17 patients (5 with ascites of short duration, 4 with long-standing ascites, 6 with severe liver damage following infectious hepatitis or biliary cirrhosis and 2 with low serum albumin but no ascites or edema), 14 of the 15 patients with ascites lost their fluid after albumin. High-vitamin, high-protein, high-calorie diets were given without salt restriction. No difference in action of high salt and salt-poor albumin was seen. Patients with marked portal obstruction, high antidiuretic titers in the urine or long-standing ascites proved most resistant. Those with low serum albumin levels and ascites of short duration (especially after infectious hepatitis) responded most readily. Many patients volunteered the information that they developed a feeling of well-being and increased appetite after albumin. Careful caloric and nitrogen balance studies confirmed the truth of this subjective observation. These results help to explain

the failures reported by Thorn and his co-workers<sup>230</sup> and Patek et al,<sup>231</sup> who used smaller doses for shorter periods, and in the Patek series the most difficult group (ascites of nine to twenty-four months' duration) were being treated. The observations of Armstrong<sup>233</sup> and Gibson,<sup>234</sup> using doses of 500 to 700 gm of albumin, more nearly parallel those of the Kunkel group<sup>232</sup>.

Obviously, chronic hypoproteinemias are very difficult to affect. The edema of a terminal case of lupus erythematosus failed to respond to 400 gm of albumin<sup>234</sup>. Acute conditions, however, seem to be more sensitive. Jacoby et al<sup>235</sup> report the excellent response of 2 infants with erythroblastosis fetalis and edema to 30.0 and 12.5 gm of albumin, respectively, which produced complete relief of symptoms and permitted survival.

**Metabolism.** Studying the fate of albumin, Eckhardt and his associates<sup>236</sup> maintained 5 normal subjects on albumin by mouth or vein as the sole source of nitrogen for seven to sixteen days. They observed that 37.5 gm of albumin was sufficient to maintain a positive nitrogen balance when given by vein, but 50 gm was required by mouth. After the albumin had been discontinued, the excess disappeared from the circulation on a four-day to six-day 50 per cent disappearance curve, reaching normal levels in three weeks. The addition of tryptophane and isoleucine (two major essential amino acid deficiencies of albumin<sup>237</sup>) did not affect these observations.

Thorn et al<sup>230</sup> achieved no therapeutic effect when they fed albumin to a patient with cirrhosis. They did observe, however, that the onset of urea nitrogen excretion was delayed several days longer after albumin was administered by vein than when given by mouth. This led Albright and his co-workers<sup>238</sup> to study the metabolism of albumin. Giving an osteoporotic female patient 50 gm of albumin intravenously daily for twelve days, they obtained the following "nitrogen balance sheet" twenty-four days after the last injection: nitrogen injected 82.94 gm, burned 66.51 gm, converted to protoplasm 8.29 gm and unchanged 8.14 gm. These figures indicate considerably less conversion to protoplasm, slower burning and more protein storage than was found in 3 patients similarly studied after receiving whole plasma. Whether this is a peculiarity of albumin metabolism or a vagary of this particular patient with disturbed calcium and phosphorus metabolism was not determined.

**Mechanism of action.** The behavior of injected albumin presents two challenging questions. Where does it go from the blood stream? How is diuresis accomplished in certain cases without a sufficient rise in circulating protein to alter the colloidal osmotic pressure significantly?

Eckhardt et al,<sup>236</sup> after observing the metabolic experiments just described, hypothesized that al-

report 100 successful infusions of this material (average dose of 400 cc), with only 3 per cent reactions — chills and fever and no anaphylaxis on reinfusion ten to fifteen days later. Melka et al.<sup>291</sup> were unable to sensitize animals with it, and found that the treatment had not diminished its osmotic pressure. Hughes, however, was unable by this method or by that of Lewis<sup>292</sup> to lower the reactivity of the recrystallized albumin used by Wangenstein et al.<sup>287</sup>

Gelatin (bovine, fish or modified) has been extensively investigated and reported.<sup>11, 14, 293</sup> It is safe, nonantigenic, effective in the immediate treatment of shock,<sup>294</sup> capable of producing a positive nitrogen balance and not usually deposited in tissue cells.<sup>295, 296</sup> It is rather quickly excreted, however, tends to depress the serum albumin level and has not been extensively investigated in the treatment of chronic hypoproteinemia.

Human hemoglobin and globin were discussed above. There are no reports of attempts to prepare bovine globin for intravenous use.

Both acacia<sup>297, 298</sup> and pectin<sup>299</sup> have been shown to be deposited in liver cells, possibly leading to damage and impaired function. Both leave the blood stream rather quickly.

The following synthetic preparations are also ineffective: glutamic acid polypeptide, sodium glycerol polysuccinate, dextran<sup>300</sup> — a Swedish glucose polysaccharide from beet sugar, with a molecular weight of 100,000, that is safe but completely excreted in twenty-four hours, and a Russian "colloidal infusion of non-anaphylactogenic protein from milk casein"<sup>301</sup> with deficiencies similar to those of dextran. The Russian "plazmol S-25"<sup>302</sup> is apparently a "tissue-therapy" product of human plasma similar to antireticular cytotoxic serum and not a blood substitute.

Amino acids and protein hydrolysates are composed of molecules small enough to diffuse through normal semipermeable membranes and perform little osmotic function. Their metabolic aspects are discussed below.

Human ascitic fluid is used from time to time but is usually too low in protein to be effective. Philippine investigators<sup>303</sup> report success in treating a nephrotic patient with 100 cc of material heated at 60°C for two hours. This has not been repeated.

A minimal molecular diameter of 30 angstrom units seems necessary for retention in normal blood vessels. Few proposed substitutes approach this size (Table 3). Until such a compound is discovered, albumin, plasma and blood remain the most reliable therapeutic agents now available.

#### PROTEIN THERAPY

##### Metabolism

With the increasing number of amino acid and proteinoid preparations available for clinical use,

it is important to review certain aspects of protein and amino acid metabolism as a basis for rational clinical therapy.

The usefulness of a protein or amino acid mixture is apparently related to its composition, route of administration and simultaneous carbohydrate intake. Rose<sup>304</sup> demonstrated the "essential" nature of 10 amino acids in the rat (8 in human adults)\* "those which cannot be synthesized by the animal organism, out of the materials ordinarily available, at a speed commensurate with the demands for normal growth." Not until later, however, was it appreciated that for optimal utilization the missing essential acids must be supplied reasonably near the same time that the incomplete protein is ingested or else much of the incomplete protein will not be utilized. A delay of two<sup>305</sup> to six<sup>306</sup> hours between "incomplete" and "essential" acid intake is sufficient to prevent utilization of the former. This may explain why some proteins such as soy bean with satisfactory total amino acid analyses have low nutritive value (some of the essential amino acid components may be more difficult to digest and more slowly absorbed).

Many investigators are beginning to believe that maximal protein utilization depends on factors other than essential amino acids. The "doubly depleted" dogs (anemic and hypoproteinemic) of Whipple et al.<sup>307, 308</sup> could manufacture hemoglobin and plasma protein satisfactorily on the ten crystalline essential amino acids but failed to maintain weight. Womack and Rose<sup>309</sup> and Woolley<sup>310</sup> noted the same difference in mice fed crystalline amino acids as opposed to casein hydrolysates. They believed, however, that both sets grew — only that the hydrolysate group grew maximally. Woolley attributes this property to a peptide or peptide-like substance, streptogenin, separated from highly purified protein by tryptic digestion but destroyed by hydrolysis. Christensen<sup>311</sup> has observed that casein peptides are less readily utilized than free amino acids and suffer considerable loss when given intravenously. Perhaps this explains the observation frequently reported that protein hydrolysates and amino acid mixtures are better utilized when given orally than intravenously.<sup>312-314</sup>

Cannon et al.<sup>305, 315, 316</sup> believe that a critical level of simultaneous carbohydrate intake is required to maintain a positive nitrogen balance on any amino acid intake. Exceeding that, however, the addition of extra calories has no apparent effect, merely adding adipose tissue. They estimate the critical value as 1240 calories for rats or 1500 calories for man per square meter of body surface per day. Kozoll and his co-workers<sup>313</sup> found 1000 calories per day adequate in man.

The question of protein storage has been much discussed.<sup>317</sup> Originally postulated as separate en-

\*Leucine, isoleucine, valine, lysine, threonine, tryptophane, phenylalanine and methionine for man; and arginine and histidine for the rat.

ciates<sup>264-267</sup> showed that considerable protection was derived from the binding to albumin of fatty acids and related compounds, which were anions with a nonpolar group. The effectiveness of this protection increased with chain length up to 12 carbons. This ability to bind other substances was found to be a property of albumin almost exclusively, probably related to its molecular conformation. Although Bennhold<sup>268</sup> had suggested in 1932 that such a mechanism might exist for transportation of substances in the blood, this was the first work to investigate it thoroughly. There are many examples of the usefulness of this property.<sup>269</sup> It may be part of the antibody defense system, coating bacteria to permit phagocytic ingestion (as pointed out under "sludged blood" above). Certainly, it is necessary for the blocking of anticomplementary action of gamma globulin to permit normal complement-fixation reactions. It may also serve to make lipid hormones water soluble, protect against hemolytic action of fatty acids and possibly salvage valuable blood constituents of small molecular size by preventing the necessity of their filtration and reabsorption. Even osmotic-pressure calculations are affected, since one molecule of albumin can bind six chloride ions.<sup>270</sup>

Davis and Dubos<sup>271-277</sup> have described in a number of communications a very practical application of this property. Seeking to dissolve the waxy layer of the tubercle bacillus with Tween 80 (polyoxyethylene sorbitan monooleate) Dubos found that it stimulated and at other times inhibited submerged culture growth. Relating the inhibition to unesterified oleic acid content, it was found by chance that serum albumin bound the oleic acid and the Tween, and then stimulated growth so that inoculums of 2 or 3 bacteria could be successfully cultured. It is not a growth factor—merely a protecting mechanism enabling growth to become established.

The most recent example of the importance of albumin binding is reported by Tompsett et al.<sup>278</sup> in investigating the clinical failure of penicillin K. Studying X, G, dihydro F, and K, they found that albumin bound them all in varying degrees from 47 per cent for X to 91 per cent for K, checking quite well with the 85 to 90 per cent loss of activity of K in studies in vivo compared with studies in vitro. It is important that all in vitro antibiotic studies include albumin in the medium used.

**Miscellaneous** The use of human or bovine albumin in 25 or 30 per cent solution<sup>280</sup> or mixed with plasma I<sup>4379</sup> has markedly improved the specificity and accuracy of Rh typing and Rh blocking antibody tests, facilitating the prenatal management of mothers of potentially erythroblastotic children. In like manner Neber and Dameshek<sup>280</sup> used albumin as a diluent in antibody tests of hemolytic syndromes and were able

to demonstrate circulating warm antibodies not found by routine methods in 5 of 17 patients.

Another useful new technic involving albumin is reported by Ferrebee et al.<sup>281</sup> and Vallee and his associates<sup>282</sup> for the separation of leukocytes from whole blood by flotation. When two parts of albumin solution of specific gravity 1.079 are added to three parts of heparinized blood and centrifuged, the plasma and leukocytes form a layer above, and the erythrocytes a layer below the albumin. The leukocytes are easily pipetted off and may be separated from the plasma by saline dilution and further centrifugation.

### BLOOD SUBSTITUTES

The expense and difficulty involved in large scale procurement of human blood and its derivatives have stimulated the search for satisfactory substitutes of animal, vegetable or synthetic origin. Janeway and Oncley<sup>14</sup> have summarized the physicochemical and clinical background of this search.

Bovine albumin is chemically most like human albumin, and much effort has been expended to develop it as a satisfactory substitute.<sup>283, 284, 285-287</sup> Unfortunately, a certain amount of antigenicity remains, even in preparations carefully recrystallized many times. Large-scale investigation was terminated in 1942 upon the death of 1 of 60 volunteers receiving 25 gm. each.<sup>288</sup> Myocardial necrosis was found post mortem. Twenty-four of the volunteers developed symptoms ten to thirty-three days after injection, with fever, purpura and hepatic, renal and cardiac damage (as demonstrated by electrocardiographic changes) of varying degree and duration. Many of these never showed demonstrable circulating antibodies to bovine albumin, and some recovered while bovine albumin was still detectable in the blood.

Wangenstein and his co-workers<sup>287</sup> did not encounter this type of reaction and have continued investigation. They recently reported 469 injections to 410 patients with 2.9 per cent immediate and 9.2 per cent delayed reaction—none fatal. Immediate reactions were anaphylactoid or pyrogenic. Delayed reactions occurred in twelve to twenty-four days as urticaria, erythema, myalgia, arthralgia and fever. The severest cases received most relief from intravenous procaine (1 gm. in 250 cc. of saline solution injected over a period of an hour). Seven autopsies of patients dying from other causes showed no disease attributable to bovine albumin. Despite this and despite its effectiveness in shock, they recommend that it not be used until further despeciated. Attempts to relate antigenicity to sulfhydryl and disulfide groups have not been confirmed.<sup>288</sup>

Edwards<sup>289</sup> attempted despeciation of whole bovine plasma by heating to 72°C. for thirty minutes and adding 0.2 per cent formalin and 0.34 per cent ammonia. Cordier and Demirleau<sup>290</sup>

the development of purple "spectral" bands permitting identification. A rough quantitative separation can be achieved by the use of a large paper turned 90° after the first "progression" is complete, and placed with the next edge in a different solvent (collidine). This effects further separation at right angles and provides areas for quantitative comparison, especially when "standard mixture" solutions are run simultaneously.

### Total Protein

The *copper sulfate* method of Phillips et al.<sup>348</sup> has come to be the simplest and most widely used of the specific-gravity methods for protein determination. It is reasonably accurate<sup>349-352</sup> for routine survey work, the largest error occurring with fatty, lipid-rich plasmas.

A *unimolecular film* method has been recently adapted by Gunton and Burton<sup>263</sup> from Bateman,<sup>353</sup> Gorter and Grendel<sup>354</sup> for use as a simple, economical, rapid clinical micromethod for determining protein in normal urine and spinal fluid. The test fluid is dropped on the surface of a 3 per cent salt solution to form a unimolecular film, and the area occupied by it is measured at standard film pressure. This is done by the addition of a drop of indicator oil and "sweeping" of the surface with a barrier until the oil is compressed sufficiently to produce a standard interference color indicating a standard pressure. Area is proportional to protein concentration within limits. It is accurate to 2 to 3 mg of protein per 100 cc. The proteins in the urine of 100 normal subjects averaged 3.7 mg per 100 cc by this method.

### Protein Fractions

The development of a clinically adaptable *electrophoretic* method by Tiselius<sup>355</sup> opened the way to a more accurate differentiation between the various plasma proteins. The clinical information obtained in this way has been summarized by Stern and Reiner<sup>356</sup> and Luetscher.<sup>18</sup> Stimulated by discrepancies between electrophoretic results and those of classic chemical fractionation,<sup>357-366</sup> several groups have run comparative series. Petermann et al.<sup>361</sup> checked 31 patients by electrophoresis and Howe<sup>367</sup> (22.2 per cent sodium sulfate) fractionation. Albumin by the latter method was 7 to 36 per cent higher, closely approximating the sum of electrophoretic albumin and alpha-globulin, which frequently showed reciprocal changes on serial study. Chow<sup>368</sup> obtained similar results on 198 samples. Protein hydrolysate therapy frequently caused variations in "Howe albumin" not reflected by electrophoresis. Although subject to inaccuracies itself<sup>369</sup> and separating together some globulins (especially beta) that have nothing in common but their mobilities, electrophoresis remains the most reliable yardstick for protein determinations at present available.

The *immunochemical precipitin* method of Heidelberger and Kendall<sup>370</sup> and Goettsch<sup>371</sup> uses rabbit serums sensitized against specific protein fractions, and measures these fractions in blood or spinal fluid by antigen-antibody precipitation and determines the degree of reaction by measuring the nitrogen content of the precipitin produced.<sup>372</sup> It is extremely accurate, and has been completely described in a new book by Kabat and Mayer.<sup>373</sup> Chow<sup>374</sup> has modified it to permit turbidimetric measurements of amount of precipitin.

*New methods* Several new technics have been proposed to give a chemical fractionation method for clinical use approximating electrophoretic separation. Pillemer and Hutchinson<sup>359</sup> used methanol to precipitate everything except albumin. This checks within less than 8 per cent of electrophoresis but requires a cold room or cold centrifuge. Milne<sup>375</sup> employed 26.8 per cent sodium sulfate to precipitate globulin and agreed with electrophoresis within 8 per cent, which was closer than Majoor's<sup>376</sup> results using the same method. Popjak and McCarthy's<sup>377</sup> saturated magnesium sulfate method gave approximately the same agreement, or better according to Schwartz.<sup>366</sup> C. Cohn et al.<sup>365</sup> use a 28 per cent sodium sulfite precipitant and colorimetric method<sup>378</sup> to obtain albumin values within 2 per cent agreement with electrophoresis in a small series. Albanese and his associates<sup>379</sup> propose a microcolorimetric method for determining both albumin and globulin involving a Sukaguchi reaction and arginine determination following 22 per cent sodium sulfate precipitation. Unfortunately, they have not reported a parallel series of electrophoretic determinations. Jager et al.<sup>380, 381</sup> have tried 33 per cent ammonium sulfate to precipitate only gamma globulin, which they have followed as a clinical indicator in rheumatic disease.

There remains an urgent need for a new fractionation method adaptable to routine clinical laboratory use so that change in the plasma proteins can be more accurately followed.

### SUMMARY

It is hardly possible to summarize a review. Some points, however, deserve re-emphasis.

Blood drawn into cooled bottles containing acid-citrate-dextrose solution (ACD) and maintained at 4-10° C will, when transfused after twenty-one days' storage, show 80 per cent cell survival for at least five days after transfusion.

By the use of the substitution technic, 350 cc of Rh— blood can replace 75 per cent of an erythroblastotic infant's blood.

Recipients other than Group O should not be given O blood unless its antiagglutinin titers are less than 1:64 or Witelsky's A and B substances have been added.

ogenous and exogenous "deposits," the concept was changed to one of "dynamic equilibrium," following Schoenheimer's<sup>318</sup> demonstrations with isotopes that body proteins (including tissue and antibody components) are constantly being interchanged. The body protein reserves (some twenty-five to thirty times as great as plasma protein<sup>319</sup>) are capable of great depletion,<sup>317, 320, 321</sup> at times greater than plasma protein levels indicate. This was nicely demonstrated by Localio et al.,<sup>322</sup> who analyzed the protein content of fascia, peritoneum and muscle in 17 controls, 21 debilitated patients and 17 patients with wound disruption. The fascia figures seemed most reliable and averaged 29.00 gm. per 100 cc for controls and 18.73 gm per 100 cc for the wound disruptions. Of the latter group, 11 had total serum proteins over 6.1 gm and 2 of these even had albumins above 3.7 gm per 100 cc. Part of the rapid depletion of reserve protein in starvation may be due to the body's effort to obtain certain poorly stored essential amino acids. If they are present in low concentration, the remaining components may be wasted in large quantity to provide an adequate supply of the needed constituent.<sup>323</sup> When an adequate intake of all the essential amino acids was given in addition to a high-protein, high-calorie diet, Emerson and Binkley<sup>324</sup> were able to show in 3 patients that nitrogen utilization was increased two or three times as much as the total nitrogen intake, whereas raising the dietary protein intake could not increase nitrogen utilization any more than the nitrogen intake increased. Apparently the presence of the essential amino acids permitted a more efficient utilization of dietary and body nitrogen.

### Use

Kremen,<sup>16</sup> Elman<sup>16, 321</sup> and Ravdin<sup>17</sup> have written excellent reviews on this subject. Blood, plasma, and amino acids can all be used to maintain nitrogen balance. Preoperative protein therapy is especially desirable in surgical patients showing any anemia or hypoproteinemia, since blood proteins rate the highest priority in the "ebb and flow" of protein between organs and blood,<sup>325</sup> and are maintained at the expense of the tissues, thus retarding healing<sup>322, 326</sup> even in patients with apparently high hemoglobin and plasma protein values.<sup>327</sup> Extremely large amounts may be required ordinarily,<sup>328, 329</sup> and in gastric cancer after operation several observers feel that there is a defect in the mechanism for protein synthesis that demands an even greater amount of protein therapy.<sup>330-332</sup>

Considerable interest has been aroused by the treatment of intractable pain in peptic ulcer with casein hydrolysate used by Co Tui et al.<sup>333</sup> In doses up to 0.6 gm of nitrogen per kilogram of body weight, as well as carbohydrate (12.5 gm per kilogram daily), they obtained immediate re-

lief in 48 of 164 cases and eventual relief in all but 16 who followed the diet and 18 who could not tolerate it. It is most important that large and frequent doses be given if any acid neutralization is to be obtained.<sup>334</sup>

### Reactions

Reactions to blood and plasma were discussed above. Amino acid and protein hydrolysate reactions are chiefly nausea, anorexia, vomiting, thrombophlebitis at the site of the injection and occasionally pyrogenic chills and fever. Apparently, nausea, anorexia and vomiting are more related to composition of the mixture than to speed of infusion or blood level of alpha amino nitrogen or dicarboxylic acids.<sup>335, 336</sup> The only remedy proposed for the thrombophlebitis has been to select one vein for administration, start peripherally and progress up the arm as it closes off.<sup>332, 337</sup> The crystalline amino acid mixtures and a lyophilized casein hydrolysate seemed to be the two preparations freest from reactions of those reported.<sup>333, 334, 336, 338</sup>

## LABORATORY METHODS

### Amino Acids

The increasing need for accurate information on amino acids has led to the development of two important analytical methods.

The *microbiologic assay* developed by Snell<sup>339-341</sup> from earlier work by Schopfer<sup>342</sup> is now the most accurate and reliable method available for assaying most amino acids<sup>343</sup> and many vitamins. By the use of the growth requirements of certain bacteria, especially lactobacillus, a culture medium is prepared containing all necessary ingredients except one amino acid, which is to be investigated. This is added in different concentrations to the medium and inoculum in a series of culture tubes and incubated, and the amount of growth obtained is measured by titration of the lactic acid produced. Growth is plotted against concentration to give a standard curve. The procedure can then be repeated with an unknown replacing the standard amino acid, and its concentration can be obtained from comparison with the curve. This method is quite accurate and is now widely used in large laboratories.

A less complicated qualitative method of *paper chromatography* was recently described by Gordon et al.,<sup>344</sup> Consden and his associates<sup>345</sup> and Dent.<sup>346, 347</sup> A small drop of test fluid is spread along a line near the end of a long strip of filter paper (2 by 45 cm). This end is then placed in a container of phenol and left to hang in a moist chamber until the phenol has progressed down the paper 25 cm past the test solution. The paper is dried, sprayed with ninhydrin and dried again. The various amino acids have different solubilities and are carried with the solvent different distances, as shown by

234. Johnson, J. B. and Mazique E. C. Disseminated lopus erythematousus unsuccessfully treated with penicillin. roentgen-ray castration and serum albumin. *Ann. Int. Med.* 25 859-862 1946
235. Jacoby, M., Litvak A. and Gruber S. Influence of human serum albumin on edema in erythraliaosis fetalis. *J. Pediatr.* 29 177-182 1946.
236. Eckhardt, R. D., Lewis J. H., Morphy, T. L., Batchelor W. H. and Davidson, C. S. Comparative studies on nutritive value of orally and intravenously administered human serum albumin in man. *J. Clin. Investigation* 27 119-134 1948
237. Brand, E., Kassell B. and Sadel L. J. Amino acid composition of plasma proteins. *J. Clin. Investigation* 23 437-444 1944
238. Albright, F., Forbes A. P. and Reifstein E. C. Jr. Fate of plasma protein administered intravenously. *Tr. A. Am. Physicians* 59 221-234 1946
239. Li, C. H. and Reinhardt W. O. Electrophoresis of rat plasma: effect of adrenocorticotrophic hormone. *J. Biol. Chem.* 167 487-493 1947
240. Starling, E. H. On absorption of fluids from connective tissue spaces. *J. Physiol.* 19 12-326 1896.
241. Keys A., Taylor H. L., Nickleson O. and Henschel, A. Famine edema and mechanism of its formation. *Science* 103-669 1946
242. Govaerts P., and Lequime J. Considerations sur la pathogenie des oedemes de famine. *Bull. Acad. roy. de med. de Belgique* Series 6 7, 260-297 1942.
243. Schemm, F. R. Observations on relationship between edema plasma proteins and diet protein which are not in accord with tenets of Starling hypothesis. *Proc. Am. Federation Clin. Research* 1 54 1944
244. Block, W. M., Jackson R. L., and Routh J. I. Lipoid nephrosis. *J. Lab. & Clin. Med.* 32 1455 1947
245. Gortved, S. P., Steinman J. F. and Kramar, B. Chemical studies in children with nephrotic syndrome. *Am. Dis. Child* 74 274-282 1947
246. Lange, E., Wener D. and Boyd L. J. Nephrosis: new concepts of functional pathology and therapy of nephrotic stage. *Mod. Med.* 16 48-53 March 15 1948
247. Rall, E. P., Rohson J. S., Clarke D. and Hoagland C. L. Factors influencing ascites in patients with cirrhosis of liver. *J. Clin. Investigation* 24 316-325 1945
248. Labby, D. H., and Hoagland, C. L. Fluid shifts to body in acute liver disease. *J. Clin. Investigation* 26 343-353 1947
249. Labby, D. H., Shank, R. E., Kunkel H. G. and Hoagland C. L. Intravenous therapy of cirrhosis of liver. *J. A. M. A.* 133 1181 1190 1947
250. Manhan, H., and Lowell, A. Osmotic factors influencing formation of ascites in patients with cirrhosis of liver. *J. Clin. Investigation* 27 145-153 1948
251. Blakemore, A. H. Operation of portacaval anastomosis: indications, report of cases. *New York State J. Med.* 47 479-485 1947
252. Idem. Indications for portacaval anastomosis — analysis of cases. *Surg. Gynec. & Obst.* 84 645-653 1947
253. Hoffman J., and Liss J. R. Significance of clinical findings in cirrhosis of liver: study of 93 autopsied cases. *Am. J. M. Sc.* 214, 527 528 1947
254. Luetischer J. A., Jr. Study of mechanism of nephrotic edema. *J. Clin. Investigation* 26 1189 1947 (abstr.)
255. Schwepppe, J. S. and Freeman S. Effect of serum protein depletion on water and salt excretion and sensitivity to pituitrin. *J. Lab. & Clin. Med.* 32 1537 1947
256. Emerson K. Jr., Fitcher P. H. and Farr L. E. Relation of high and low urea clearances to inulin and creatinine clearances in children with nephrotic syndrome. *J. Clin. Investigation* 20 361 368 1941
257. Emerson K. Jr. and Dole, V. P. Diodrast and inulin clearances in nephrotic children with supernormal urea clearances. *J. Clin. Investigation* 22 447-450 1945
258. Cargill, W. H. Effect of human serum albumin on renal hemodynamics and tubular excretion of para-amino hippuric acid. *Am. J. Med.* 4 461 1948 (abstr.)
259. Dock, W. Proteinuria and associated renal changes. *New Eng. J. Med.* 227-633-636 1942.
260. Offer J. New directions in renal morphology: method its results and its future. *Hare, Lect.* 40 102-155 1944
261. Bradley S. E., and Tyson C. J. Nephrotic syndrome. *New Eng. J. Med.* 238 225 227 and 260-266 1948
262. Smetana H. Permeability of renal glomeruli of several mammalian species to labelled proteins. *Am. J. Path.* 23, 255-267 1947
263. Ganton R. and Barton A. C. On concentration of protein in samples of normal urine measured by its surface activity. *J. Clin. Investigation* 26 892-898 1947
264. Ballou G. A., Boyer, P. D., Luck, J. M., and Lum, F. G. Influence of non polar anions on thermal stability of serum albumin. *J. Clin. Investigation* 23 454-457 1944
265. Ballou G. A., Boyer P. D. and Luck J. M. Electrophoretic mobility of human serum albumin as affected by lower fatty acid salts. *J. Biol. Chem.* 159 111-116 1945
266. Boyer P. D., Lum F. G., Ballou G. A., Luck J. M., and Rice, R. G. Combination of fatty acids and related compounds with serum albumin. I. Stabilization against heat denaturation. *J. Biol. Chem.* 162 181-198 1946.
267. Boyer P. D., Ballou G. A. and Luck, J. M. Combination of fatty acids and related compounds with serum albumin: nature and extent of combination. *J. Biol. Chem.* 167 407-424 1947
268. Beneshold, H. Über die Viskositätsfunktion der Serumweisheitskörper. *Ergeb. d. inn. Med. u. Kinderh.* 42, 273-375 1932.
269. Davis B. D. Physiological significance of binding of molecules by plasma proteins. *Am. Scientist* 34 611-618 1946.
270. Seatchard G., Batchelder A. C. and Brown A. Preparation and properties of serum and plasma proteins. VI. Osmotic equilibria in solutions of serum albumin and sodium chloride. *J. Am. Chem. Soc.* 68 2320-2329 1946.
271. Dubos R. J. Rapid and submerged growth of mycobacteria in liquid media. *Proc. Soc. Exper. Biol. & Med.* 58 561 1945
272. Davis, B. D. and Dubos R. J. Serum albumin as protective rather than nutritive growth factor in bacteriological media. *Federation Proc.* 5 246, 1946.
273. Idem. Interaction of serum albumin, free and esterified oleic acid and lipase in relation to cultivation of tubercle bacilli. *Arch. Biochem.* 11 201-205 1946
274. Dubos R. J., Davis, B. D., Middlebrook, G., and Pierce C. Effect of water soluble lipids on growth and biological properties of tubercle bacilli. *Am. Rev. Tuberc.* 54, 204-212 1946.
275. Dubos R. J. and Davis B. D. Factors affecting growth of tubercle bacilli in liquid media. *J. Exper. Med.* 83 409-423 1946.
276. Dubos, R. J. Effect of lipids and serum albumin on bacterial growth. *J. Exper. Med.* 85 9-22 1947
277. Davis B. D. and Dubos R. J. Binding of fatty acids by serum albumin: protective growth factor in bacteriological media. *J. Exper. Med.* 86 215-228 1947
278. Tappett, R., Shultz, S. and McDermott, W. Relation of protein binding to pharmacology and antibacterial activity of penicillins. A. G. d. bydro F. and K. *J. Bact.* 53, 581 595 1947
279. Wiener A. S., Hurst, J. G., and Sonn-Gordon E. B. Studies on coagulation reaction with special reference to nature of conglutinin. *J. Exper. Med.* 86 267-284 1947
280. Neher J., and Dameshek, W. Improved demonstration of circulating antibodies to hemolytic anemia by use of bovine albumin medium. *Blood* 2 371-380 1947
281. Ferrebee J. W. and Geiman Q. M. Studies on malarial parasites. III. Procedure for preparing concentrates of plasmodium vivax. *J. Infect. Dis.* 78 175-179 1946
282. Valler B. L., Hughes W. L. Jr., and Gibson J. G., 2nd. Method for separation of leukocytes from whole blood by flotation on serum albumin. *Blood (Supplement to special issue)* 1 52-87 1947
283. Davis H. A. and Eaton A. G. Intravenous administration of bovine serum albumin as blood substitute in experimental secondary shock. *Proc. Soc. Exper. Biol. & Med.* 49 20-22 1942. Comparative effects of horse serum, horse serum albumin and horse serum globulin in experimental shock. *Ibid.* 49, 359-361 1942. Intravenous and subcutaneous administration of alkali-treated bovine serum albumin to man and lower animals. *Ibid.* 50 246-248 1942
284. Davis H. A., Eaton A. G. and Williamson, J. Transfusion of bovine serum albumin into human beings. *Proc. Soc. Exper. Biol. & Med.* 49 96-98 1942.
285. Marun D. S., Enckoo, J. O., Putnam, F. W. and Neurath, H. Native and regenerated bovine albumin, immunological properties. *J. Gen. Physiol.* 26 533-559 1943
286. Heyl J. T. and Janeway C. A. Serum sickness due to crystallized bovine albumin. *J. Clin. Investigation* 26 1185 1947 (abstr.)
287. State, D., Romero F. T., Castellanos, M. M. and Waagstein O. H. Clinical evaluation of bovine serum albumin as blood substitute. *Surgery* 22 424-441 1947
288. Williams R. R. Relationship of sulfhydryl and disulfide groups to antigenic power of bovine serum albumin. *J. Immunol.* 55 161-168 1947
289. Edwards F. R. Form of bovine serum suitable for plasma substitute in treatment of shock. *Proc. Roy. Soc. Med.* 35, 337 1943
290. Corder G. and Demireau J. L. Utilisation de plasma ou serum animal chez l'homme: plasma ou serum universel detoxique. *Presse med.* 54 883 1946
291. Melka, J., Rapant, V. and Zapletal B. Denatured calf plasma for transfusion. *Lancet* 2 82 1947
292. Lewis J. H. Deaerated beef blood plasma as possible substitute for human blood plasma. *Science* 98 571 1943
293. Koop C. E. Plasma substitutes. *Am. J. M. Sc.* 213 235-240 1947
294. Levinson S. O., Janota M., Arimoto F., and Necheles H. Gelatin solution in treatment of shock from graded hemorrhage. *Surg. Gynec. & Obs.* 84-925 932 1947
295. VanderBrook, M. J., Lyster S. C., Graham, B. E., Pomeroy A. E. and Cortland G. F. Intravenously administered gelatin toxicity study. *J. Lab. & Clin. Med.* 32 1115-1120 1947
296. Skinsnes O. K. Gelatin nephrosis: renal tissue changes in man resulting from intravenous administration of gelatin. *Surg. Gynec. & Obs.* 85, 563 571 1947
297. Yule C. L., and Kontz R. E. Blood plasma proteins as influenced by intravenous injection of gum acacia. II. Production of chronic hypoproteinemia. *J. Exper. Med.* 70-605-615 1959
298. Mannix E. P., Jr. Arabinosis: exogenous macromolecular storage disease. *Brooklyn Ho. J.* 5 200 1947
299. Hueper W. C. Pectan intravenously. *Science* 102 253 1945
300. Bahmanson G., Rosekrantz, H., Thorsén G., and Wilander O. Clinical experiences with dextran as plasma substitute. *Acta chir. Scandinav.* 94 149-167 1946.
301. Fedorov A. A. New albumin blood substitutes. *Am. Rev. Soviet Med.* 4 245 249 1947
302. Sabaneev D. P. Clinical applications of plazmol S-25 dried plasma preparation. *Trac. delo (No. 9)* 26 617-622 1946.
303. Molina R. D., Santos H. A., and Altmann M. M. Intravenous use of human serum fluid in shock, nephrosis and allied conditions. *Am. J. M. Sc.* 213 44-440 1947
304. Rose, W. C. Nutritive significance of amino acids. *Physiol. Rev.* 18 103-156, 1938
305. Cannon P. R. Amino acid utilization in surgical patient. *J. A. M. A.* 135 1041-1046 1947

The normal erythrocyte life span is probably one hundred and ten to one hundred and thirty days.

All unhealthy people show a tendency for their erythrocytes to stick together and capillaries to constrict, resulting in diminished oxygen supply to various tissues. This is known as blood sludge.

The American Red Cross is supporting a national peace-time blood-procurement program to provide free blood and its derivatives to everyone.

A presumably noninfected person who has received malaria-suppressive therapy should wait at least two years without symptoms before donating blood. No person who has had malaria should ever donate blood to be used whole.

Because of the danger of homologous serum hepatitis, pooled plasma should be used only when nothing else is available. Transmission by whole blood is much less frequent. No satisfactory specific prophylaxis or treatment has been developed. The routine heating of salt-poor albumin at 60°C for ten hours destroys the hepatitis etiologic agent.

Fibrin foam and film are finding increasing use in all branches of surgery for hemostasis and tissue-defect repair. Recent film uses include eardrum repair and blood-vessel anastomosis.

Antihemophilic globulin found in Fraction I is an effective temporary treatment for hemophilic bleeding.

Gamma globulin is an effective prophylactic agent against measles and epidemic hepatitis.

Serum iron is carried in the plasma in combination with a beta globulin, which is usually only about 34 per cent saturated. The normal iron-binding capacity is 314 microgm per 100 cc, and the iron content 106 microgm per 100 cc.

Some cases of nephrosis and some of cirrhosis have responded to large amounts of albumin (700 to 2000 gm), but others have not.

Data from the use of large amounts of albumin contribute further evidence that in many cases of hypoproteinemia the Starling hypothesis is inapplicable or of minor importance.

Albumin has a peculiar property of binding to itself many nonpolar anion compounds. This has facilitated the development of an excellent culture medium for tubercle bacilli, since the albumin binds growth-inhibiting oleic acids. It also explains the ineffectiveness of penicillin K in vivo, since the penicillin is 91 per cent bound by albumin. This may also be responsible for the useful role albumin plays as a diluent in many immunologic reactions.

Leukocytes can be almost quantitatively separated from erythrocytes by the use of an albumin solution of proper specific gravity.

No satisfactory substitute for blood has yet been developed. Bovine albumin is most effective but has a 10 per cent reaction rate. Gelatin is non-reactive but is rather quickly excreted.

For optimal utilization, amino acid mixtures should be given by mouth, should contain all essential amino acids and should be accompanied by a minimal carbohydrate intake of 1000 to 2500 calories per day.

Amino acid reactions seem to be related more to composition than speed of administration—crystal line mixtures give least difficulty.

The microbiologic assay and paper chromatography are useful analytic methods for amino acids.

The classic 22.2 per cent sodium sulfate (Howe) fractionation method for determining serum albumin gives values 10 to 40 per cent too high, since it includes alpha<sub>2</sub> globulin, which may vary reciprocally with albumin. Several newer methods are presented attempting to rectify this error in routine clinical laboratory determinations.

721 Huntington Avenue

## REFERENCES

- 213 Heyl, J. T., and Janeway, C. A. Use of human albumin in military medicine. I. Theoretical and experimental basis for its use. *U. S. Nav. M. Bull.* 40: 785-791, 1942.
- 214 Heyl, J. T., Gibson, J. G. II, and Janeway, C. A. Studies on plasma proteins. V. Effect of concentrated solutions of human and bovine serum albumin on blood volume after acute blood loss in man. *J. Clin. Investigation* 22: 763-773, 1943.
- 215 Woodruff, L. M., and Gibson, S. T. Use of human albumin in military medicine. II. Clinical evaluation of human albumin. *U. S. Nav. M. Bull.* 40: 791-796, 1942.
- 216 Janeway, C. A., et al. Concentrated human serum albumin albumin in treatment of shock: safety of albumin albumin in treatment of hypoproteinemia. *J. Clin. Investigation* 23: 465-450, 1944.
- 217 Janeway, C. A. Other uses of plasma fractions with particular reference to serum albumin. *Ann. Int. Med.* 26: 368-377, 1947.
- 218 Courmand, A., et al. Clinical use of concentrated human serum albumin in shock, and comparison with whole blood and with rapid saline infusion. *J. Clin. Investigation* 23: 491-506, 1944.
- 219 Warren, J. V., Stead, E. A., Jr., Merrill, A. J., and Brannon, E. S. Treatment of shock with concentrated human serum albumin: preliminary report. *J. Clin. Investigation* 23: 506-509, 1944.
- 220 Stead, E. A., Jr., Brannon, E. S., Merrill, A. J., and Warren, J. V. Concentrated human albumin in treatment of shock. *Arch. Int. Med.* 77: 564-575, 1946.
- 221 Lowell, A., Courmand, A., and Richards, D. W., Jr. Changes in plasma volume and mean arterial pressure after intravenous injection of concentrated human serum albumin in 38 patients with oligemia and hypotension. *Surgery* 22: 442-452, 1947.
- 222 Haynes, B. W., Jr. Alterations of cardiac output and plasma volume in normal subjects with administration of concentrated human serum albumin. *Proc. Am. Federation Clin. Research* 27: 74, 1945.
- 223 Beecher, H. K., and Burnett, C. H. Field experience in use of blood and blood substitutes (plasma, albumin) in seriously wounded men. *U. S. Bull. North African Theat. Op.* (No. 1) 2: 17, 1944.
- 224 Beecher, H. K. Preparation of battle casualties for surgery. *Am. Surg.* 121: 769-792, 1945.
- 225 Scarthard, G., Batchelder, A. C., and Brown, A. Osmotic pressure of plasma and serum albumin. *J. Clin. Investigation* 23: 458-464, 1944.
- 226 Loetscher, J. A., Jr. Effect of single injection of concentrated human serum albumin on circulating proteins and proteinuria in nephrosis. *J. Clin. Investigation* 23: 365-371, 1944.
- 227 Thorn, G. W., Armstrong, S. H., Jr., Dickerson, V. C., Woodruff, L. M., and Tyler, F. H. Chemical, clinical and immunological studies on products of human plasma fractionation: use of salt-poor concentrated human serum albumin solution in treatment of chronic Bright's disease. *J. Clin. Investigation* 24: 822-828, 1945.
- 228 Gibson, S. T. Unpublished data.
- 229 DeSanctis, A. G., and Sullivan, A. M. Nephrosis case treated with concentrated low salt, human serum albumin. *J. Pediatr.* 30: 91-95, 1947.
- 230 Thorn, G. W., Armstrong, S. H., Jr., and Davenport, V. D. Use of salt-poor concentrated human serum albumin solution in treatment of hepatic cirrhosis. *J. Clin. Investigation* 25: 304-323, 1946.
- 231 Patek, A. J., Jr., Mankin, H., Colcher, H., Lowell, A., and Earle, D. P., Jr. Effects of intravenous injection of concentrated human serum albumin upon blood plasma, acetates and renal functions in 5 patients with cirrhosis of liver. *J. Clin. Investigation* 27: 133-144, 1948.
- 232 Kunkel, H. G., Labby, D. H., Abrams, E. H., Jr., Shack, R. E., and Hoagland, C. L. Use of concentrated human serum albumin in treatment of cirrhosis of liver. *J. Clin. Investigation* 27: 305-319, 1948.
- 233 Armstrong, S. H., Jr. Mechanisms of action of serum albumin therapy in internal medicine. *Am. J. Med.* 4: 390-397, 1948.

72. Kabat, E. A., Ginsman, M. and Knaub, V. Quantitative estimation of albumin and gamma globulin in normal and pathologic cerebrospinal fluid by immunochemical methods. *Am J Med* 4: 653-662 1948
73. Kabat, E. A. and Mayer, M. M. *Experimental Immunochemistry* 575 pp. Springfield Ill. Charles C Thomas 1948
74. Chow, B. F. Determination of plasma or serum albumin by means of precipitation reaction. *J Biol Chem.* 167: 757-763 1947
75. Milne, J. Serum protein fractionation: comparison of sodium sulfate precipitation and electrophoresis. *J Biol Chem* 167: 595-600 1947
76. Major, C. L. H. Possibility of detecting individual proteins in blood serum by differentiation of solubility curves in concentrated sodium sulfate solutions. II. Comparison of solubility curves with results of electrophoresis experiments. *J Biol Chem* 169: 583-594 1947
77. Popjak, G. and McCarthy, E. F. Osmotic pressures of experimental and human lymphic sera: evaluation of albumin globulin ratios with aid of electrophoresis. *Biochem. J* 40: 789-803 1946
78. Weiselsbaum, T. E. Accurate and rapid method for determination of proteins in small amounts of blood serum and plasma. *Am J Clin Path. (Tech. Sect.)* 10: 40-49 1946
79. Albanese, A. A., Sauer, B. and Irby, V. Microcolorimetric estimation of plasma proteins. *J Lab & Clin Med.* 32: 296-299 1947
80. Jager, B. V. and Greenberg, G. R. Preliminary studies of gamma globulins as determined by chemical methods. *Proc Am Federa tion Clin Research* 2: 95 1945
81. Jager, B. V. and Nickerson, M. Clinical application of simple method for estimating gamma globulin. *J Clin Investigation* 27: 2: 1-238 1948

## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

EDITH E. PARRIS, *Assistant Editor*

### CASE 34421

#### PRESENTATION OF CASE

**First admission.** A fifty-one-year-old retired policeman entered the hospital with complaints of intermittent dysphagia, crampy pains in both calves, which were unrelated to exercise, tight feelings in the left chest, right shoulder and upper arm, and low back pain relieved by lying down, all of eighteen months' duration.

Except for chronic maxillary sinusitis treated ten years previously by Caldwell-Luc operations, he had always been in good health until two years before entry, when he was admitted to another hospital. The complaints at that time were exertional dyspnea and sharp pains beginning at the right costal margin, which radiated to the scapular region. Physical findings were basal rales in both lungs, moderate tenderness in the right upper quadrant, mild jaundice and moderate ankle edema. A Graham test showed a normal gall bladder. An upper gastrointestinal series was normal. An electrocardiogram showed alterations in the ST segments and T waves and absence of the R waves in all the precordial leads. The patient was hospitalized for approximately four months at that time, and toward the end of his stay he first noted difficulty in swallowing solid foods and also began to notice pain and stiffness of the left leg on arising in the morning. The leg pain and stiffness continued, and a year prior to admission he was admitted to another hospital for study. On several occasions he coughed up bloody sputum, and

bilateral superficial femoral-vein ligations were done.

Physical examination revealed a well developed and well nourished ruddy man in no acute distress. There was elevation of the left shoulder on inspiration. A few coarse rales were heard at the left base posteriorly. The heart was not enlarged to percussion. There was a Grade I apical systolic murmur. The remainder of the examination was entirely negative.

The temperature was 99°F, and the pulse regular at a rate of 80. The blood pressure was 150 systolic, 100 diastolic.

Examination of the blood showed a red-cell count of 5,380,000, with a hemoglobin of 12.5 gm, and a white-cell count of 10,300, with 75 per cent neutrophils. The sedimentation rate was 1.33 mm per minute, uncorrected, and 1 mm per minute corrected. Examination of the urine revealed a specific gravity of 1.024 with a ++ test for albumin and the sediment contained 1 to 5 white cells and rare hyaline and granular casts per high-power field. A stool specimen was guaiac negative. The fasting blood sugar was 108 mg, the nonprotein nitrogen 28 mg, and the total protein 7.1 gm per 100 cc. The spinal fluid was entirely normal. An electrocardiogram showed depression of the ST segments in Leads 2 and 3, a flat T wave in Lead 1 and upright T waves in Leads 2 and 3, absent RV<sub>1</sub>, prominent QV<sub>1</sub>, QV<sub>2</sub>, and QV<sub>3</sub>, elevated STV<sub>1</sub>, STV<sub>2</sub>, and STV<sub>3</sub>, upright TV<sub>2</sub> and TV<sub>3</sub>, inverted TV<sub>1</sub>, elevated STVL and depressed STVF.

X-ray examination of the chest showed blunting of the costophrenic sinuses and emphysematous areas in the left lower lobe. The heart was prominent in the region of the left ventricle; the aorta was somewhat tortuous. The cardiothoracic ratio was 14.5/32.5. A barium swallow showed a constriction in the midportion of the esophagus, with moderate dilatation proximal to the constriction. The constriction extended over approximately 2 cm. There was no evidence of shelf formation. Films of the dorsal and lumbar spine were not remarkable.

Esophagoscopy was done, and there was an area of narrowing 32 cm from the teeth. The margins were fairly smooth but unusually indurated. Biopsies

- 306 Elman R. Time factor in retention of nitrogen after intravenous injection of mixture of amino acids *Proc Soc Exper Biol & Med* 40 484-487, 1939
- 307 Robschert-Robbins F S, Miller L L and Whipple G H. Plasma protein and hemoglobin production: deletion of individual amino acids from growth mixture of 10 essential amino acids: significant changes in urinary nitrogen *J Exper Med* 85 243-265 1947
- 308 Miller L L, Robschert-Robbins F S and Whipple, G H. Anemia and hypoproteinemia: weight maintenance effected by food proteins but not by mixtures of pure amino acids *J Exper Med* 85 267-275, 1947
- 309 Womack M, and Rose W C. Evidence for existence of unidentified growth stimulant in proteins *J Biol Chem* 162 735 1946
- 310 Woolley D W. Some correlations of growth-promoting powers of proteins with their streptogenin content. *J Biol Chem* 162 383 388 1946
- 311 Christensen H N., Lynch E L, Decker D G and Powers J H. Conjugated nonprotein, amino acids of plasma. IV. Difference in utilization of peptides of hydrolysates of fibrin and casein *J Clin Investigation* 26 849 852, 1947
- 312 Koop C E, Riegel C, Grigger R P and Barnes M T. Study of protein hydrolysates, ossein gelatin and glucose in parenteral nutrition *Surg, Gynec & Obst* 84 1065-1070 1947
- 313 Kozoll D and Mok W T. Studies in nitrogen metabolism *J Lab & Clin Med* 32 1403 1947
- 314 Hoffman W S, Kozoll D D, Mok, W T and Popper H. Determination of nitrogen balance index of new lyophilized casein acid hydrolysate in protein deficient patients *J Lab & Clin Med* 32 1538, 1947
- 315 Benditt E P et al. Dynamics of protein metabolism. I. Interrelationship between protein and caloric intakes and their influence upon utilization of ingested protein for tissue synthesis by adult protein-depleted rat. *J Lab & Clin Med* 33 257-269 1948
- 316 Benditt E P, Woolridge R L., and Stepto R. Dynamics of protein metabolism. II. Relationship between level of protein intake and rate of protein utilization by protein-depleted men and rats *J Lab & Clin Med* 33 269-279 1948
- 317 Kosterlitz, H W., and Campbell R. M. Storage of protein in adult animal. *Nutrition Abstr & Rev* 15 1-14 1945
- 318 Schoenheimer, R. *The Dynamic State of Body Constituents* 78 pp Cambridge Harvard University Press 1942
- 319 Sachar L. A, Horvitz, A and Elman, R. Studies on hypoalbuminemia produced by protein deficient diets. I. Hypoalbuminemia as quantitative measure of tissue protein depletion *J Exper Med* 75 453-464 1942
- 320 Elman R. Protein nutrition in surgery *New York State J Med* 47 382-386 1947
- 321 Elman R. Use of proteins and protein hydrolysates for intravenous alimentation. In *Advances in Protein Chemistry* Edited by J T Edsall and M L Anson 3 vol New York Academic Press 1947 Vol 3 Pp 269-295
- 322 Localio, S A, Chassin J L and Hinton J W. Tissue protein depletion factor in wound disruption *Surg Gynec & Obst* 86 107-113, 1948
- 323 Beattie J. Metabolic disturbances after injury *Brit M J* 2 813 817 1947
- 324 Emerson K Jr and Binkley O F. Effect of administration of essential amino acids on utilization of dietary protein in malnutrition among war casualties *J Clin Investigation* 25 184-189 1946
- 325 Whipple, G H, Miller L L and Robschert-Robbins F S. Raising of body tissue protein to form plasma protein and hemoglobin *J Exper Med* 85 277-286 1947
- 326 Localio S A, Morgan M E and Hinton, J W. Biological chemistry of wound healing. I. Effect of dl-methionine on healing of wounds in protein depleted animals *Surg Gynec & Obst* 86 582 590 1948
- 327 Riegel, C, Koop, C E, Drew, J., Stevens L W and Rhoads J E. Nutritional requirements for nitrogen balance in surgical patients during early postoperative period *J Clin Investigation* 26 18-23 1947
- 328 Allen J G, Bogardus, G, Egner W and Phemister, D B. Correction of hypoproteinemia by administration of plasma and blood *Surg Gynec & Obst* 86 604-616 1948
- 329 Meyer F L et al. Nitrogen balance and blood volume studies on man during and following repeated plasma transfusions *Am J M Sc* 213 160-169 1947
- 330 Efskind L. Problem of hypoproteinemia in delayed gastric emptying after stomach resection *Acta chir Scandinav* 95 81-95 1947
- 331 Homburger F, Young N F, Petermann M L, and Ahels J C. Defective plasma protein regeneration in patients with gastric cancer *Proc Am Federation Clin Research* 3 54 1947
- 332 Wiley, H M. Postoperative protein deficiency with special reference to cancer patient. *Surgery* 21 889 900 1947
- 333 Co Tui. Ambulatory treatment of peptic ulcers with protein hydrolysates and dextrin maltose *Rev Gastroenterol* 14 108-114 1947
- 334 Feller J and Tidmarsh A J. Effect of amino acids on gastric acidity *Canad A J* 57 23-25 1947
- 335 Smyth C J, Laschak, A G and Levey S. Effect of orally and intravenously administered amino acid mixtures on voluntary food consumption in normal man *J Clin Investigation* 26 439-445 1947
- 336 Idem. Effect of rate of administration of amino acid preparations and blood amino acid nitrogen level on production of nausea and vomiting *J Lab & Clin Med* 32 889 894 1947
- 337 Hecht, H H. Reactions to intravenously administered amino acids (casein hydrolysates) *Am J M Sc* 212 35-44 1946
- 338 Hoffman W S, Kozoll D D, Mok W T, Meyer E A, and Popper, H. Determination of nitrogen balance index of new lyophilized amino acid preparation in protein-deficient patients *J Lab & Clin Med* 33 280-293 1948
- 339 Snell E E and Strong F M. Microbiological assay for nitrogen. *Indust & Engin Chem (Anal Ed)* 11 346-350 1939
- 340 Snell, E E. Microbiological assay of amino acids. In *Assays in Protein Chemistry* Edited by J T Edsall and M L Anson 3 vol New York Academic Press 1945 Vol 2 Pp 8-116
- 341 Idem. Microbiological methods in amino acid analysis. *Ann New York Acad Sc* 47 161-179 1946
- 342 Schopfer W H. Les vitamines cristallines B comme hormones de croissance chez un microorganisme (Phycomyces) *Arch f Mikrobiol* 6 139, 1935
- 343 Block R J and Bolling D. *The Amino Acid Composition of Proteins and Foods. Analytical methods and results* 396 pp Springfield Ill Charles C Thomas 1945
- 344 Gordon A H, Martin A J P and Synge R L M. Paraffin chromatography in study of protein constituents *Biochem J* 37 79 86 1943
- 345 Conden R, Gordon A H and Martin A J P. Qualitative analysis of proteins: paraffin chromatographic method and paper *Biochem J* 38 224-232 1944
- 346 Dent, C E. Detection of amino acids in urine and other fluids *Lancet* 2 637-639 1946
- 347 Idem. Amino-aciduria in Fanconi syndrome *Biochem J* 41 240-253, 1947
- 348 Phillips R A et al. *Copper Sulfate Method for Measuring Specific Gravities of Whole Blood and Plasma*. Cited in Peters J P, and Van Slyke D D. *Quantitative Chemical Chemistry* Vol 2. Mt. I Baltimore: Williams & Wilkins Co 1932 (reprinted in 1943) Pp 941-958
- 349 Atchley J, Bacon R, Curran G and David K. Clinical estimation of copper sulfate method for measuring specific gravities of whole blood and plasma *J Lab & Clin Med* 30 830-838 1945
- 350 Adams M A and Ballou A N. Comparison between values for plasma or serum protein as obtained by specific gravity and micro-Kjeldahl methods *J Lab & Clin Med* 31 507 513 1946
- 351 Edwards J C. Copper sulfate method for rapid estimation of whole blood requirements *Arch Surg* 55 1 12, 1947
- 352 Meyer, F L, Abbot, W E, Allison M., and McKay, C. Comparison of plasma protein concentration, hemoglobin and hematocrit values determined by chemical method, and calculated from specific gravity *Arch. Biochem.* 12 359 366 1947
- 353 Bateman J B. Determination of protein in serum and cerebrospinal fluid by formation of nimmolecular films *J Cell & Carr, Physiol* 29 85-89 1947
- 354 Gorter, E and Grendel F. Die Eiweissbreitung als Method zur Bestimmung von Serumalbumin und Serumglobulin. *Biochem Ztschr* 201 391-411 1928
- 355 Tischner A. New apparatus for electrophoretic analysis of colloidal mixtures *Tr Faraday Soc* 33 524 1937
- 356 Stern, K. G and Reiner M. Electrophoresis in medicine *Yale J Biol & Med* 19 67-99 1946
- 357 Taylor H L and Keys A. Fractionation of normal serum protein by electrophoretic and sodium sulfate methods *J Biol Chem.* 148 379 381 1943
- 358 Dole V P. Electrophoretic patterns of normal plasma *J Clin Investigation* 23 708-713 1944
- 359 Pillemmer L., and Hutchinson, M. C. Determination of albumin and globulin contents of human serum by methanol precipitation *J Biol Chem* 158 299-301 1945
- 360 Dole V P, Yeomans A and Tierney N A. Electrophoretic changes in serum protein pattern of patient with typhus fever *J Clin Investigation* 26 298-300 1947
- 361 Petermann, M L, Young N F, Hoagness K. R. and Rhoads C F. Determination of plasma albumin by chemical and electrophoretic methods *Proc Am Federation Clin Research* 3 75 1947
- 362 Petermann M L, Young N F and Hoagness K R. Comparison of Howe and electrophoretic methods for determination of plasma albumin *J Biol Chem* 169 379 388 1947
- 363 Stacey R S. Serum proteins in acute infectious *J Lab & Clin Med* 32 1002 1007 1947
- 364 Cohn C and Wolfson, W Q. Studies in serum proteins. I. Chemical estimation of albumin and of globulin fractions in serum. *J Lab & Clin Med* 32 1203-1207 1947
- 365 Idem. Studies in serum proteins. II. Rapid clinical method for accurate determination of albumin and globulin in serum or plasma *J Lab & Clin Med* 33 367-370 1948
- 366 Schwartz T B. Comparison of chemical determination of serum albumin concentration with corresponding electrophoretic patterns *Am J Med* 4 786 1948 (abstr)
- 367 Howe P E. Use of sodium sulfate as globulin precipitant in determination of proteins in blood *J Biol Chem* 49 93 107 1921
- 368 Chow B F. Correlation between albumin and globulin contents of plasma *J Clin Investigation* 26 883-886 1947
- 369 Armstrong S H, Jr, Budka M E and Murrain K. C. Preparation and properties of serum and plasma proteins: quantitative interpretation of electrophoretic schlieren diagrams of normal human plasma protein *J Am Chem Soc* 69 416-429 1947
- 370 Heidelberger M and Kendall F E. Quantitative studies on precipitation reaction: determination of small amounts of specific polysaccharide *J Exper Med* 55 555-561 1932
- 371 Goettsch E. and Kendall F E. Analysis of albumin and globulin in biological fluids by quantitative precipitation method *J Biol Chem* 109 221 231 1935

ness in the calves of the leg. The more I think about this, the more I am inclined to think that there is one possible diagnosis that might explain all the symptoms and signs rather than to say that he had thrombophlebitis, pulmonary infarcts, cardiospasm and chronic coronary-artery disease with ruptured myocardium. Before this diagnosis is mentioned, the possibility of carcinoma of the esophagus must be considered. However, I think that I have no more right at this post-mortem discussion to call this carcinoma than those who treated the patient had at the time he was alive. The x-ray findings at the time he was in the hospital apparently were interpreted as those of a benign stricture or cardiospasm rather than those due to any new growth in the esophagus itself. This was further borne out by the esophagoscopy, and the biopsy taken at that time recorded only inflammatory changes. That, of course, does not rule out the possibility of a malignant lesion deeper than the level from which the biopsy material was obtained. I think that I will say there was a possibility of cancer with nerve-root involvement, and such involvement posteriorly could have explained some of the chest pain and also the leg pain. However, I believe that that probably was not so.

Another diagnosis, although it is perhaps a little far-fetched because of the duration of the symptoms, is that of a dissecting aneurysm with final rupture of the aorta. I have never heard of one giving symptoms for two years before death, but I have heard of some that have gone for a year. The fact that this man had pain in the back, in the legs and in the chest before he developed dysphagia leads me to believe that he might have had an aneurysm. First of all, we know he had generalized arteriosclerosis, and I am going to say that he had an atheromatous aorta and that the presenting symptoms early in the illness were those of early dissection of the aorta. We can even explain the vomiting of blood on that basis. If there was a slow leakage into the lower trachea or bronchus from the aorta, the progressive dysphagia and the difficulty in swallowing in spite of bouginage lead me to believe that there was increasing inflammation of the esophagus. I think that if it had been due to cancer, the lesion would have been visible in some of the films. A mass, a blood vessel and an aorta slightly distended, possibly eroded might not have shown up in the x-ray film. The final symptoms, which include pain in the arm, in the flank and in the legs radiating around the costal margin, give such an unusual distribution of pain that again I cannot explain it in any way other than by a slowly dissecting lesion of the aorta.

I have considered the possibilities of simple cardiospasm with generalized arteriosclerosis, thrombophlebitis and old pulmonary infarcts. Having considered carcinoma of the esophagus and metastasis to the spine that we have not been able to

demonstrate and having considered that he may have had coronary thrombosis and that the final episode was one of ruptured heart, I think I am going to stick my neck out and make a final diagnosis of a slowly dissecting aneurysm of the aorta, which possibly had eroded into the bronchial tree at some stage of the game, causing bleeding, and that it finally ruptured producing massive, fatal hemorrhage.

A PHYSICIAN: Were the heart sounds weak or strong?

DR TRACY B. MALLORY: Dr Scannell, can you answer that?

DR J. GORDON SCANNELL: I do not remember particularly—our attention was evidently not called to them.

DR M. ISAACSON: I should like to ask Dr Ellis what he thinks of the possibility of aneurysm of the posterior wall of the left ventricle on the basis of infarct causing esophageal constriction. A few cases have been reported, and I\* recently reported a case of myocardial aneurysm causing esophageal obstruction. This case is similar.

DR ELLIS: I think it is a distinct possibility. The reasons for thinking it probably is an aortic rather than a myocardial aneurysm are the slowly progressive symptoms over a long period and the distribution of pain. He may well have had a ruptured myocardial aneurysm.

DR WYMAN: From the x-ray point of view the diagnosis of cancer is quite feasible. We have seen a good many that did not show definite shelf formation but merely narrowing with or without ulceration centrally. I wonder if the last chest film does not suggest lymphatic spread of metastases to the lung fields.

DR JACOB LERMAN: I would like to ask if a circular constriction of that sort could be explained on the basis of aneurysm, with pressure on one side, anterior or posterior. It is hard to conceive of an aneurysm producing that picture.

DR WYMAN: It would not usually unless associated with inflammatory reaction and constriction.

#### CLINICAL DIAGNOSES

Coronary occlusion  
Stricture of esophagus, unknown etiology

#### DR ELLIS'S DIAGNOSIS

Dissecting aneurysm of aorta, with rupture

#### ANATOMICAL DIAGNOSES

Coronary arteriosclerosis with thrombosis  
Myocardial infarction, left ventricle  
Acute bacterial endocarditis mitral valve  
Benign stricture of esophagus  
Lipoid pneumonia  
Arteriosclerosis, general

\*Isaacson M. Myocardial aneurysm causing esophageal obstruction: report of case presenting double cardiac aneurysm with severe dysphagia necessitating gastrostomy. *New Orleans M J* 100:565-57, 1945.

were taken and reported as acute and chronic inflammation

During the one-month stay in the hospital repeated barium swallows were done, with little change in the appearance of the lesion. The original complaints persisted, but the patient was able to eat semisolid foods and was only occasionally troubled by regurgitation. Dilatation of the esophagus was started, and the patient was discharged from the hospital.

*Final admission* (six months later) The patient was seen at approximately one-week intervals over the next five months for bouginage, but despite this was able to eat only semisolid and liquid foods. The pains in the chest, back and leg were constantly present during this period. One week before admission he was seen in the Emergency Ward with complaints of severe, sharp, stabbing pain in the left calf, left lower chest and flank, and right upper arm. At this time it was noted that the blood pressure was 105 systolic, 70 diastolic, but there were no other changes. X-ray study of the chest showed moderate enlargement of the heart in the transverse diameter. There was also moderate fibrosis in both lung fields, but no definite pulmonary edema. Electrocardiograms revealed changes from the previous one with prolongation of the QRS complex, slight elevation of the ST segment and more marked elevation of STV<sub>2</sub> and STV<sub>4</sub> and deeper Q<sub>1</sub> and V<sub>4</sub>.

The patient returned home to re-enter the hospital a week later. The pain in the chest had grown steadily worse. It began in the low left posterior chest and radiated anteriorly beneath the rib margins. There was no cough or sputum. The dysphagia had become much worse, and he was able to take only liquid foods. The blood pressure was 100 systolic, 70 diastolic. He suddenly vomited greenish fluid, began to sweat profusely, complained of weakness but no pain, began to breathe rapidly and died within a few seconds.

#### DIFFERENTIAL DIAGNOSIS

DR DANIEL S ELLIS It seems to me that up to the time of the second admission we have a fairly clear picture of a patient who had some vascular disturbance in the lower extremities and probably had pulmonary infarction and for some reason developed cardiospasm of the esophagus. The second admission puzzles me a great deal, and I do not know where I am going to end up at this point.

May we see the x-ray films? Is there any evidence of pulmonary infarct or anything that might be called pulmonary infarct in the first chest film?

DR STANLEY M WYMAN There are a few scars—linear bands of density. If this represents pulmonary infarct, it is only the old residual scar. In general, the picture is that of a chronically emphysematous chest, with signs of diffuse fibrosis out to the periphery in both lung fields. The dia-

phragm is low in position, the heart shadow is enlarged toward the left, probably owing to left ventricular hypertrophy. The aorta is quite tortuous for a man of fifty-one. The barium-filled esophagus can be seen through the heart shadow, it can be seen much better in the lateral view of the chest, which shows this area of narrowing just below the carina. On several spot films taken at this time there is a suggestion of a small crater centrally, it is seen on all the films. There is a characteristic shelf formation, and there seems to be a suggestion of a little nodularity in the upper border of the area. The area extends in all about 2 cm. The films taken a month later again show essentially the same picture, but the crater can no longer be so well identified on the large films. However, on the small films, again, there may be a crater in this area. The next film of the chest taken about three or four months after the original examination again shows a rather considerably enlarged heart but no definite change in the pulmonary pattern. Three months later there is an increase in linear shadows in both lung fields, which may be partly due to technic, though it seems a little more than artifact. The last film taken eight days later shows considerable density extending upward into both lung fields and radiating from the region of the hilus.

DR ELLIS Was that taken before he died?

DR WYMAN I do not know, but I think so.

DR ELLIS Is the aorta enlarged in the last film?

DR WYMAN It is definitely tortuous.

DR ELLIS How about the aorta in these films? Is there any dilatation there?

DR WYMAN I cannot say on these films, the reason being that I can see only the right border of the aorta in the posteroanterior view, the left border is hidden by the mediastinum. In the films taken to project the aorta away from the surrounding structures the aorta does not seem wide, but it is definitely tortuous.

DR ELLIS Is there any evidence of destruction of the vertebrae anywhere?

DR WYMAN I do not see it on these films nor did I on some other films of the spine that I have not shown.

DR ELLIS I think I will have to attack this from the end of the story and work toward the beginning. The one thing I am certain of is that a large vessel ruptured and that death was due to hemorrhage.

The presenting complaints at the time of entry to the other hospital were crampy pain in the legs and pain in the back and chest, and at that time he was known to have coughed up bloody sputum. Over a period of hospitalization there he developed the gastrointestinal complaints and dysphagia. Without any question it was believed that the chest pain and the bloody sputum were due to pulmonary infarcts because the femoral veins were tied. At no time was mention made of any swelling of either leg or anything more than pain and some stiff-

6.7 gm per 100 cc The urine gave a ++ test for albumin, and the sediment contained 10 to 12 white cells and 3 to 4 red cells per high-power field An x-ray film of the chest showed the left side obscured by homogeneous density The heart and mediastinum were displaced to the right

The patient was oriented but unco-operative and incontinent On the second hospital day 300 cc of thick, purulent nonputrid material mixed with old blood was aspirated from the sixth and eighth interspaces posteriorly and the sixth interspace in the axillary line A smear of this fluid showed pus cells and clumps of gram-positive cocci This procedure was repeated on the fourth and seventh hospital days with similar findings The material was negative for tumor cells and grew out abundant colonies of *Staphylococcus aureus* and nonhemolytic streptococci The temperature varied from 99 to 102°F The patient received 192,000 units of penicillin daily On the eighth hospital day a rib resection was done The pleura was very thick but no large cavity was encountered His condition was unchanged until the third postoperative day when he was found apneic and in shock, and attempts at resuscitation were ineffectual

#### DIFFERENTIAL DIAGNOSIS

DR W WILSON SCHIER This is the story of a lawyer who developed cough and fever following a prefrontal lobotomy We do not know the details of the operation or the anesthesia used or how long after the operation the symptoms appeared but presumably shortly after it At that time an x-ray film of the chest was reported as showing patchy mottling

The patient received a course of penicillin, said to be intensive but for how long or how much was received is not known This pulmonary process progressed until two months later another x-ray film showed extensive consolidation in the upper half of the left lung, with a 4-cm excavation on the second anterior rib and also, homogeneous density of the left-lung field May we see the films at this point

DR JAMES J McCORT We have the chest films taken on admission to this hospital A homogeneous density obscures the entire left thorax so that details of the underlying left lung cannot be made out The mediastinum shows a marked shift to the right The left leaf of the diaphragm is not seen, but the

gas-filled fundus of the stomach is seen to be higher than normal, which indicates that the left leaf of the diaphragm is very high No evidence of bone erosion or destruction is detectable in the ribs

DR SCHIER On admission this man showed evidence of long-existent emaciation and avitaminosis The swelling of the face and eyes may have been due to partial obstruction of the venous drainage of the upper part of the body

We are given a single total protein value, 6.7 gm per 100 cc He may possibly have had a low albumin We do not know whether he was hospitalized in a mental hospital or not, but we do know that the tuberculosis rate in mental hospitals is higher than it is in the average population

Two other thoughts come to mind Electric shock therapy was given two years before lobotomy Lung abscesses have been described following shock therapy The second possibility is primary carcinoma of the lung with cerebral metastases giving rise to personality change The long course of events, however makes these two diagnoses unlikely

The swelling of the face and eyes may also have been due to chronic nephritis, resulting from focal emboli or focal nephritis in the kidneys The physical signs are consistent with cavity at the left base and fluid in the left pleural space

The laboratory data are compatible with an infectious process of long standing and associated anemia The urinary findings are interesting because of the possibility they raise of metastatic abscesses in the kidneys The question of a palpable liver edge might be the result of multiple hepatic abscesses Also sepsis of this long standing might have given rise to amyloid disease The description of the sputum is lacking We do not know whether it was foul or bloody and whether acid-fast organisms were seen

I think that this man had a lung abscess primarily I do not believe he had a carcinoma of the lung Whether he had empyema with broncho-pleural fistula, I do not know Visibility of the abscess especially on the upper half of the left lung favors carcinoma or a tuberculous process rather than aspiration abscess

The fact that the fluid aspirated was nonputrid merely means that no putrefying organisms were present

The deviation of the trachea to the right is less in favor of tuberculosis Actinomycosis must be considered in a septic process of this duration Lack

## PATHOLOGICAL DISCUSSION

DR MALLORY The very widespread, bizarre distribution of pain was suggestive of dissecting aneurysm to me when I read the story over. I do not believe we have an adequate explanation for the pain because the patient did not have a dissecting aneurysm nor did we find anything else to account for it. He had a markedly sclerotic aorta for a man of only fifty-one, if he gave his age correctly, but there were no ulcerations or aneurysmal formation. He had a greatly hypertrophied heart, which weighed 720 gm. There were occlusions in both left descending and right coronary arteries, and there was a large area of infarction involving the lower third of the left ventricle and of the interventricular septum. The complete surprise was the presence of acute bacterial endocarditis of the mitral valve. There is nothing in the history that would remotely have led one to think of such a diagnosis. The obstruction of the coronary arteries could have been due to embolism from the cardiac vegetations or to ordinary thrombosis secondary to atheroma because he had severe atheromatous changes. I favor the latter. The progressive changes in the lungs, which Dr Wyman has brought out in this series of x-ray films, we did explain. There was extensive lipoid pneumonia of the type seen following aspiration of liquid paraffin. It was sufficiently chronic to have produced much pulmonary fibrosis. This is a fairly common pulmonary complication in patients who have difficulty in swallowing, whether it is due to organic obstruction or to muscular weakness.

DR JAMES HEYL About how old was the process?

DR MALLORY It was a matter of months, possibly longer. It is not uncommon, in some of these cases, to see some of the oil transported to other parts of the body. We see it frequently in the spleen. This is the first time I have ever seen it in the liver. Many vacuolated phagocytes were present in the portal areas and sometimes within the lobules. The esophagus showed perfectly normal mucosa except for a small area of ulceration, but the sub-epithelial tissue was greatly thickened and fibrous with some infiltration of monocytes and plasma cells.

DR ALFRED KRANES Was there any gastric mucosa?

DR MALLORY None was visible, and I believe the lesion was too high to make such a possibility likely.

DR ELLIS What about the legs? Did the patient have thrombophlebitis?

DR MALLORY We have no evidence. They showed nothing externally. There were no pulmonary infarcts.

A PHYSICIAN What did he die of?

DR MALLORY Acute heart failure.

DR KRANES How do you account for the sudden change after eight days if the coronary-artery disease had been present a long time?

DR MALLORY We do not know how long the bacterial endocarditis may have been present or how much pulmonary insufficiency contributed to the fatal outcome.

## CASE 34422

## PRESENTATION OF CASE

A forty-three-year-old lawyer was admitted to the hospital because of persistent cough and fever. The cough and fever began five months before admission, following a prefrontal lobotomy. X-ray studies showed patchy mottling of the left-upper-lung field. There was little response to penicillin, and three months before admission another x-ray film showed extensive consolidation in the upper half of the left lung with a central, clear area 4 cm in diameter at the level of the second anterior rib. The mediastinum was displaced to the right. A week later multiple cavities could be seen in the left-upper-lung field. The patient continued to run a fever and leukocytosis and developed a marked anemia despite two blood transfusions.

Three years before admission the patient became depressed, with suicidal tendencies. Electric shock therapy resulted in improvement for a year, but symptoms recurred and a frontal lobotomy was performed.

Physical examination revealed an emaciated man with moderate edema of the face, eyes and sacrum. There were patchy areas of scaling and hyperkeratosis over the extensor surfaces of the extremities. The tongue was smooth and glossy. The trachea was shifted to the right. Over the upper half of the left lung there were dullness and bronchial breathing, with flatness and absence of tactile fremitus and breath sounds in the lower half. The liver edge was questionably palpable.

Examination of the blood revealed a white-cell count of 18,200, with 89 per cent neutrophils, and a hemoglobin of 11.5 gm. The total protein was

# The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established 1828

Official Organ of

THE MASSACHUSETTS MEDICAL SOCIETY

and

THE NEW HAMPSHIRE MEDICAL SOCIETY

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND

PUBLISHED WEEKLY UNDER THE JURISDICTION OF THE

COMMITTEE ON PUBLICATIONS

James P. O'Hara M.D. Richard M. Smith M.D., *Chairman*  
Otto Cope, M.D. Conrad Wesselhoeft M.D.  
John Fallon M.D.

Joseph Garland M.D. *Editor*

ASSOCIATE EDITORS

Thomas H. Lachman M.D. Donald Munro M.D.

Henry Jackson Jr., M.D.

Clara D. Davies *Executive Editor*

Robert O. Leary *Assistant Editor*

EDITORIAL BOARD

C. Guy Lane, M.D. Maxwell Finland, M.D.  
Henry R. Viera, M.D. James M. Faulkner, M.D.  
Robert M. Green, M.D. Carroll B. Larson, M.D.  
Dwight O'Hara, M.D. Francis D. Moore, M.D.  
Flora H. Colby, M.D. C. Stuart Welch, M.D.  
Robert L. Goodale, M.D. Vernon P. Williams, M.D.  
Carter M. Jones, M.D. Benjamin Castleman, M.D.  
Harvey R. Morrison, M.D. Hugh R. Leavell, M.D.

SUBSCRIPTION TERMS \$7.00 per year in advance, postage paid, for the United States (medical students, \$4.00 per year). Canada, \$8.00 per year (Boston funds). \$9.00 per year for all foreign countries belonging to the Postal Union.

MATERIAL should be received not later than noon on Thursday three weeks before date of publication.

THE JOURNAL does not hold itself responsible for statements made by any contributor.

COMMUNICATIONS, including those concerning classified advertising, but *without* regarding other advertising, should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts. Telephone EE 6-2094.

NEW ENGLAND ADVERTISING REPRESENTATIVE (except for classified advertising) Edwin B. Tyler, 89 State Street, Boston, Massachusetts. Telephone LA 5-5516.

## GREATER BOSTON COMMUNITY FUND

NEXT week the Greater Boston Community Fund begins its annual drive to ensure continued operation of more than three hundred Red Feather agencies. The campaign, which will last for five weeks, will as usual ask the support of all sections of the community.

This year's goal of \$6,950,000 is estimated as the absolute minimum that will enable the Red Feather agencies to operate on the same scale as last year. The needs are stated to be greater than ever before. All the eight main fields of service—child care, family service, aid to the handicapped, visiting-nurse and other health agencies, hospitals, service for the aged, youth organizations and neighborhood

houses for young and old—are essential to the well-being of the community, and all depend on the contributions made during the campaign. The USO, which has been reactivated at the request of Secretary of Defense Forrestal, will depend in large part on the support given to the Fund.

Doctors daily contribute medical service to many of the Red Feather agencies, but they are asked also to respond as generously as possible to the appeal for financial help made during the campaign. Physicians connected with hospitals will be approached by a chairman or a vice-chairman on the hospital staff and individual practitioners by the regular volunteer workers either at home or in the office.

There is no question that the enormous service rendered by the Red Feather agencies must continue. This voluntary means of helping others to help themselves represents the American way of life at its best. Doctors are urged to give the campaign all possible support. The Red Feather, symbol of both the worker and the giver, should be proudly worn by physicians as indicating their dual role in the community.

## ARTERIAL TRANSPLANTS

THE investigations into the use of arterial grafts presented elsewhere in this issue of the *Journal* by Gross and his associates deserve particular mention. Their importance is measured in terms of the recent development of cardiovascular surgery to which Gross himself has made such outstanding contributions and in which the necessity for bridging gaps in the arterial system is so urgent, further, the possibility that arterial transplants might be made constantly available for these needs has been suggested by the development of methods of preserving blood, corneal transplants and bone tissue.

These careful studies on the possibilities of arterial grafts have proceeded in orderly fashion. First it was determined using the abdominal aortas of dogs as test material that fresh segments of artery could be transplanted from a donor to a recipient animal, that the recipient animal could survive the operation and that the transplanted tissue could be incorporated into the arterial sys-

of response to penicillin favors both actinomycosis and tuberculosis as possible etiologic agents. Response to surgery was no better than to penicillin.

The terminal episode may have been the result of flooding of the right lung with secretions from the left lung and development of a bronchopleural fistula. Massive pulmonary embolus and brain abscess are other possibilities. My final diagnosis is lung abscess, following the original operation, with terminal bacteremia and septic emboli in the kidneys and possibly in the brain. I cannot rule out primary lung tumor, tuberculosis or primary actinomycotic infection.

DR McCORT: The high left leaf of the diaphragm is hard to explain. One wonders about phrenic paralysis, favoring tumor. This could have been definitely determined by fluoroscopy, which unfortunately was not done.

A PHYSICIAN: Empyema of long standing might also explain it.

DR McCORT: The mediastinum is displaced to the right side. I am not sure that the left leaf of the diaphragm should be elevated if there is fluid under tension above it.

#### CLINICAL DIAGNOSIS

Lung abscess, with empyema

#### DR SCHIER'S DIAGNOSES

Lung abscess

Terminal bacteremia

Septic emboli in kidneys and possibly in brain

#### ANATOMICAL DIAGNOSES

*Carcinoma of left bronchus, with extension into mediastinum and metastases to cervical, medias-*

*tinal and abdominal lymph nodes, liver and right kidney*

*Pneumonitis, with abscess formation*

Thrombosis of left jugular and subclavian veins

Bicuspid aortic valve

#### PATHOLOGICAL DISCUSSION

DR TRACY B MALLORY: The diagnosis on the wards was the same as Dr Schier's — primary lung abscess with empyema. At autopsy we found a lung abscess but not primary; it was distal to a tumor of the left bronchus that had grown to fill a considerable portion of the left lung. There were many foci of necrotic tumor and secondary abscess formation beyond the point of obstruction. The tumor had metastasized to the liver and kidney but only with relatively few and small metastases. The liver was not enlarged. The tumor had invaded it and expanded locally through the pleura and involved the pericardium. The phrenic nerve was not specifically sought for but in all probability was involved by the tumor, since it spread through the pleura to the pericardium. A coincidental finding, evidently of no importance, was a congenital bicuspid aortic valve.

We did not have permission to examine the brain, but I think it is rather improbable, as Dr Schier said, that the cerebral manifestations were due to metastases. I think they were probably due to psychosis.

A PHYSICIAN: Did the kidney show anything other than metastases?

DR MALLORY: There was slight bilateral hydro-nephrosis and a very slight degree of chronic pyelonephritis.

---

**Correction** On Page 482, in the last sentence of Dr Means's discussion of Case 34391, which appeared in the September 23 issue of the *Journal*, the word "heart" was erroneously used for "leg veins." This should have read as follows:

Taking all the cases of pulmonary embolism with infarction, what percentage would you say come from the leg veins?

DR MALLORY: What would your opinion be, Dr Castleman?

DR BENJAMIN CASTLEMAN: Probably about 95 per cent.

for the solving of complicated statistical problems, but their readiness to give aid does not relieve the clinical investigator of the need to familiarize himself with the basic principles and general application of the statistical method. A brief and admirably lucid book, written specifically for those who require no more than this, is that by Hill\*. Heretofore, many clinical investigators have handicapped themselves by failing to familiarize themselves with works such as this, and the current trend toward routine appropriate statistical analysis of clinical research data is a constructive, and probably an overdue, development.

### ARMY MEDICAL TRAINING PROGRAM

THE Army Medical Corps has extended to November 1 its time limit for medical-school graduates to apply for commissions under the Civilian Resident and Intern Training Program. This opportunity must impress itself upon all recent graduates in view of the increased need for medical personnel to care for the nation's expanding forces, and the obvious intention of the authorities to fill the need.

Under the program, according to a recent release from the Office of the Surgeon General, selected individuals serve out their internships and residencies in civilian hospitals of their choice — interns as first lieutenants of the Medical Reserve Corps and residents with the same rank in the Regular Army Medical Corps. Both receive full pay and allowances of their rank with \$100 a month in addition as a professional volunteer bonus.

Upon completion of a year's training interns must apply for Regular Army commissions and may qualify for resident training. Residents, upon concurrence of the hospital, may continue their training with a view to qualifying for specialty courses leading to certification by American Specialty Boards. The Graduate Training Program may here continue as the Career Management Program under which medical officers are assured of continuation in their specialties during Army service, except in the case of administrative or staff careers. Participating officers are expected to serve a year of active duty for each year of training they receive.

\*Hill B. *Principles of Medical Statistics*. Second edition. 185 pp. London: The Lancet Ltd. 1939.

## MASSACHUSETTS MEDICAL SOCIETY

### APPLICANTS FOR FELLOWSHIP

PUBLISHED IN ACCORDANCE WITH THE PROVISIONS OF  
CHAPTER V, SECTION 2, OF THE BY-LAWS

#### BARNSTABLE

PICKFORD, EDWARD MORSE, The Loydon, Dennisport  
Johns Hopkins University School of Medicine, 1925  
Frederick Sanborn, *Secretary*,  
Bates Avenue, Osterville

#### BERKSHIRE

ERAMO, LINCOLN, 16 Williams Street, Pittsfield  
Tufts College Medical School, 1945  
GOWNEY, JOHN FREDERIC, House of Mercy Hospital,  
Pittsfield  
University of Vermont College of Medicine, 1940  
GUERRIERI, ANTONIO GEORGE, Stockbridge  
Marquette University School of Medicine, 1944  
HENNELLY, THOMAS P., 51 Broad Street, Pittsfield  
College of Physicians and Surgeons, Columbia University,  
1942  
NELSON, WILLIAM A., 157 Main Street, Williamstown  
Baltimore Medical College, 1904 Sponsor Michael  
Gangemi, 96 Summer Street, North Adams  
NORTON, THOMAS MANNING, 181 Bartlett Avenue, Pittsfield  
Georgetown University School of Medicine, 1941  
WRIGHT HENRY COLLIER, Stetson Road, Williamstown  
New York University College of Medicine, 1941  
Daniel N. Beers, *Secretary*  
74 North Street, Pittsfield

#### BRISTOL NORTH

DESTEFANO, FRANCIS THOMAS, 76 South Main Street,  
Mansfield  
Middlesex University School of Medicine, 1941 Sponsor  
Carl J. DePrizio, 1 Park Street, Mansfield  
ROUNSEVILLE, WILFRED VAN ETTEN, 40 Bank Street,  
Attleboro  
Tufts College Medical School, 1943  
William E. Dawson, *Secretary*  
58 Winthrop Street, Taunton

#### BRISTOL SOUTH

CAPLAN, SHELDON MAURICE, 2 Arch Street, New Bedford  
Middlesex University School of Medicine, 1943 Sponsor  
Clarence E. Burt, 261 Union Street, New Bedford  
GOLNSTEIN, MEYER ROBERT, 3 Clinton Place, New Bedford  
Middlesex University School of Medicine, 1936 Sponsor  
Curtis C. Tripp, 416 County Street, New Bedford  
GREEN, FRANCIS PAUL, 276 Sawyer Street, New Bedford  
Middlesex University School of Medicine, 1939 Sponsor  
Joseph A. Sciuto, 26 Grove Street, New Bedford  
HUGHES, WILSON EMERY, 146 Purchase Street, Fall River  
Yale University School of Medicine, 1942  
KENNEY, WILLIAM EDMUND, 452 Linden Street, Fall River  
Yale University School of Medicine, 1941  
MACKLER, EDWARD DANIEL, 359 Pleasant Street, New  
Bedford  
Tufts College Medical School, 1945  
O'NEILL, WALTER JAMES, 340 Summer Street, New Bedford  
Midwest Medical College, 1938 Sponsor Frank R. Leary,  
279 Union Street, New Bedford  
PITTA, CARL ALMEIDA, 37 Pleasant Street South Dart-  
mouth  
Kansas City University of Physicians and Surgeons, 1933  
Sponsor Albert H. Sterns, 31 Seventh Street, New  
Bedford

tem of the host and could perform the function for which it was intended. Here it became evident, as might be expected, that the greater the delay between donor and recipient, the less were the chances of tissue survival.

The development of a method of tissue preservation came next, preservation by freezing was attempted, and it was demonstrated that arterial tissue cannot survive this process. The next experiment consisted of the storing of aortic segments in an electrolyte solution to which had been added glucose, dog serum, a buffer, penicillin and streptomycin and a phenol-red indicator. Segments so preserved and refrigerated at a temperature between 1 and 4°C remained viable for over a month and were transplanted into recipient animals with a high percentage of successful "takes."

The culminating step, toward which all animal experimentation must be directed, has been its application to the human being. Segments of arteries removed from recent victims of automobile accidents were preserved and stored in the manner described above. Nine such grafts have been used to bridge gaps between the aortic and pulmonary arterial systems in the tetralogy of Fallot, with 7 successful results, 2 patients died soon after operation. Furthermore, 3 grafts have been used without a failure in surgical correction of coarctation of the thoracic aorta.

As medical science has developed blood banks, eye banks and bone banks, so the way now seems clear for the establishment of artery banks. In the great human repair shop that the modern hospital has become, the spare-parts department assumes increasing importance.

## THE PHYSICIAN AND THE STATISTICAL METHOD

MANY physicians, particularly those who do clinical research, appear to regard the statistical method as the exclusive property of their colleagues in public health or laboratory research. They often dismiss the exact technic somewhat defensively, by repeating the time-worn statement that anything can be proved by statistics. In recent years, however, more and more clinical in-

vestigators are found to be using statistical tests to examine their data, and it may be that the older view needs drastic revision.

The author of a case report hardly needs to turn to the statistical method to support his presentation, but authors dealing with groups of cases should consider the advantages of proper statistical evaluation of their data. The initial planning of any such study is immeasurably benefited by consideration of certain statistical principles such as those dealing with sampling. The results of well planned work can be displayed to much greater advantage if they are treated statistically than if they are not. For example, an average figure is much more meaningful if the variation around the average is presented along with it. One of the most frequent research devices is to compare treated and untreated groups of cases, and, too frequently, one finds the investigator basing his conclusions on a difference that is more apparent than real. Relatively simple statistical techniques for testing the significance of such differences are available, and by the proper application of these tests it can readily be determined whether the result is truly significant or whether it is a chance one. The tests are useful not only in evaluating one's own results but also in determining whether those published by other workers are significant, merely suggestive or clearly unreliable.

One may argue that plain horse sense can do the same thing and that there is no need to resort to a mere sophistic, mathematical device for the purpose. The statistical method, however, properly applied, is in fact more than this and might well be defined as horse sense quantitated. It will if judiciously used, keep the overenthusiastic researcher from drawing unjustified conclusions and enable the overcautious investigator to express with confidence the full meaning of his findings. All this can and should be achieved with due consideration of the confusion that results to the reader if a writer adorns his treatise with countless standard deviations, chi squares, T-tests and other statistical symbols.

Few physicians have the time, and perhaps not a great many have the ability, to become master statisticians. Trained statisticians are available

or the solving of complicated statistical problems, but their readiness to give aid does not relieve the clinical investigator of the need to familiarize himself with the basic principles and general application of the statistical method. A brief and admirably lucid book, written specifically for those who require no more than this is that by Hill.\* Heretofore, many clinical investigators have handicapped themselves by failing to familiarize themselves with works such as this, and the current trend toward routine, appropriate statistical analysis of clinical research data is a constructive, and probably an overdue, development.

### ARMY MEDICAL TRAINING PROGRAM

THE Army Medical Corps has extended to November 1 its time limit for medical-school graduates to apply for commissions under the Civilian Resident and Intern Training Program. This opportunity must impress itself upon all recent graduates in view of the increased need for medical personnel to care for the nation's expanding forces, and the obvious intention of the authorities to fill the need.

Under the program, according to a recent release from the Office of the Surgeon General, selected individuals serve out their internships and residencies in civilian hospitals of their choice — interns as first lieutenants of the Medical Reserve Corps and residents with the same rank in the Regular Army Medical Corps. Both receive full pay and allowances of their rank with \$100 a month in addition as a professional volunteer bonus.

Upon completion of a year's training interns must apply for Regular Army commissions and may qualify for resident training. Residents, upon concurrence of the hospital, may continue their training with a view to qualifying for specialty courses leading to certification by American Specialty Boards. The Graduate Training Program may here continue as the Career Management Program under which medical officers are assured of continuation in their specialties during Army service, except in the case of administrative or staff careers. Participating officers are expected to serve a year of active duty for each year of training they receive.

\*Hill, B. *Principles of Medical Statistics*. Second edition. 185 pp. London: The Lancet Ltd., 1939.

## MASSACHUSETTS MEDICAL SOCIETY

### APPLICANTS FOR FELLOWSHIP

PUBLISHED IN ACCORDANCE WITH THE PROVISIONS OF  
CHAPTER V, SECTION 2, OF THE BY-LAWS

#### BARNSTABLE

PICKFORD, EDWARD MORSE, The Loydon, Dennisport.  
Johns Hopkins University School of Medicine, 1925  
Frederick Sanborn, *Secretary*,  
Bates Avenue, Osterville

#### BERKSHIRE

ERAMO LINCOLN, 16 Williams Street, Pittsfield  
Tufts College Medical School, 1945  
GOWDEY, JOHN FREDERIC, House of Mercy Hospital,  
Pittsfield  
University of Vermont College of Medicine, 1940  
GUERRIERI, ANTONIO GEORGE, Stockbridge  
Marquette University School of Medicine, 1944  
HENNELLY, THOMAS P., 51 Broad Street, Pittsfield  
College of Physicians and Surgeons, Columbia University,  
1942  
NELSON, WILLIAM A., 157 Main Street, Williamstown  
Baltimore Medical College, 1904 Sponsor Michael  
Gangemi, 96 Summer Street, North Adams  
NORTON, THOMAS MANNING, 181 Bartlett Avenue, Pittsfield  
Georgetown University School of Medicine, 1941  
WRIGHT, HENRY COLLIER, Stetson Road, Williamstown  
New York University College of Medicine, 1941  
Daniel N. Beers, *Secretary*,  
74 North Street, Pittsfield

#### BRISTOL NORTH

DESTEFANO, FRANCIS THOMAS, 76 South Main Street,  
Mansfield  
Middlesex University School of Medicine, 1941 Sponsor  
Carl J. DePizio, 1 Park Street, Mansfield  
ROUNSEVILLE, WILFRED VAN ETTEN, 40 Bank Street,  
Attleboro  
Tufts College Medical School, 1945  
William E. Dawson, *Secretary*,  
58 Winthrop Street, Taunton

#### BRISTOL SOUTH

CAPLAN, SHELDON MAURICE, 2 Arch Street, New Bedford  
Middlesex University School of Medicine, 1943 Sponsor  
Clarence E. Burt, 261 Union Street, New Bedford  
GOLDSTEIN, MEYER ROBERT, 3 Clinton Place, New Bedford  
Middlesex University School of Medicine, 1936 Sponsor  
Curtis C. Tipp, 416 County Street, New Bedford  
GREEN, FRANCIS PAUL, 276 Sawyer Street, New Bedford  
Middlesex University School of Medicine, 1939 Sponsor  
Joseph A. Sciuto, 26 Grove Street, New Bedford  
HUGHES, WILSON EMERY, 146 Purchase Street, Fall River  
Yale University School of Medicine, 1942  
KENNEY, WILLIAM EDMUND, 452 Linden Street, Fall River  
Yale University School of Medicine, 1941  
MACKLER, EDWARD DANIEL, 359 Pleasant Street, New  
Bedford  
Tufts College Medical School, 1945  
O'NEILL, WALTER JAMES, 340 Summer Street, New Bedford  
Midwest Medical College, 1938 Sponsor Frank R. Leary,  
279 Union Street, New Bedford  
PITTA, CARL ALMEIDA, 37 Pleasant Street, South Dart-  
mouth  
Kansas City University of Physicians and Surgeons, 1933  
Sponsor Albert H. Sterns, 31 Seventh Street, New  
Bedford

- ROSENBERG, ROBERT, 148 Carroll Street, New Bedford  
Middlesex University School of Medicine, 1936 Sponsor  
Charles H Griffin, 404 County Street, New Bedford
- ROSTLER, ALEXANDER ERICH, 966 Robeson Street, Fall  
River  
University of Basle, 1939 Sponsor Daniel L Mooney,  
422 North Main Street, Fall River
- RUGGERI, NICHOLAS, 458 Ashley Boulevard, New Bedford  
Midwest Medical College, 1934 Sponsor Maurice Jacobs,  
98 Cottage Street, New Bedford
- SARLO, VINCENT M., 1650 Acushnet Avenue, New Bedford  
Middlesex University School of Medicine, 1938 Sponsor  
Joseph A Sciuto, 26 Grove Street, New Bedford
- SIMMONS, HAROLD LEONARD, JR., 55 Dudley Street, New  
Bedford  
Boston University School of Medicine, 1944

James E Fell, *Secretary*  
181 Purchase Street, Fall River

#### ESSEX NORTH

- ANDERSON, RICHARD WILLIAM, 167 Central Street, George-  
town  
University of Minnesota Medical School, 1943
- DAWSON, GEORGE ARTHUR, 33 East Brook Place, Methuen  
McGill University School of Medicine, 1941
- DIAMOND, BERNARD, 281 Haverhill Street, Lawrence  
University of Edinburgh School of Medicine, 1937 Sponsor  
Harold R Kurth, 57 Jackson Street, Lawrence
- FREEDMAN, JACOB JOSEPH, 589 Haverhill Street, Lawrence  
Middlesex University School of Medicine, 1941 Sponsor  
Max Bier, 46 Amesbury Street, Lawrence
- HADHAB, HOMODE JOSEPH, 17 Leroy Avenue, Bradford  
Middlesex University School of Medicine, 1942 Sponsor  
Lucien R Chaput, 3 Washington Square, Haverhill
- LAND, WILLIAM, Lawrence General Hospital, Lawrence  
Boston University School of Medicine, 1945
- LORENTZ, JOHN J., 180 Berkeley Street, Methuen  
Georgetown University School of Medicine, 1947
- MCGOVERN, RICHARD ALOYSIUS, 1046 Essex Street, Lawrence.  
Middlesex University School of Medicine, 1942 Sponsor  
Richard J Neil, 255 Broadway, Methuen
- ROTHMAN, MARTIN, 562 Main Street, Haverhill  
Tufts College Medical School, 1943
- ROTHSEID, ALBERT SEYMOUR, 484 Prospect Street, Methuen  
Middlesex University School of Medicine, 1943 Sponsor  
Joseph A Levek, 32 Lawrence Street, Lawrence

Harold R Kurth, *Secretary*  
57 Jackson Street, Lawrence

#### ESSEX SOUTH

- BROWN, DONALD EMERSON, 6 Lefavour Avenue, Beverly  
Harvard Medical School, 1943
- DONOVAN, JAMES M., 263 Lynn Shore Drive, Lynn  
Georgetown University School of Medicine, 1940
- HOFFMAN, WILLIAM, 25 Franklin Street, Lynn  
Middlesex University School of Medicine, 1942 Sponsor  
Albert H Conner, 285 Lynn Shore Drive, Lynn
- KELLER, MAURICE JOSEPH, 412 Jefferson Avenue, Salem  
Columbia University College of Physicians and Surgeons,  
1940
- KOH, FRANCIS JOHN, 13 Pickman Road Salem  
Middlesex University School of Medicine, 1935 Sponsor  
Walter G Phippen, 31 Chestnut Street, Salem
- KUNIAN, LOUIS, 11 Holly Street, Salem  
Middlesex University School of Medicine, 1942 Sponsor  
Richard Thompson, 26 Chestnut Street, Salem
- MACDONALD, ALEXANDER STERLING, JR., 810 Hale Street,  
Beverly Farms  
Cornell University School of Medicine, 1941
- MARMER, GEORGE, 66 Lewis Street, Lynn  
Middlesex University School of Medicine, 1941 Sponsor  
Solomon E Steiman, 23 Broad Street, Lynn
- MILLS, HERBERT FRANCIS, 257 Broadway, Lynn  
College of Physicians and Surgeons, Boston 1941 Sponsor  
John W Trask, 90 Ocean Street, Lynn

- MUSMAN, SAMUEL, 274 Western Avenue, Lynn  
Middlesex University School of Medicine, 1934 Sponsor  
Samuel Levine, 40 Baltimore Street, Lynn.
- ORRIS, HARRY WILLIAM, 244 Ocean Street, Lynn  
Wayne University Medical College, 1942
- PARKER, SYDNEY SANFORD, 10 Poplar Street, Gloucester  
Middlesex University School of Medicine, 1941 Sponsor  
William Irving, 35 Middle Street, Gloucester
- SEGAL, ALLAN LOUIS, 8 Naples Road, Salem  
Queen's University School of Medicine, 1938
- SHUB, ALBERT WAYNE, 421 Broadway, Lynn  
Middlesex University School of Medicine, 1943 Sponsor  
Leo Maletz, 80 Nahant Street, Lynn

Henry D Stebbins, *Secretary*  
342 Essex Street, Salem

#### FRANKLIN

- BENNETT, JOHN WESLEY, Northfield  
Temple University School of Medicine, 1940
- NIECKOSKI, JULIAN, 26 Solon Street, Greenfield  
Harvard Medical School, 1941

Milton M Sisson, *Secretary*  
31 Federal Street, Greenfield

#### HAMPDEN

- BAKER, WALLACE J., 741 Chicopee Street, Williamansett.  
Middlesex University School of Medicine, 1942 Sponsor  
Stephen A Mahoney, 378 High Street, Holyoke.
- CORCORAN, GEORGE BARTLETT, JR., 84 Park Street, West  
Springfield  
Yale University School of Medicine, 1944
- FRIED, MARCUS BERNARD, 4 Rittenhouse Terrace, Spnna  
field  
Kansas City University of Physicians and Surgeons, 1933  
Sponsor Alfred Glickman, 95 State Street, Springfield
- GOLD, SOL MARTIN, 15 Greenwood Avenue, Holyoke.  
Middlesex University School of Medicine, 1943 Sponsor  
Edward P Bagg, 207 Elm Street, Holyoke.
- GOODHUE, FREDERICK WELLS, Westfield State Sanatorium,  
Westfield  
Tufts College Medical School, 1941
- GREWAL, JOGINDAR SINGH, Westfield State Sanatorium,  
Westfield  
Boston University School of Medicine, 1926
- JAGODA, LEONARD S., 712 Parker Street, East Longmeadow  
Creighton University School of Medicine, 1935
- KLIBANOFF, SAMUEL, 52 Colfax Street, Springfield.  
Harvard Medical School, 1941
- McMILLAN, ALBERT SLOCOMB, 69 North Alhambra Circle,  
Agawam  
University of Virginia School of Medicine, 1943
- STONE, SAMUEL MONTAGUE, 58 Manor Road, Springfield  
Middlesex University School of Medicine, 1934 Sponsor  
George L Steele, 20 Maple Street, Springfield
- TEITEL, MILTON HENRY, 115 Sumner Avenue, Springfield  
College of Physicians and Surgeons, Boston, 1936 Sponsor  
James L Smead, 26 Temple Street, Springfield
- VASH, GEORGE, 412 Webster Street, New Orleans, La.  
University of Vienna, School of Medicine, 1937 Sponsor  
Archibald J Douglas, Westfield
- YETWIN, I JACQUES, 84 Mayfair Avenue, Springfield  
Middlesex University School of Medicine, 1940 Sponsor  
Frederick S Hopkins, 146 Chestnut Street, Springfield

Walter W Williams, *Secretary*  
20 Magnolia Terrace, Springfield

#### HAMPSHIRE

- EDELSTEIN, JOSEPH MELVIN, 44 North Elm Street, North  
ampton  
Tufts College Medical School, 1943
- KOH, KURT HEINZ, 300 Main Street, Easthampton  
State Medical School of Vinnitza, 1937 Sponsor Edward  
D Williams, 1 High Street Easthampton

F Mary P Snook, *Secretary*  
Worthington

## MIDDLESEX EAST

- HALEY WARREN DRAPER, 14 Oxford Street, Winchester  
Harvard Medical School, 1945
- HICKEY WILLIAM FRANCIS JR., 5 Edgehill Road, Winchester  
Harvard Medical School, 1940
- SCHWARTZ HARRY, 20 Yale Avenue Wakefield  
Middlesex University School of Medicine, 1942 Sponsor  
Howard A. Bouie, 22 Yale Avenue Wakefield
- Roy W. Layton *Secretary*  
8 Porter Street, Melrose

## MIDDLESEX NORTH

- HOLTZMAN SAUL CHARLES 10 Carlisle Road Bedford  
Boston University School of Medicine, 1945
- KAHN WALTER, 68 Littleton Road Chelmsford  
University of Bonn School of Medicine 1921 Sponsor  
Philip G. Berman 174 Central Street, Lowell
- SOUTHWICK EDWARD HENRY 169 Fairmount Street, Lowell  
Albany Medical College, 1941
- Brendan D. Leahy *Secretary*  
9 Central Street, Lowell

## MIDDLESEX SOUTH

- ANNUNZIATA, JOSEPH FERDINAND Main Street, Hopkinton  
Midwest Medical College, 1938 Sponsor John K. Ruggles,  
Jr., Hayden Rowe Street, Hopkinton.
- AUBIN, FRANCIS J. 114 Danehill Road Newton Highlands  
University of Buffalo School of Medicine 1941
- BAYDLER, BERNARD, 157 Brattle Street, Cambridge  
Columbia University College of Physicians and Surgeons  
1938
- BOTLE, JEREMIAH JOSEPH 1737 Cambridge Street, Cam-  
bridge.  
Tufts College Medical School 1945
- BROWN BRUCE ROW, Lane's End Singletary Lane Framing-  
ham Centre  
Tufts College Medical School, 1943
- CAVALIERI, DOMINIC, 92 Thurston Street, Somerville.  
Middlesex University School of Medicine, 1938 Sponsor  
Angelo J. Capone, 390A Broadway Somerville.
- CENTNER, PAUL JOSEPH, 21 Grevstone Road, Malden  
University of Cincinnati College of Medicine, 1943
- COREY, DAVID ROY, 4 Shawmut Avenue, Cohasset  
Middlesex University School of Medicine 1939 Sponsor  
Arthur E. Taddeo, 75 West Central Street, Natick
- CORRIGAN SYLVESTER EDWARD 751 Main Street, Waltham  
Harvard Medical School, 1928
- CROSBY, ROY CAMPBELL, 290 Prospect Street, Framingham  
Tufts College Medical School, 1944
- DELUCA, MARIE A., 319 Union Avenue Framingham  
Kansas City University of Physicians and Surgeons 1929  
Sponsor Joseph C. Merriam 198 Union Avenue, Framing-  
ham
- DE NICOLAIS EDWARD J., 255 Hollis Street, Framingham  
Middlesex University School of Medicine 1942 Sponsor  
Joseph C. Merriam, 198 Union Avenue, Framingham
- FEINGOLD, MYER, 384 Salem Street, Malden  
Middlesex University School of Medicine 1937 Sponsor  
Daniel J. Duggan, 3 Hawthorne Street, Malden
- FIORENTINO, DOMENICO Saverio, 79 East Main Street, Marl-  
boro  
Middlesex University School of Medicine 1945 Sponsor  
William D. Roche, 196 Main Street, Marlboro
- FISHER, RUSSELL SYLVESTER, 60 Hatfield Road West  
Newton  
Medical College of Virginia 1942
- GOLD HENRY 15 West Central Street, Natick  
Kansas City University of Physicians and Surgeons 1942  
Sponsor Arthur E. Taddeo 75 West Central Street Natick
- HARNO SIDNEY HYMAN, 71 Magazine Street, Cambridge  
College of Physicians and Surgeons Boston, 1943 Sponsor  
William C. Archibald, 837 Massachusetts Avenue, Cam-  
bridge
- HURLEY MELVIN TIMOTHY, 24 Longmeadow Road, Newton  
Centre  
Stanford University School of Medicine, 1942
- JACOBS ELI I. 219 Belmont Street, Belmont.  
Middlesex University School of Medicine, 1943 Sponsor  
James H. Townsend, Mt. Auburn Hospital Cambridge
- KANTER STANLEY SAMUEL, 18 Merrigan Street, Arlington  
Washington University School of Medicine, 1943
- KERR, RICHARD CARPENTER, 30 Washburn Street, Newton  
Harvard Medical School, 1943
- LITTER, JULIUS, 106 Strathmore Road Brighton  
Boston University School of Medicine, 1940
- MACVILLAN, ROBERT JOHNSON 25 Maple Avenue, Newton  
University of Cincinnati College of Medicine, 1943
- MILES HENRY H. W. 240 Bellevue Street, Newton  
Tulane University School of Medicine, 1939
- MILLER, PAUL RALPH 89 Parker Avenue, Newton  
Boston University School of Medicine, 1945
- NEWMAN ARTHUR SAMUEL 41 Pearl Street, Newton  
Middlesex University School of Medicine, 1945 Sponsor  
Charles N. Gettes 481 Beacon Street Boston
- O'BRIEN FREDERICK FRANCIS, 2307 Massachusetts Avenue,  
Cambridge  
Tufts College Medical School, 1939
- O'KEEFE, ARTHUR FRANCIS 24 Oldham Road West Newton  
Duke University School of Medicine, 1945
- OSTROGER, JOSEPH GEORGE, 203 Middlesex Avenue, Medford  
Middlesex University School of Medicine, 1942 Sponsor  
Arthur D. Guthrie 408 Salem Street, Medford
- REGAN ELLEN FRANCES, 625 Winter Street, Framingham,  
Yale University School of Medicine, 1945
- ROSENMAN LEONARD DANIEL, 12 Lantern Lane, Newton  
Centre  
University of Michigan Medical School, 1942
- SCARINGI JOSEPH 165 Powder House Boulevard West  
Somerville.  
Middlesex University School of Medicine 1937 Sponsor  
Walter Jellis, 71 College Avenue, West Somerville
- SHIPP, FRANK LOUDON, 122 Pine Grove Avenue, Newton  
Lower Falls  
University of Toronto, 1935
- SHUSHAN ARTHUR A., 316 Belmont Street, Watertown  
Kansas City University of Physicians and Surgeons, 1932  
Sponsor David Rose, 483 Beacon Street, Boston
- TALBOT, HERBERT SELMAN 104 Pond Street, Natick  
Columbia University College of Physicians and Surgeons,  
1928
- WEINBERGER MAXIMILIAN, Walter Fernald School, Waverley  
University of Vienna, School of Medicine, 1915 Sponsor  
Malcolm J. Farrell, Walter Fernald School, Waverley
- WESSLER, STANFORD 38 Dwhinda Road Waban  
New York University College of Medicine, 1942
- WILLIAMSON, CHARLES READY 95 Allen Avenue, Waban  
Harvard Medical School, 1942.
- WYSTON MURRAY RICHARD, 75 Outlook Drive, Lexington  
University of Lausanne School of Medicine, 1939 Sponsor  
Norman Wilson 1101 Beacon Street, Brookline
- WITTENBORG MARTIN HERMAN, Wavside Inn Road Fram-  
ingham  
Johns Hopkins University School of Medicine, 1939
- Alexander A. Levi, *Secretary*  
481 Beacon Street, Boston

## NORFOLK

- BARNUM FRANCIS G. JR., 1776 Beacon Street, Brookline.  
Harvard Medical School, 1944
- BIXON, ALVIN MYRON 220 Mason Terrace, Brookline.  
Tufts College Medical School, 1947
- BLACK, MELVIN BERTROM, 16 Parkway Road, Brookline  
Harvard Medical School, 1943
- BONNER, JOSEPH NORBERT 209 Gerty Road Chestnut Hill  
Georgetown University School of Medicine 1942
- COHEN NATHANIEL MAURICE, JR., 77 Colchester Street,  
Brookline  
Harvard Medical School, 1946

COLPOYS, WILLIAM PATRICK, 106 Melville Avenue, Dorchester  
Boston University School of Medicine, 1940

CONVERSE, J GERARD, 1152 Brook Road, Milton  
Tufts College Medical School, 1943

DUB, LEO, 35 Park Street, Brookline  
Medical School of the University of Prague, 1914 Sponsor Joseph H Pratt, 94 Upland Road, Brookline

DUNCAN, THOMAS FRANCIS, 54 Barry Street, Dorchester  
Tufts College Medical School, 1943

ECHLOV, THEODORE GILBERT, 1682 Beacon Street, Brookline  
Middlesex University School of Medicine, 1940 Sponsor William Dameshek, 192 Beacon Street, Boston

EYRE, JOHN DUNHAM, JR., 117 Sherman Road, Chestnut Hill  
Columbia University College of Physicians and Surgeons, New York, 1940

FINNERTY, EDMUND FRANCIS, JR., 640 Newton Street, Brookline  
Tufts College Medical School, 1943

GOLDBERG, JACK JACOB, 1614 Beacon Street, Brookline  
College of Physicians & Surgeons, Boston, 1942 Sponsor Harry Blotner, 419 Commonwealth Avenue, Boston

GUTMAN, MURRAY, 62 Washington Street, Wellesley  
Chicago Medical School, 1943 Sponsor Allen Locke, 76 Washington Street, Wellesley

HICKS, SAMUEL PENDLETON, 98 Sherman Road, Chestnut Hill  
University of Pennsylvania School of Medicine, 1940

HILL, ROBERT CLAYTON, 24 Stockwell Street, Roxbury  
Hahnemann Medical College of Philadelphia, 1942

JONES, WILLIAM NORMAN, 9 Chestnut Street, Boston  
University of Chicago, The School of Medicine, 1940

KAUFMAN, ALAN L., 65 Green Street, Brookline  
Middlesex University School of Medicine, 1942 Sponsor Eli Friedman, 416 Marlboro Street, Boston

KAYE, MAXWELL ELIAS, 86 Neponset Street, Canton  
Midwest Medical College, 1938 Sponsor Valmore A Pelletier, 38 Cottage Street, Norwood

KNEISEL, JOHN JUNIOR, 2 Netherlands Road, Brookline  
Harvard Medical School, 1938

KUTKA, LAWRENCE, 39 Arlington Road, Brookline  
Middlesex University School of Medicine, 1943 Sponsor Henry Baker, 4 Greenway Street, Brookline

MAHN, BERNARD FREEMAN, JR., 34 Highview Street, Westwood  
Boston University School of Medicine, 1940

MURRAY, JOSEPH E., 316 St Paul Street, Brookline  
Harvard Medical School, 1943

QUINN, EDWARD JAMES, 87 St Mary's Street, Brookline  
University of Vermont College of Medicine, 1921

ROGERS, THEODORE, 929 Blue Hill Avenue, Dorchester  
Middlesex University School of Medicine, 1942 Sponsor Saul M Marcus, 520 Beacon Street, Boston

SOLOW, ALFRED LEONARD, 62 South Main Street, Sharon  
Middlesex University School of Medicine, 1943 Sponsor William Bourke, Union Street, Walpole

STAHLER, SIDNEY, 106 E Foxboro Street, Sharon  
New York Medical College, Flower and Fifth Avenue Hospital, 1942

STANLEY, MALCOLM MCCLAIN, 37 Garrison Road, Brookline  
University of Louisville School of Medicine, 1941

STERLING, HASKELL, 389 Harvard Street, Brookline  
Middlesex University School of Medicine, 1943 Sponsor Hyman Morrison, 483 Beacon Street, Boston

TRAFTON, MARION ZOTTOLI, 26 Upland Avenue, Dorchester  
Boston University School of Medicine, 1940

WEISS, JESS BERNARD, 150 Washington Street, Dorchester  
Middlesex University School of Medicine, 1943 Sponsor David Hurwitz, 520 Beacon Street, Boston

ZAMBON, LEO UBALDO, 127 Lexington Avenue, Needham  
Middlesex University School of Medicine, 1939 Sponsor David E Mann, 863 Great Plain Avenue, Needham

Basil E Barton, *Secretary*  
10 Richwood Street, W Roxbury

## NORFOLK SOUTH

ENTIN, MOSES JACOB, 37 Woodward Avenue, Quincy  
Middlesex University School of Medicine, 1943 Sponsor Harry Braverman, 43 School Street, Quincy

HAGLER, SUMNER, 144 Kingsley Road, Kennerly  
Columbia University College of Physicians and Surgeons, 1943

KEIGAN, ARCHIE GRAHAM, 276 Quincy Avenue, East Braintree  
Tufts College Medical School, 1944

KINGSLAND, LAWRENCE CHAPPELL, JR., 19 Howe Street, Hingham  
Harvard Medical School, 1940

LEMON, HENRY MARTYN, 66 Albatross Road, Quincy  
Harvard Medical School, 1940

NEVINS, SIMON HARRY, 611 Adams Street, Quincy  
Middlesex University School of Medicine, 1925 Sponsor James M Ward, 1186 Hancock Street, Quincy

RUBIN, FRANK FRED, 795 Southern Artery, Quincy  
Middlesex University School of Medicine, 1936 Sponsor Frederick N Manley, 1200 Hancock Street, Quincy

SLOANE, WILLIAM CHARLES, 15 So Main Street, Randolph  
Middlesex University School of Medicine, 1933 Sponsor Robert O Gilmore, 1159 Hancock Street, Quincy

SLOMKOWSKI, THADDEUS JOSEPH, 78 Alstead Street, North Quincy  
Boston University School of Medicine, 1943

WOOD, DWIGHT REYNOLDS, 1070 Main Street, South Weymouth  
Tufts College Medical School, 1943

Ebenezer K Jenkins, *Secretary*  
Norfolk County Hospital, So Braintree

## PLYMOUTH

CALITRI, JOSEPH FRANCIS, 17 Central Square, West Bridgewater  
College of Physicians and Surgeons, Boston, 1942 Sponsor George A Moore, 167 Newbury Street, Brockton

CARPINELLA, CHARLES JEREMIAH, 94 Moraine Street, Brockton  
Middlesex University School of Medicine, 1931 Sponsor Michael F Barrett, 231 Main Street, Brockton

CORDARO, VINCENT FRANK, Bryant Hotel, Brockton  
College of Physicians and Surgeons, 1941 Sponsor Michael F Barrett, 231 Main Street, Brockton

DAVIS, SAUL PAUL, 16 Cottage Street, Brockton  
Middlesex University School of Medicine, 1943 Sponsor William Walker, 11 Arlington Street, Brockton

HASSETT, ARTHUR JOSEPH, JR., 26 Pierce Road, Weymouth  
Tufts College Medical School, 1943

JACOUBS, EDWARD LEE GREGORY, 43 Center Street, North Easton  
Middlesex University School of Medicine, 1942 Sponsor Fred Weiner, 231 Main Street, Brockton

KAPLAN, MORRIS, Bridgewater State Hospital, Bridgewater  
College of Physicians and Surgeons, Boston, 1937 Sponsor John H Weller, Bridgewater State Hospital, Bridgewater

OPPENHEIM, HARRY, 239 Howard Street, Rockland  
College of Physicians and Surgeons, Boston, 1937 Sponsor Ernest E Wiesner, 129 West Elm Street, Brockton

THIERY, RAYMOND DONLE, Bridgewater State Hospital, Bridgewater  
Harvard Medical School, 1923

VALATKA, JOSEPH AUGUST, 335 Washington Street, Abington  
Middlesex University School of Medicine, 1941 Sponsor John M Peckham, 131 North Avenue, North Abington

Samuel Gale, *Secretary*  
The Checkerton, Brockton

## SUFFOLK

ALLEN, HENRY FREEMAN, 200 Beacon Street, Boston  
Harvard Medical School, 1943

BONNER, CHARLES DOUGLASS, 2 Lattimore Court, Boston  
Boston University School of Medicine, 1944

BOYER, FRANCES JONES, 2 Lattimore Court, Boston  
Boston University School of Medicine, 1943

BOYNET, PHILIP DIRLAM, 296 Allston Street, Brookline  
Harvard Medical School, 1936

BRONIE, SINNEY, 17 Stearns Road, Brookline  
George Washington University School of Medicine, 1943

CRANE, CHILTON, 135 Aspinwall Avenue, Brookline  
Harvard Medical School, 1938

CURTISS, CONSTANCE, Glezen Lane, Weyland  
Western Reserve University School of Medicine, 1945

FORSHAM, PETER HUGH, 779 Huntington Avenue, Boston  
Harvard Medical School, 1945

FRANSEN, ELMER FREDERICK, 45 Hereford Street, Boston  
Harvard Medical School, 1940

FUNKENSTEIN, DAN HERTZ, 50 Peterborough Street, Boston  
Tulane University School of Medicine, 1934

GRAY, SEYMOUR JEROME, 282 Warren Street, Brookline  
University of Pennsylvania School of Medicine, 1936

HEFFERNAN, ELMER WESLEY, 118 Riverway, Boston  
Tufts College Medical School, 1944

HOWE, CALDERON, 29 Hillcroft Road, Jamaica Plain  
Harvard Medical School, 1942

JEFFERIES, WILLIAM MCKENDREE, 30 No Anderson Street, Boston  
University of Virginia Department of Medicine, 1940

KEYWORTHY, ROGER ARTHUR, Carney Hospital, South Boston  
University of Vermont College of Medicine, 1940

KERBULAS, ANDREW ANTHONY, 108 Henry Street, Cambridge  
Duke University School of Medicine, 1945

KUGERMAN, SIDNEY, 469 Commonwealth Avenue, Boston  
University of Illinois College of Medicine, 1939

LUONGO, MICHAEL ANTHONY, 69 Gladstone Street, East Boston  
Boston University School of Medicine, 1945

PEARSON, CARL MAXWELL, 750 Harrison Avenue, Boston  
Boston University School of Medicine, 1946

PETERSON, NORVELL LOUIS, 30 Evans Way, Boston  
Kansas City University of Physicians and Surgeons, 1942  
Sponsor E Allan Brown, 75 Bar State Road, Boston

PROCTOR, WALLACE, 750 Harrison Avenue, Boston  
University of California Medical School, 1935

RYDER, BROOKS, 49 East Springfield Street, Boston  
Tufts College Medical School, 1944

SAUNDERS, PETER, 4 Montrose Street, Roxbury  
Hungarian Royal University, 1937 Sponsor Sidney C Wiggins, 270 Commonwealth Avenue, Boston

SCIACCA, GUY FRANCIS, 23 Unity Court, Boston  
Middlesex University School of Medicine, 1939 Sponsor Salvatore Lima, 281 Hanover Street, Boston

SINGER, PERETZ, 63 Thomas Park, South Boston  
Middlesex University School of Medicine, 1936 Sponsor John J Todd, 587 Beacon Street, Boston

SPANGLER, ARTHUR STEPHENSON, 154 Riverway, Boston  
Harvard Medical School, 1945

STANBURY, JOHN BRUTOV, 185 Mt. Auburn Street, Cambridge  
Harvard Medical School, 1939

STINSON, ALLAN BRANDOCK, 300 Longwood Avenue, Boston  
Harvard Medical School, 1945

THALER, RICHARD WINSTON, 25 Bennet Street, Boston  
Harvard Medical School, 1945

WERNER, HENRY, 97 Strathmore Road, Brookline  
University of Vienna, School of Medicine, 1936 Sponsor Harry C. Solomon, 74 Fenwood Road, Boston

WEXLER, JACOB, 60 Seaver Street, Roxbury  
Middlesex University School of Medicine, 1935 Sponsor David B Stearns, 416 Marlboro Street, Boston

WILSON, JOHN LONG, 99 Myrtle Street, Boston  
Harvard Medical School, 1939

Charles G Shedd, *Secretary*  
422 Beacon Street, Boston

## WORCESTER

BUTLER, PHILIP SUMNER, 14 North Parkway, Worcester  
Tufts College Medical School, 1943

CASALE, WALTER, 40 Cedar Street, Worcester  
Long Island College of Medicine, 1936

CHANDLER, CHARLES FASSETT, Sterling Junction  
Harvard Medical School, 1940

MACGILPIN, HAROLD HARRINGTON, JR., 8 Suburban Road, Worcester  
University of Pennsylvania School of Medicine, 1942

MAIMQUIST, CARL YALE, JR., 4 Coventry Road, Worcester  
Yale University School of Medicine, 1946

MARTIN, WILLIAM KIRWAN JOSEPH, JR., 74 Commodore Road, Worcester  
New York Medical College, Flower and Fifth Avenue Hospitals, 1937

MORRISON, JAMES MARTIN, 14 Oberlin Street, Worcester  
St. Louis University School of Medicine, 1944

PIERCE, JAMES FRANCIS, 11 Charlotte Street, Worcester  
Georgetown University School of Medicine, 1946

SHANNON, MARY C., 334 Highland Street, Worcester  
Kansas City University of Physicians and Surgeons, 1927  
Sponsor Smith G Philips, 36 Pleasant Street, Worcester

AMIAS, ANTHONY D., JR., 7 Old Brook Drive, Worcester  
Boston University School of Medicine, 1946

Donald Hight, *Secretary*  
57 Cedar Street, Worcester

## WORCESTER NORTH

COBB, SINNEY, 3901 Eliot Road, Fort Devens  
Harvard Medical School, 1942

DESCHENES, ALBERT ALPHONSE, 72 Delisle Street, Fitchburg  
Boston University School of Medicine, 1941

GELINAS, JOSEPH ARMAND, 190 Milk Street, Fitchburg  
Laval University Faculty of Medicine, 1945

James G Simmons, *Secretary*  
30 Myrtle Avenue, Fitchburg

MASSACHUSETTS DEPARTMENT  
OF PUBLIC HEALTHCOMMUNICABLE DISEASES IN  
MASSACHUSETTS FOR AUGUST, 1948

DISEASES	RESUME		
	AUGUST 1948	AUGUST 1947	SEVEN YEAR MEDIAN
Chancroid	4	2	2*
Chicken pox	165	179	123
Diphtheria	18	17	11
Dog bite	1201	1021	1021
Dysentery bacillary	12	9	14
German measles	47	41	46
Gonorrhea	354	308	374
Granuloma inguinale	0	1	0*
Lymphogranuloma venereum	2	1	0*
Malaria	1	7	13
Measles	595	125	281
Meningitis meningococcal	6	0	5
Meningitis Pfeiffer bacillus	1	1	1
Meningitis pneumococcal	0	0	0†
Meningitis staphylococcal	0	1	0†
Meningitis streptococcal	0	1	0†
Meningitis other forms	2	1	0†
Meningitis undetermined	7	2	3†
Mumps	428	170	271
Pneumonia lobar	76	77	76
Poliomyelitis	69	80	62
Salmonellosis	12	19	22
Scarlet fever	74	72	195
Syphilis	166	187	341
Tuberculosis pulmonary	285	171	255
Tuberculosis other forms	15	10	18
Typhoid fever	6	7	5
Undulant fever	2	2	6
Whooping cough	209	475	498

\*Four-year median

†Six year median.

## COMMENT

Diseases with an incidence above the seven-year median included chicken pox, diphtheria, dog bite, measles, mumps and poliomyelitis

Diseases with an incidence below the seven-year median included salmonellosis, scarlet fever, undulant fever and whooping cough

A number of cases reported as meningitis, undetermined, poliomyelitis and lymphocytic choriomeningitis had the same clinical and spinal-fluid findings

Measles had the highest incidence for August since 1916 Mumps had the highest August incidence since it was made reportable Whooping cough continues to be reported at the lowest level since 1915

#### GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Diphtheria was reported from Arlington, 2, Boston 10, Chicopee, 1, Everett, 1, Natick, 2, Revere, 1, Somerville, 1, total, 18

Dysentery, amebic, was reported from Newton, 2, total, 2  
Dysentery, bacillary, was reported from Chelsea, 1, Waltham, 1, Worcester, 10, total, 12

Lymphocytic choriomeningitis was reported from Fitchburg, 4, Malden, 1, total, 5

Malaria was reported from Cambridge, 1, total, 1

Meningitis, meningococcal, was reported from Boston, 2, Framingham, 1, Holyoke, 1, Springfield, 1, Worcester, 1, total, 6

Meningitis, Pfeiffer-bacillus, was reported from Auburn, 1, total, 1

Meningitis, other forms, was reported from Haverhill, 1, Holden, 1, total, 2

Meningitis, undetermined, was reported from Brockton, 1, Leominster, 4, Melrose, 1, Worcester, 1, total, 7

Poliomyelitis was reported from Abington, 1, Adams, 1, Andover, 1, Ayer, 1, Becket, 1, Boston, 1, Brookline, 2, Carver, 1, Danvers, 2, Dracut, 1, Gloucester, 3, Groveland, 2, Ipswich, 1, Lincoln, 1, Middleboro, 1, New Bedford, 1, Newton, 3, Northampton, 1, Norwood, 1, Peabody, 1, Quincy, 1, Revere, 1, Salem, 3, Springfield, 3, Swampscott, 1, Waltham, 2, Watertown, 2, Wellesley, 1, West Boston, 17, West Bridgewater, 1, West Stockbridge, 1, Weston, 2, Whitman, 1, Winthrop, 1, Worcester, 5, total, 69

Salmonellosis was reported from Lowell, 2, Malden, 1, Methuen, 2, Norfolk, 6, Somerville, 1, total, 12

Septic sore throat was reported from Fall River, 1, Rutland, 1, total, 2

Tetanus was reported from Lexington 1, Newton, 1, total 2

Trichinosis was reported from Fall River, 3, Lawrence, 1, Swansea, 2, Waltham, 1, total, 7

Typhoid fever was reported from Beverly, 1, Boston, 1, Gardner, 1, Lowell, 1, New Bedford, 1, Somerset, 1, total, 6

Undulant fever was reported from Malden, 1, Warren, 1, total, 2

## BLUE CROSS — BLUE SHIELD

### THE BLUE SHIELD DOLLAR

Associated Medical Care Plans, in a recent release, presents an analysis of payments to physicians for benefits provided under the average surgical type of subscriber contract

Four types of surgical procedure — appendectomies, tonsillectomies and obstetric and gynecologic operations — account for approximately sixty cents of every dollar paid to physicians The next twenty-five cents goes to pay for approximately seventy surgical procedures Payments for x-ray and anesthesia are on the increase, owing perhaps to an increasing number of physicians entering these fields

Female subscribers cost about three times as much for surgical benefits as do male subscribers, with female dependents only slightly less expensive While these costs are due largely to obstetrics and

gynecology, female costs in general surgery are also above the average, principally on account of breast operations

Male dependents cost more than female dependents, because of herniotomies, circumcisions, fractures and dislocations, boys breaking almost exactly twice as many bones as their sisters do

## CORRESPONDENCE

### DEPRIVATION AND RESTORATION OF LICENSES

To the Editor At the meeting of the Board of Registration in Medicine held September 16, it was voted to revoke the registrations of Dr Samuel C Zundell, 332 Blue Hills Parkway, Milton, Massachusetts, and Dr Alfred J Leary, 190 Ashmont Street, Dorchester (because of ill health), and to restore the registration of Dr David Ginsburg, 505 Armour Street, Springfield, Massachusetts

GEORGE L SCHADT, M D, Secretary  
Board of Registration in Medicine

State House  
Boston

## BOOK REVIEW

*Heart A physiologic and clinical study of cardiovascular diseases* By Aldo A Luisada, M D With a foreword by Herrman L Blumgart, M D 4°, cloth, 653 pp, with 352 illustrations Baltimore The Williams and Wilkins Company, 1948 \$10.00

The disrupting effects of two world wars upon European medicine have accelerated the development of the United States as the international center of medical science. The turbulence of the political situation led in the past twenty years to the emigration of many outstanding foreign physicians Dr Luisada brought to this country some years ago the knowledge of the Italian school of medicine. It is to the benefit of American physicians that books by foreign investigators be available in English, since Americans are notoriously unwilling, or unable, to utilize material in other languages

This book is an attempt to cover the field of cardiovascular diseases, a task, as Dr Blumgart says in the foreword, that is "herculean" There are thirty-three chapters followed by a section on diets, and one on prescriptions, and inserted at the end there is a folded table of "summary of treatment in cardiovascular emergencies"

There are as many schemes of classification of cardiovascular diseases as there are authors — this one avoids the etiologic, except when correlated with the fundamental anatomicoclinical syndromes on which the classification is based The historical data and extensive bibliography make the book valuable as a reference, particularly in its use of eponyms, many of which, though unfamiliar, may help in establishing priority in description of certain syndromes

The physiologic approach to cardiovascular problems has advantages, and the schematic illustrations and descriptions of experiments with models should be useful to students

Anatomy is well covered with many figures The chapter on "Normal Functions" is followed by those on "Clinical Study" and "Technical Study" Newer methods of investigation with radioactive isotopes and cardiac catheterization will undoubtedly make much of the latter chapter of his tonical interest only, within a few years, and such procedures as diagnostic pneumomediastinum seem already so The section of phonocardiography is extensive and presents the author's notable experience in this relatively new field, and gives a practical background for those using this technique

The causes of cardiovascular diseases are considered, and this chapter precedes the descriptions of rheumatic disease, endocardial diseases, valvular defects of the left and right sides of the heart, simple shunts and complex malformations

The disturbances of rate and rhythm of the heart are illustrated with diagrams, electrocardiograms and phonocardiograms and the clinical descriptions, tests, diagnosis and treatment combined with these objective records

Diseases of the myocardium, metabolic and endocrine diseases and coronary-artery diseases are given separate chapters. Although it is obvious that detailed consideration of these conditions cannot be given in a single volume covering all cardiovascular disease, it is commendable that so much of the literature has been noted and so many procedures mentioned that can be studied in the original references.

Pericardial diseases are given twenty-seven pages, and diseases of the aorta twenty-six, whereas hypertension is covered in twelve pages. This reflects the special interests and investigations of the author, as noted in his preface. In the treatment of hypertension sodium restriction is referred to only by the statement that a "reduction of salt may be indicated." The rice diet is not mentioned. Surgical treatment is allotted less than half a page.

The final chapters cover cor pulmonale, hypotension, diseases of the arteries and veins, borderline syndromes, complex heart diseases, paroxysmal dyspnea, heart failure, the cardiac patient as an obstetric and surgical risk, drugs, the management of the cardiac patient and medical treatment of common cardiac conditions.

The book is well printed on high-grade paper in the two column to a page method that has become popular. It is so designed as to be useful to medical students, practitioners, cardiovascular specialists and reference libraries.

## BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

*Surgical Applied Anatomy*. By Sir Frederick Treves, Bart. Eleventh edition, revised by Lambart Rogers, MSc, FRCS, FRCSSE, FRACS, FACS, professor of surgery, University of Wales, and member of the Court of Examiners, Royal College of Surgeons of England. 12°, cloth, 560 pp., with 192 illustrations, including 66 in color. Philadelphia: Lea and Febiger, 1947. \$6.00.

This manual has enjoyed a long and honorable career. It first appeared in 1883, and after the death of Sir Frederick Treves was continued in succession by Sir Arthur Keith, Professor C. C. Choyce and Professor Rogers. Despite limitations of time the present edition has been revised radically. Composed and printed in Great Britain and bound in the United States, the book is well published. It was originally intended for students of surgery as a manual of applied anatomy. It should prove of value to surgeons as a quick reference source.

*The Yearbook of Psychoanalysis*. Volume 3, 1947. Managing editor, Sándor Lóran, MD 8°, cloth, 309 pp. New York: International Universities Press, 1948. \$7.50.

In this serial volume are brought together for convenient reference twenty papers, originally published in a number of different periodicals. The paper of A. Garma on psychoanalytic investigations in melancholias and other types of depressions was published originally in Italian but has been translated into English for this publication. The volume is well published and should be in all large medical libraries and in psychiatric collections.

*Mar Weather Sun*. By William F. Petersen, MD 8°, cloth, 462 pp., with 294 illustrations. Springfield, Illinois: Charles C. Thomas, 1947. \$10.00.

Dr. Petersen presents a detailed study of man in relation to the air mass in which he lives. The author summarizes the work upon the subject during the decades 1920-1930 and 1930-1940. The studies of the first decade demonstrated that the weather was an important factor in the life of man, but that progress was retarded because of the lack of encouragement from medical and scientific circles. In the second decade progress was advanced, and observations were made relating to the reaction of the normal and the sick person to weather changes. Dr. Petersen summarizes the results as follows: conditioning by the weather, whether the subject is exposed directly or sheltered in the home or hospital, the reflection

of the weather in the precipitation of diverse clinical pictures, the conditioning of genetic trends during the earliest stages of development, the conditioning of the mental reaction of the normal, and of the abnormal reaction in the psychopathic person, and the obvious reflection of the weather in births and deaths in the population at large. In 1940 the exceptional opportunity of studying daily a set of adult triplets over a period of six weeks was presented to the author, and the results of these comprehensive studies demonstrated that genetically like persons react similarly to the meteorologic environment in which they exist. Previously studies were made on isolated persons. Of importance in these studies of the triplets was the demonstration of the magnitude of the biochemical and biophysical reactions. The book is divided into five parts: the first, comprising one hundred and twenty-one pages, gives in detail the observations on the triplets; the second describes the reaction of the population in births, deaths, suicides, twinning and psychopathic admissions, based on the results of the triplet observations; the third considers man as a cosmic resonator and discusses cosmic, weather and organic rhythms, organic cycles, blood reaction, vital indexes of scarlet fever, epilepsy and death, and the trends of 1930 to 1943 applied to longer rhythms than one year; the fourth, entitled "The symphony of sun and man," considers the possible integration of human reactions and solar rhythm of long range, including the discussion of the sun and the sunspot cycle, epidemics, death, blood reaction, modification of genetic trends of conceptions, weight and length ratio of the newborn and twinning, and genius; the fifth, "The great year," is a study of the Egyptian period from 5400 B.C. to 1240 A.D., which develops the probability of long-range trends in cultures and civilizations, and their significance for the present and the future. Appended to the text are detailed individual charts of the observations on the triplets. Indexes of authors, subjects and illustrations conclude the volume. Some of the part headings are fanciful and not indicative of the contents of the chapters. There is a large amount of statistical material, including charts and curves throughout the text. The publisher has solved a difficult matter in makeup and has produced a well published volume. The book should be in all public-health collections.

*Psychosomatic Medicine: A study of the sick society*. By James L. Halliday, MD, DPH 8°, cloth, 277 pp. New York: W. W. Norton & Company, Inc., 1948. \$3.50.

This study is based on the application of psychosomatic medicine to the illnesses of communities and social groups. The author puts forward the thesis that groups may become physically ill and become sick populations, characterized by high morbidity and mortality rates, owing to mass malnutrition, infectious diseases, infestations and so forth. Likewise, a group has psychologic or social needs, and if these needs are not satisfied its psychologic or social health declines and the group becomes a sick society, he calls the medical approach to this sick society psychosocial medicine. The author would have preferred the term "social medicine" but was debarred from its use by the pre-emption of the term by others. The material in the book is largely derived from original researches—clinical, statistical and methodologic—that employed the psychosomatic approach and extended over a period of ten years. The text is divided into three main divisions: medical logic, in which some principles of etiology are discussed, psychosomatic medicine, subdivided into four chapters, in which the concept and incidence of psychosomatic affections, psychosomatic medicine and the problems of chronic and recurring illness, and the ontogenetic theory and psychosomatic affections are considered; the sick society, in six chapters, which discusses epidemiology, a declining birth rate and psychologic health, psychosocial medicine, the case of Britain as a sick society, the mining community as a sick society and problems of reintegration, including the social function of medicine and the social functions of politics. In conclusion, the author states that as social sickness is a disease the basic observations upon it are appropriately made in terms of medicine and arranged in familiar medical categories, but that much further field investigation needs to be done, before social therapeutics becomes a subject of medicine in its own right. The text is concluded with an appendix comprising notes on five chapters, including the bodily mechanism of emotion, the significance of a psychosomatic illness, social health and the United States, and the

Diseases with an incidence below the seven-year median included salmonellosis, scarlet fever, undulant fever and whooping cough

A number of cases reported as meningitis, undetermined, poliomyelitis and lymphocytic choriomeningitis had the same clinical and spinal-fluid findings

Measles had the highest incidence for August since 1916 Mumps had the highest August incidence since it was made reportable Whooping cough continues to be reported at the lowest level since 1915

#### GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Diphtheria was reported from Arlington, 2, Boston 10, Chicopee, 1, Everett, 1, Natick, 2, Revere, 1, Somerville, 1, total, 18

Dysentery, amebic, was reported from Newton, 2, total, 2  
Dysentery, bacillary, was reported from Chelsea, 1, Waltham, 1, Worcester, 10, total, 12

Lymphocytic choriomeningitis was reported from Fitchburg, 4, Malden, 1, total, 5

Malaria was reported from Cambridge, 1, total, 1

Meningitis, meningococcal, was reported from Boston, 2, Framingham, 1, Holyoke, 1, Springfield, 1, Worcester, 1, total, 6

Meningitis, Pfeiffer-bacillus, was reported from Auburn, 1, total, 1

Meningitis, other forms, was reported from Haverhill, 1, Holden, 1, total, 2

Meningitis, undetermined, was reported from Brockton, 1, Leominster, 4, Melrose, 1, Worcester, 1, total, 7

Poliomyelitis was reported from Abington, 1, Adams, 1, Andover, 1, Ayer, 1, Becket, 1, Boston, 1, Brookline, 2, Carver, 1, Danvers, 2, Dracut, 1, Gloucester, 3, Groveland, 2, Ipswich, 1, Lincoln, 1, Middleboro, 1, New Bedford, 1, Newton, 3, Northampton, 1, Norwood, 1, Peabody, 1, Quincy, 1, Revere, 1, Salem, 3, Springfield, 3, Swampscott, 1, Waltham, 2, Watertown, 2, Wellesley, 1, West Boylston, 17, West Bridgewater, 1, West Stockbridge, 1, Weston, 2, Whitman, 1, Winthrop, 1, Worcester, 5, total, 69

Salmonellosis was reported from Lowell, 2, Malden, 1, Methuen, 2, Norfolk, 6, Somerville, 1, total, 12

Septic sore throat was reported from Fall River, 1, Rutland, 1, total, 2

Tetanus was reported from Lexington 1, Newton, 1, total 2  
Trichinosis was reported from Fall River, 3, Lawrence, 1, Swansea, 2, Waltham, 1, total, 7

Typhoid fever was reported from Beverly, 1, Boston, 1, Gardner, 1, Lowell, 1, New Bedford, 1, Somerset, 1, total, 6

Undulant fever was reported from Malden, 1, Warren, 1, total, 2

## BLUE CROSS — BLUE SHIELD

### THE BLUE SHIELD DOLLAR

Associated Medical Care Plans, in a recent release, presents an analysis of payments to physicians for benefits provided under the average surgical type of subscriber contract

Four types of surgical procedure — appendectomies, tonsillectomies and obstetric and gynecologic operations — account for approximately sixty cents of every dollar paid to physicians The next twenty-five cents goes to pay for approximately seventy surgical procedures Payments for x-ray and anesthesia are on the increase, owing perhaps to an increasing number of physicians entering these fields

Female subscribers cost about three times as much for surgical benefits as do male subscribers, with female dependents only slightly less expensive While these costs are due largely to obstetrics and

gynecology, female costs in general surgery are also above the average, principally on account of breast operations

Male dependents cost more than female dependents, because of herniotomies, circumcisions, fractures and dislocations, boys breaking almost exactly twice as many bones as their sisters do

## CORRESPONDENCE

### DEPRIVATION AND RESTORATION OF LICENSES

*To the Editor* At the meeting of the Board of Registration in Medicine held September 16, it was voted to revoke the registrations of Dr Samuel C Zundell, 332 Blue Hills Parkway, Milton, Massachusetts, and Dr Alfred J Leary, 195 Ashmont Street, Dorchester (because of ill health), and to restore the registration of Dr David Ginsburg, 505 Armory Street, Springfield, Massachusetts

GEORGE L. SCHADT, M.D., Secretary  
Board of Registration in Medicine

State House  
Boston

## BOOK REVIEW

*Heart A physiologic and clinical study of cardiovascular diseases* By Aldo A Luisada, M.D With a foreword by Herrman L Blumgart, M.D 4<sup>th</sup> ed., cloth, 653 pp., with 352 illustrations Baltimore The Williams and Wilkins Company, 1948 \$10.00

The disrupting effects of two world wars upon European medicine have accelerated the development of the United States as the international center of medical science. The turbulence of the political situation led in the past twenty years to the emigration of many outstanding foreign physicians Dr Luisada brought to this country some years ago the knowledge of the Italian school of medicine. It is to the benefit of American physicians that books by foreign investigators be available in English, since Americans are notoriously unwilling, or unable, to utilize material in other languages

This book is an attempt to cover the field of cardiovascular diseases, a task, as Dr Blumgart says in the foreword, that is "herculean" There are thirty-three chapters followed by a section on diets, and one on prescriptions, and inserted at the end there is a folded table of "summary of treatment in cardiovascular emergencies"

There are as many schemes of classification of cardiovascular diseases as there are authors — this one avoids the etiologic, except when correlated with the fundamental anatomicoclinical syndromes on which the classification is based The historical data and extensive bibliography make the book valuable as a reference, particularly in its use of eponyms, many of which, though unfamiliar, may help in establishing priority in description of certain syndromes

The physiologic approach to cardiovascular problems has advantages, and the schematic illustrations and descriptions of experiments with models should be useful to students

Anatomy is well covered with many figures The chapter on "Normal Functions" is followed by those on "Clinical Study" and "Technical Study" Newer methods of investigation with radioactive isotopes and cardiac catheterization with undoubtedly make much of the latter chapter of his historical interest only, within a few years, and such procedures as diagnostic pneumomediastinum seem already so The section of phonocardiography is extensive and presents the author's notable experience in this relatively new field, and gives a practical background for those using this technique

The causes of cardiovascular diseases are considered, and this chapter precedes the descriptions of rheumatic disease, endocardial diseases, valvular defects of the left and right sides of the heart, simple shunts and complex malformations

The disturbances of rate and rhythm of the heart are illustrated with diagrams, electrocardiograms and phonocardiograms and the clinical descriptions, tests, diagnosis and treatment combined with these objective records

# NOTICES (Concluded from page 604)

## SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, OCTOBER 21

FRIDAY OCTOBER 22

\*9:00-10:00 a.m. Rice Diet Some experimental and clinical observations Dr. William B. Schwartz, Joseph H. Pratt Diagnostic Hospital

\*9:00 a.m.-12:00 m. Combined Medical and Surgical Staff Rounds Peter Bent Brigham Hospital

\*12:00 m. Clinical Conference on General Surgery Margaret Jewett Hall Mt. Auburn Hospital Cambridge

MONDAY OCTOBER 25

\*12 p.m. S.A.E. Meeting Harris Hall New England Deaconess Hospital

TUESDAY OCTOBER 26

\*12:15-1:15 p.m. Clinico-pathogenetic Conference Peter Bent Brigham Hospital

\*1:00-2:30 p.m. Pediatric Rounds Barnham Memorial Hospital for Children Massachusetts General Hospital

WEDNESDAY OCTOBER 27

\*9:00-10:00 a.m. Some Problems in Clinical Cancer Research D. Fred Homburger Joseph H. Pratt Diagnostic Hospital

\*11:00 a.m.-12:00 m. Medical Rounds Amphitheater Children's Hospital

\*12:00 m.-1:00 p.m. Clinicopathological Conference (Children's Hospital) Amphitheater Peter Bent Brigham Hospital

\*2:00-3:00 p.m. Combined Clinic by the Medical Surgical and Orthopedic Services Amphitheater Children's Hospital

\*Open to the medical profession

OCTOBER 1-MAY 20 Metropolitan State Hospital Page 418 issue of September 9

OCTOBER 15 American Trudeau Society Page 418 issue of September 9

OCTOBER 18 New England Society of Anesthesiologists Page 564 issue of October 7

OCTOBER 18-22 American College of Surgeons Page 417 issue of September 9

OCTOBER 19 South End Medical Club Page 564 issue of October 7

OCTOBER 20 Middlesex South District Medical Society Page 604

OCTOBER 20 Massachusetts Medical Legal Society Page 604

OCTOBER 20 New England Diabetes Association Page 564 issue of October 7

OCTOBER 20 New England Dermatological Society Page 50 issue of September 30

OCTOBER 27 New England Obstetrical and Gynecological Society Annual Meeting Hotel Somerset Boston

OCTOBER 27 New England Pediatric Society Page 50 issue of September 9

OCTOBER 31 and NOVEMBER 1 American Society for the Study of Arteriosclerosis Page 530 issue of September 30

NOVEMBER 1-5 American Clinical and Climatological Association Page 582 issue of April 15

NOVEMBER 3 and 4 Annual Meeting of National Committee for Mental Hygiene Inc. Page 282 issue of August 12

NOVEMBER 3-5 Seventh New England Post-graduate Assembly Copley Plaza Hotel, Boston

NOVEMBER 4-6 American Society of Anesthesiologists Page 418 issue of September 9

NOVEMBER 8-12 American Public Health Association Page 420 issue of March 18

NOVEMBER 10-12 Association of Military Surgeons of the United States Page 722 issue of May 15

NOVEMBER 12 The Use of Hormones in Breast Cancer Dr. Ira T. Vahlsing, Pentucket Association of Physicians 8:30 p.m. Haverhill.

NOVEMBER 20-23 American Academy of Pediatrics Annual Meeting Chalfonte-Haddon Hall Hotel Atlantic City New Jersey

NOVEMBER 20 Hampden District Medical Society Page 492 issue of September 23

DECEMBER 2 Suffolk Censors Meeting Page 492 issue of September 23

DECEMBER 7-9 Southern Surgical Association Annual Meeting Page 543 issue of April 8

DECEMBER 9 and 10 New York State Society of Anesthesiologists Page 4 issue of July 1

FEBRUARY 4 1940 American Board of Obstetrics and Gynecology L.C. Page 244 issue of August 5

MARCH 28-April 1 1940 American College of Physicians Page 1-8 issue of July 22

MAY 16-19, 1940 American Urological Association Baltimore Hotel Los Angeles California.

MAY 26-28 1940 American Gutter Association Hotel Lorraine Madison Wisconsin

NOVEMBER 11-17 1940 Third Inter American Congress of Radiology Page 158 issue of July 22

## DISTRICT MEDICAL SOCIETIES

### HAMPDEN

NOVEMBER 30 8:00 p.m. Academy of Medicine Springfield. Carcoma of the Breast. Dr. Grantley W. Taylor

### MIDDLESEX SOUTH

OCTOBER 20 11:30 a.m. Murphy General Hospital Waltham

### SUFFOLK

DECEMBER 2 Suffolk Censors Meeting

### WORCESTER NORTH

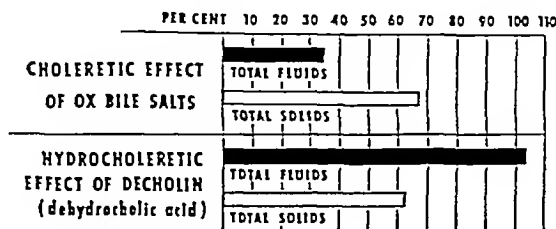
OCTOBER 27 Henry Heywood Memorial Hospital Gardner

DECEMBER 8 Leominster Hospital Leominster

FEBRUARY 25 Burbank Hospital Fitchburg

APRIL 27 Annual Meeting

# DECHOLIN HYDROCHOLERESIS Encourages Biliary Tract Drainage



● Percentage Increase in Composition and Quantity of Bile Flow

Ivy A. C. et al. Am J Dig Dis 7:333 (Aug) 1940

## HYDROCHOLERESIS—

an increased production of thin liver bile—is a desirable approach to therapy of non-obstructive biliary tract disturbances

## DECHOLIN—

by producing an increased flow of bile—washes stagnant infected bile from the intra-hepatic and extrahepatic biliary passages, removing pus-laden material and discouraging the ascent of infection

## HOW SUPPLIED

Decholin in 3 3/4 gr tablets Packages of 25, 100, 500 and 1000

**Decholin**  
BRAND REG U S PAT OFF  
(DEHYDROCHOLIC ACID)



**AMES COMPANY, INC.**  
ELKHART, INDIANA

incidence of psychosomatic affections in underground miners. A good index concludes the volume. The monograph is well published and should be in all public-health collections.

*You and Your Doctor*. A frank discussion of group medical practice and other modern trends in American medicine. By Benjamin F. Miller, M.D., clinical professor of medicine, George Washington University School of Medicine, and research associate in medicine, National Research Council. 8°, cloth, 183 pp. New York: Whittlesey House, 1948. \$2.75.

In this popular book Dr. Miller analyzes the various aspects of medical practice of the present time, including the status of the general practitioner, the diagnostician, group clinics and the modern hospital. He also discusses freedom from emotional illness, periodic medical checkups, post-mortem examinations, medical education and research, and interstate medical care. On the national level is noted the need of an adequate disaster service preferably operated by a federal agency. Under the heading "Who Should Administer National Medical Care?" Dr. Miller considers impartially the agencies best able to promote and operate a national plan, and although a member of the American Medical Association and favoring it in his analysis, he is convinced that the United States Public Health Service is at present in the best position to operate a plan co-ordinating preventive medicine, curative or clinical medicine and medical research, the three major essentials of such a national plan. If the Public Health Service cannot assume the promotion and operation of a national plan, Dr. Miller suggests that a special federal agency be established for that purpose. The book is well published, except that it lacks an index. The volume should be in all public-health collections.

*Textbook of Gynecology*. By Emil Novak, M.D., assistant professor of gynecology, Johns Hopkins University School of Medicine, and gynecologist, Bon Secours and St. Agnes Hospitals, Baltimore. Third edition. 8°, cloth, 742 pp., with 484 illustrations. Baltimore: The Williams and Wilkins Company, 1948. \$8.00.

Dr. Novak has brought up to date this third edition of his standard textbook on gynecology. A considerable number of illustrations, some in color, have been added. Dr. H. S. Everett has revised his chapter on female urological conditions of special interest to the gynecologist. A list of selected references is appended to each chapter, and there is a good index. The publishing is well done. The book should be in all medical libraries and in the private collections of gynecologists and physicians interested in the subject.

*Clinical Toxicology*. By Clinton H. Tienes, M.D., Ph.D., professor of pharmacology and head of the Department of Pharmacology and Toxicology, School of Medicine, University of Southern California, Los Angeles, an attending pathologist (toxicology), Los Angeles County Hospital, and Thomas J. Haley, Ph.D. Second edition. 12°, cloth, 373 pp. Philadelphia: Lea and Febiger, 1948. \$3.50.

The second edition of this popular manual for students and general practitioners has been thoroughly revised and enlarged to the extent that the text has been entirely reset and printed from new type. Sections have been added on dicoumarol, heparin, thiouracil, DDT, gold, BAL and streptomycin. Material has also been added on proteins, amino acids and vitamins in the treatment and prevention of poisoning. The section on the chemical identification of poisons has been enlarged to include tables, comparing color and other reactions, as well as new tests for arsenic, the barbiturates, cyanide and the sulfonamides. The nomenclature has been brought into line with the thirteenth edition of *United States Pharmacopoeia*, the eighth edition of the *National Formulary* and the 1947 edition of *New and Nonofficial Remedies*. The material is well arranged, and the volume is well published. The manual should prove useful as a reference source to libraries and to all persons interested in the subject.

*Organic Form and Related Biological Problems*. By Samuel J. Holmes. 8°, cloth, 169 pp. Berkeley: University of California Press, 1948. \$5.00.

This small volume practically consists of thirteen separate essays on closely related subjects in biology. The short essay on the regeneration of blood and its bearing on morphogenic theory and the long one on cancer as a biologic problem are

of direct medical significance. In the essay on cancer the author presents a comprehensive survey of the current theories on the causation of cancer, with emphasis on genetic factors. Likewise of interest is the article on autocatalytic enzymes and the origin of life. Six of the articles were published previously in scientific periodicals. A bibliography arranged by chapters follows the text, and an index concludes the volume. The text is well written, and although it makes admittedly difficult reading is recommended for all medical libraries and, naturally, for biologic collections. It should be available to all persons interested in carcinogenesis. The book is well published.

## NOTICES

### ANNOUNCEMENTS

Dr. Jackson M. Thomas announces the opening of an office at 311 Beacon Street, Boston, for the practice of psychiatry.

Dr. James L. Tullis announces the opening of an office at 1101 Beacon Street, Brookline, for the practice of internal medicine and hematology.

### MASSACHUSETTS MEDICO-LEGAL SOCIETY

The fall, winter and spring meetings of the Massachusetts Medico-Legal Society will be held, respectively, on Wednesday, October 20, 1948, in the Magrath Library, Building E, Harvard Medical School, Boston, on Wednesday, February 9, 1949, in the Magrath Library, Building E, Harvard Medical School, Boston, and on Wednesday, May 25, 1949, in the Worcester Memorial Auditorium, Worcester. The program for the fall meeting at 2:30 p.m. on October 20 is as follows:

#### Business Meeting

Air Embolism as a Complication of Abortion. Leroy T. Stokes, M.D., and Richard Ford, M.D.

Acute Isolated Myocarditis. David Dow, M.D., Daniel J. Kiley, M.D., and Michael Luongo, M.D.

Unexpected Death from Ben-ben Heart Disease. Walter W. Jetter, M.D.

Suicidal Gunshot Injury. James H. McCann, M.D., and Russell S. Fisher, M.D.

#### Collation

The following amendment to the by-laws, as proposed by the Standing Committee, will be considered:

That Article 1, Paragraph 2, of the by-laws be amended by the addition of the words "or honorary," so as to read as follows: "The Society may, at any stated meeting, elect to associate or honorary membership such persons distinguished in medical, legal or technical science as the Standing Committee, acting as a nominating committee, may recommend."

### MIDDLESEX SOUTH DISTRICT MEDICAL SOCIETY

A meeting of the Middlesex South District Medical Society will be held at the Murphy General Hospital, Waltham, on Wednesday, October 20.

#### PROGRAM

11:30 a.m. Business

12:00 noon Clinical papers "Management of Hyperthyroidism" by Colonel Otto L. Churney, M.C., and Lieutenant Colonel Ralph L. Cox, M.C.

1:00 p.m. Luncheon

Future meetings will be held on December 6, 1948, at Sanders Theater, Cambridge, on January 26, 1949, at Newton-Wellesley Hospital, and on April 20, 1949 (annual meeting), at the Hotel Continental, Cambridge. The December meeting will consist of a symposium on diabetes and will be a joint meeting with Suffolk, Norfolk and Middlesex South in connection with National Diabetes Week.

(Notices concluded on page xiv)

# The New England Journal of Medicine

Copyright 1948 by the Massachusetts Medical Society

Volume 239

OCTOBER 21, 1948

Number 17

## HEPATIC COMA\*

### Clinical and Laboratory Observations on Forty Patients

T LYNCH MURPHY, M.D.,† THOMAS C CHALMERS M.D.,‡ RICHARD D ECKHARDT M.D.,§ AND  
CHARLES S DAVIDSON, M.D.¶

BOSTON

**P**ROLONGED coma has been recognized as a frequent terminal event of both acute hepatic necrosis and chronic hepatic fibrosis. Frerichs,<sup>1</sup> in 1860, described the terminal mental changes in patients with acute yellow atrophy and with cirrhosis of the liver.

Cases have occurred to me in which individuals who for a long period have suffered from cirrhosis of the liver have suddenly presented a series of morbid symptoms which are foreign to that disease. They have become unconscious, and have been afterwards seized with noisy delirium, from which they passed to deep coma, and in this state have died. In most cases, slight jaundice made its appearance at the same time.

Frerichs ascribed the mental symptoms to hepatic insufficiency with a decreased output of bile and termed the condition "acholia." Since that time little progress has been made in elucidating the pathological physiology of the condition, and confusion has arisen concerning the clinical features and laboratory findings. In this report attention is drawn to certain of the clinical manifestations, several etiologic factors are suggested, and the use of various therapeutic measures is evaluated.

## MATERIAL

Forty patients were studied who died in coma and who both clinically and pathologically had severe primary liver disease. All were observed during life in the years 1945 and 1946. The coma, which occurred after a variable period of decreasing alert-

ness and which lasted from twelve hours to six days, was the outstanding feature. No cases are included of metastatic liver disease, obstructive biliary-tract disease or massive gastrointestinal hemorrhage severe enough to cause death in shock. A number of otherwise acceptable cases were excluded because a pathological diagnosis was not made.

The cases so selected fall into two groups, equal in number: "uncomplicated" hepatic coma, in which no cause for death other than liver disease was found, and "complicated" hepatic coma, in which the patient had, in addition to severe liver disease, some major complication that may have played an important part in precipitating the coma (Table 1).

Pathological examination consisted of complete autopsy in 29, abdominal exploration and liver biopsy in 8, and punch biopsy of the liver in the remaining 3 cases. In the uncomplicated cases there were 15 of portal cirrhosis, 2 of healed acute yellow atrophy, and 1 each of subacute yellow atrophy, acute yellow atrophy and acute alcoholic hepatitis. In the group with complication there were 17 cases of portal cirrhosis, 2 of healed acute yellow atrophy, and 1 of advanced fatty metamorphosis of the liver.

## RESULTS

### *Uncomplicated Hepatic Coma*

The 20 patients in this group, in whom no cause for death was found other than severe liver disease, were from thirty-five to seventy-two years of age with almost half in the sixth decade, 12 were men. Six of the patients denied the use of any alcohol whereas 3 said that they had consumed no more than an occasional glass of beer or whisky. The remaining 11 admitted consuming at least 2 quarts of beer or a pint of whisky a day for years. Characteristically, they ate poorly when drinking. A summary of the pertinent findings in the history and

\*From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital and the Department of Medicine, Harvard Medical School.

This work was supported in part by a grant from the Abbott Laboratories, North Chicago, Illinois, and in part by a grant given by the Ella Sachs Plotz Foundation in recognition of Dr. Francis W. Peabody's services to the Foundation.

†Assistant in gastroenterology, Henry Ford Hospital; formerly research fellow in medicine, Harvard Medical School; research fellow, Thorndike Memorial Laboratory, Boston City Hospital; assistant in medicine, Boston City Hospital.

‡Assistant in medicine, Harvard Medical School; junior visiting physician, Boston City Hospital.

§Research fellow in medicine, Harvard Medical School; chief research fellow, Thorndike Memorial Laboratory, Boston City Hospital; assistant in medicine, Boston City Hospital.

¶Associate in medicine, Harvard Medical School; junior visiting physician and associate director, Second and Fourth Medical Services, Boston City Hospital; associate physician, Thorndike Memorial Laboratory, Boston City Hospital.

70th Year

## RING SANATORIUM AND HOSPITAL

ARLINGTON HEIGHTS, MASS

For the diagnosis, care and treatment of mental  
nervous and chronic medical diseases

Facilities for all accepted therapeutic measures  
including artificial fever and shock therapy

Outpatient department for referred cases only  
Moderate all-inclusive rates

CHARLES E. WHITE, M D  
Medical Director

HALLAM T. RING, Administrator

163 Hillside Avenue

Tel AR 5-0081

## WESTWOOD LODGE

Incorporated

A modern sanitarium for the treatment and care  
of mental and nervous disorders by a staff experi-  
enced in psychotherapy, electro-shock therapy  
and other psychiatric treatments

Homelike atmosphere in quiet country surround-  
ings near Boston. Tennis court and occupational  
therapy building on the grounds. Other recrea-  
tional facilities available near by for suitable cases

SIDNEY M. BUNKER, M D, Superintendent

MARTHA BRUNNER, M D, Psychiatrist

WILLIAM J. HAMMOND, Business Manager

WESTWOOD, MASSACHUSETTS

## WOODSIDE COTTAGES

FRAMINGHAM, MASS

A sanitarium specially adapted for nervous  
and convalescent patients who need rest and  
upbuilding in normal surroundings

No committed mental cases

ARTHUR H. WARD, M D, Medical Director

## WISWALL SANATORIUM

203 GROVE ST., WELLESLEY, MASS

For the care of mild mental and nervous  
patients in country surroundings. Small  
grouping allows a homelike atmosphere  
and personal contact

E. H. WISWALL, M D  
Superintendent

HALE POWERS, M D  
Resident Physician

Tel WE 5-0261

## ADAMS HOUSE

(ADAMS NERVINE HOSPITAL)

Established 1877

A day sanitarium  
A resident sanitarium

For the psychoneuroses only  
For psychotherapy only

Not for commitment  
Not for the psychotic

JAMES MARTIN WOODALL, M D  
Medical Director

990 Centre Street, Jamaica Plain  
Boston 30, Massachusetts

## PERKINS SCHOOL

LANCASTER, MASS

Devoted to the scientific understanding and  
education of children of retarded development.  
Five homelike and attractive buildings sur-  
rounded by 85 acres of campus and gardens

FRANKLIN H. PERKINS, M D

## Baldpate, Inc.

Georgetown, Mass.

GEO 2131 — Boston Office KE 6-8100

For the treatment of psychoneuroses,  
personality disorders, psychoses, alco-  
holism and drug addiction

Psychotherapy is the basis of treatment,  
other methods such as shock therapy,  
malaria and fever box are used when  
indicated

Occupation under a trained therapist,  
diversions and outdoor activities

GEORGE M. SCHLONER, M D  
Medical Director

## GLENSIDE

JAMAICA PLAIN, BOSTON, MASS.

A small, attractively located sanitarium for  
nervous, mild mental or chronic illnesses.

MADELL D. ORDWAY, M D  
6 Parley Vale Tel JA 4-0044

## DAVID MEMORIAL NURSING HOME

BROOKLINE 46, MASS

S. D. COHEN, R N, Sup't  
Convalescents — Invalid-Elderly  
Special and diabetic diets

61 Park Street

BE 2-3530

# SPEECH DEFECTS

are usually correctable. All kinds of speech defects are being success-  
fully treated. Individual instruction. Write for descriptive booklet.  
S. D. Robbins, INST FOR SPEECH CORRECTION, Inc.  
Formerly Boston Stammerers' Institute — Founded 1867  
419 Boylston Street, Boston Tel KE 6-6800

## Channing Sanitarium

ESTABLISHED 1879

A pleasant country community of cottages built for the  
homelike care and treatment of nervous patients. Electro-  
shock therapy to selected cases

Occupational therapy Tennis court Sports building

JACKSON M. THOMAS, M D, Superintendent  
CATHERINE ARMSTRONG, M D, Resident Physician

WELLESLEY, MASSACHUSETTS

Telephone — WE 5-0464

## Bournewood Hospital

300 SOUTH STREET, BROOKLINE, MASSACHUSETTS  
Established 1884

A private hospital for a limited number of cases of mental  
and nervous diseases. Pleasant country surroundings in  
metropolitan Boston. Facilities for modern treatment  
and outpatient service

S. GAGNON, M D  
Superintendent

A. FINESINGER, M D  
Psychiatrist

Post Office, Chestnut Hill 67

J. P. THORNTON, M D  
Director of Clinical Psychiatry

C. SALTZMAN, M D  
Psychiatrist

Telephone PA 7-0300

# The New England Journal of Medicine

Copyright 1948 by the Massachusetts Medical Society

Volume 239

OCTOBER 21, 1948

Number 17

## HEPATIC COMA\*

### Clinical and Laboratory Observations on Forty Patients

T LYNCH MURPHY, M.D.,† THOMAS C CHALMERS, M.D.,‡ RICHARD D ECKHARDT, M.D.,§ AND  
CHARLES S DAVIDSON, M.D.¶

BOSTON

**P**ROLONGED coma has been recognized as a frequent terminal event of both acute hepatic necrosis and chronic hepatic fibrosis. Frerichs,<sup>1</sup> in 1860, described the terminal mental changes in patients with acute yellow atrophy and with cirrhosis of the liver.

Cases have occurred to me in which individuals who for a long period have suffered from cirrhosis of the liver have suddenly presented a series of morbid symptoms which are foreign to that disease. They have become unconscious, and have been afterwards seized with noise and delirium, from which they passed to deep coma, and in this state have died. In most cases, slight jaundice made its appearance at the same time.

Frerichs ascribed the mental symptoms to hepatic insufficiency with a decreased output of bile and termed the condition "acholia." Since that time little progress has been made in elucidating the pathological physiology of the condition, and confusion has arisen concerning the clinical features and laboratory findings. In this report attention is drawn to certain of the clinical manifestations, several etiologic factors are suggested, and the use of various therapeutic measures is evaluated.

## MATERIAL

Forty patients were studied who died in coma and who both clinically and pathologically had severe primary liver disease. All were observed during life in the years 1945 and 1946. The coma, which occurred after a variable period of decreasing alert-

ness and which lasted from twelve hours to six days, was the outstanding feature. No cases are included of metastatic liver disease, obstructive biliary-tract disease or massive gastrointestinal hemorrhage severe enough to cause death in shock. A number of otherwise acceptable cases were excluded because a pathological diagnosis was not made.

The cases so selected fall into two groups, equal in number: "uncomplicated" hepatic coma, in which no cause for death other than liver disease was found, and "complicated" hepatic coma, in which the patient had, in addition to severe liver disease, some major complication that may have played an important part in precipitating the coma (Table 1).

Pathological examination consisted of complete autopsy in 29, abdominal exploration and liver biopsy in 8, and punch biopsy of the liver in the remaining 3 cases. In the uncomplicated cases there were 15 of portal cirrhosis, 2 of healed acute yellow atrophy, and 1 each of subacute yellow atrophy, acute yellow atrophy and acute alcoholic hepatitis. In the group with complication there were 17 cases of portal cirrhosis, 2 of healed acute yellow atrophy, and 1 of advanced fatty metamorphosis of the liver.

## RESULTS

### *Uncomplicated Hepatic Coma*

The 20 patients in this group, in whom no cause for death was found other than severe liver disease, were from thirty-five to seventy-two years of age with almost half in the sixth decade, 12 were men. Six of the patients denied the use of any alcohol, whereas 3 said that they had consumed no more than an occasional glass of beer or whisky. The remaining 11 admitted consuming at least 2 quarts of beer or a pint of whisky a day for years. Characteristically, they ate poorly when drinking. A summary of the pertinent findings in the history and

\*From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital and the Department of Medicine, Harvard Medical School.

†This work was supported in part by a grant from the Abbott Laboratories, North Chicago, Illinois and in part by a grant given by the Ella Sachs Plotz Foundation in recognition of Dr. Francis W. Peabody's services to the Foundation.

‡Assistant in gastroenterology, Henry Ford Hospital; formerly research fellow in medicine, Harvard Medical School; research fellow, Thorndike Memorial Laboratory, Boston City Hospital; assistant in medicine, Boston City Hospital.

§Assistant in medicine, Harvard Medical School; junior visiting physician, Boston City Hospital.

¶Research fellow in medicine, Harvard Medical School; chief research fellow, Thorndike Memorial Laboratory, Boston City Hospital; assistant in medicine, Boston City Hospital.

\*Associate in medicine, Harvard Medical School; junior visiting physician and associate director, Second and Fourth Medical Services, Boston City Hospital; associate physician, Thorndike Memorial Laboratory, Boston City Hospital.

physical examination is presented in Table 2. On admission 5 patients had been jaundiced for from one to eight weeks. Abdominal swelling for one week to eleven months was observed by 13 patients, of whom 4 had had an abdominal paracentesis before admission.

Patients with severe hepatic cirrhosis exhibit to a variable degree alteration in intellectual function and personality. Loss of affect and a defect

senting increasing mental depression to the final stage of deep coma.

Although detailed neurologic examinations were not done, it was obvious that 17 of the patients presented some change in the state of consciousness on admission to the hospital, and in 7 cases mental or neurologic symptoms were the chief reason for admission. Six of these 7 patients admitted with lethargy, stupor or coma were dead

TABLE 1 *Identifying Data and Pathological Diagnoses in 40 Patients Dying in Liver Coma*

CASE No.	AGE	SEX	HISTORY OF CHRONIC ALCOHOLISM*	DURATION OF HOSPITALIZATION	DURATION OF COMA	PATHOLOGICAL DIAGNOSES	
	yr			days	days	LIVER	ADDITIONAL
<i>Uncomplicated coma</i>							
1	54	M	+	5	3	Laennec's cirrhosis	Terminal bronchopneumonia
2	43	F	++++	9	3	Laennec's cirrhosis	—
3	63	M	+	17	1	Healed acute yellow atrophy	Hypertensive heart disease
4	52	M	++++	17	6	Laennec's cirrhosis	Terminal bronchopneumonia
5	66	M	0	11	5	Laennec's cirrhosis	—
6	58	M	+	16	1	Subacute yellow atrophy	Chronic cholecystitis
7	59	F	0	17	6	Laennec's cirrhosis	Duodenal ulcer terminal bronchopneumonia
8	48	M	++++	49	4	Laennec's cirrhosis	Arteriosclerotic heart disease decompensated
9	49	M	++++	60	1	Laennec's cirrhosis	Rheumatic heart disease
10	70	F	0	15	2	Laennec's cirrhosis	Terminal bronchopneumonia
11	57	F	0	5	1	Healed acute yellow atrophy	—
12	52	M	++++	150	1	Laennec's cirrhosis	—
13	48	M	++++	75	4	Laennec's cirrhosis	—
14	58	M	++++	100	5	Laennec's cirrhosis	Healed bacterial endocarditis
15	52	M	++++	14	2	Laennec's cirrhosis	Terminal bronchopneumonia
16	72	F	0	25	1	Laennec's cirrhosis	Hypertensive and arterio sclerotic heart disease
17	63	M	+++	3	1	Laennec's cirrhosis	—
18	35	F	++++	1	1	Acute alcoholic hepatitis	—
19	68	F	0	2	2	Acute yellow atrophy	—
20	46	F	++++	2	1	Laennec's cirrhosis	—
<i>Complicated coma</i>							
21	39	M	++++	1	1	Laennec's cirrhosis	Pneumococcal pneumonia
22	50	M	++++	11	3	Laennec's cirrhosis	Pneumococcal pneumonia
23	52	M	++++	2	2	Laennec's cirrhosis	Pneumococcal pneumonia
24	50	M	0	1	2	Laennec's cirrhosis	Pneumonia and meningitis due to Friedlander's bacillus
25	48	F	++	3	3	Laennec's cirrhosis	Pneumococcal pneumonia
26	33	M	++++	1	1	Advanced fatty metamorphosis	Pneumococcal pneumonia
27	69	M	++++	3	3	Laennec's cirrhosis	Pneumococcal pneumonia
28	50	F	++++	30	3	Laennec's cirrhosis	Miliary tuberculosis
29	44	M	++++	7	5	Laennec's cirrhosis	Miliary tuberculosis
30	52	M	++++	28	2	Laennec's cirrhosis	Pulmonary tuberculosis
31	44	F	++++	12	12	Laennec's cirrhosis	Miliary tuberculosis with meningitis
32	70	M	++++	3	3	Laennec's cirrhosis	Rheumatic heart disease with bacterial endocarditis and meningitis
33	62	F	++++	11	3	Laennec's cirrhosis	Acute bacterial endocarditis with meningitis
34	47	F	0	30	1	Laennec's cirrhosis	Ruptured gastric varix
35	56	M	++	70	2	Healed acute yellow atrophy	Ruptured esophageal varix
36	60	M	++++	3	1	Laennec's cirrhosis primary hepatoma	Cerebral metastases with hemorrhage
37	38	F	++++	106	6	Healed acute yellow atrophy	Peritonitis following insertion of peritoneal button
38	54	M	++++	120	2	Laennec's cirrhosis	Peritonitis following insertion of peritoneal button
39	42	M	++++	45	4	Laennec's cirrhosis	Peritonitis following insertion of peritoneal button
40	44	M	++++	12	2	Laennec's cirrhosis	Peritonitis

\*0 to +++++

in judgment are usually outstanding. Thus, the jaundiced, pot-bellied cirrhotic patients are usually the jovial clowns of the ward. Many of them leave the hospital time and again, insisting that they are perfectly well in spite of obvious edema, ascites and jaundice. At times, however, they are apathetic or negativistic. Hepatic coma takes its departure from this base line, variable as it is from patient to patient, and develops slowly through phases repre-

within five days, otherwise, there was no correlation between initial mental changes and duration of hospitalization, which ranged from one to a hundred and fifty days. Twelve of the patients in the entire group of 20 died within four days after admission, and only 5 were living after twenty days.

The changes in consciousness followed a rather constant sequence from lethargy to noisy confusion,

and finally to coma. Thus, lethargy and drowsiness marked the onset in 13 patients, who slept most of the time and were disinclined to eat or talk, but were easily aroused and were oriented as to person, place and time. An adequate intake of food could usually be maintained in this phase only by tube or parenteral feeding. The rate of progression of the mental changes was variable, in fact, several patients passed through one or more periods of drowsiness and confusion before coma ensued.

Confusion, characteristically noisy, superseded the period of lethargy after a few days to several weeks, although in 5 patients preceding lethargy was not observed. In 8 patients the confusion was minimal, at times being manifested by a harmless wandering, particularly at night. Frank hallucinations were distinctly rare. Hypnotics were given to most of the patients who exhibited this disturbed state, and in 10 patients were followed by a deep sleep, which merged imperceptibly into coma. Paraldehyde was the most frequently used sedative, being given to 7 patients. The dose, administered orally or intramuscularly, varied from 6 to 68 cc given in from one to six doses. The largest individual dose was 14 cc, which was repeated in two hours. Of these 7 patients who received paraldehyde, 1 also received morphine sulfate and 1 a barbiturate. Because of severe abdominal pain, 1 patient received repeated doses of demerol, and 1, morphine sulfate. Another patient received repeated doses of paregoric because of persistent diarrhea.

Death occurred after twelve hours to six days of deep coma, although 14 patients died within the first two days. In our experience deep coma occurring spontaneously has invariably been fatal. The patients appeared as though they were merely sleeping, made no purposeful voluntary movements and responded less and less to painful stimuli. Thus, the comatose state was remarkable in the paucity of clinical signs other than the mental state, which almost alone distinguished it from the precoma period. The signs of liver disease remained essentially unchanged except for the appearance of clinical jaundice in 4 patients not previously jaundiced. Six patients were not jaundiced at death. The temperature, pulse and respiratory rate gradually rose during the coma, and in 5 patients the rise was associated with a terminal bronchopneumonia. Deep, regular respiration, particularly early in the coma, was one of the most characteristic observations. The blood pressure, usually normal or slightly low before the onset of coma, fell during coma and in 4 patients was below 90 systolic, 60 diastolic.

The pertinent laboratory data before and during coma are presented in Table 3. There was little change in the hemoglobin concentration (Sahli). The total white-cell count generally rose terminally so that it was below 5000 in only 2 cases, being

between 10,000 and 20,000 in 6 and greater than 20,000 in 3. In spite of presumably adequate fluid intake, oliguria was the rule during coma and was reflected by a moderate rise in the blood nonprotein nitrogen concentration in the 15 patients in whom the determination was made. The plasma carbon dioxide combining power was usually moderately reduced, although in 2 patients somewhat high values were found. In half the patients the blood sugar (Folin-Wu method) was determined, and in no case was a dangerously low value found. The

TABLE 2 Pertinent Findings on Admission in 40 Patients Dying in Liver Coma

FINDINGS	UNCOMPLICATED COMA*		COMPLICATED GROUP*	
	NO OF CASES	PER CENTAGE	NO OF CASES	PER CENTAGE
Anorexia	15	75	14	70
History of jaundice	5	25	9	45
Jaundice on physical examination	10	50	9	45
History of ascites	15	65	6	30
Ascites on physical examination	16	80	6	30
History of edema	10	50	5	25
Edema on physical examination	12	60	7	35
Abdominal pain	2	25	6	30
Palpable liver	9	45	15	65
Palpable spleen	5	15	2	10
Collateral abdominal veins	11	55	5	25
Spider angiomas	11	55	10	50
History of peripheral neuritis		25	4	20
History of hematemesis	3	15	2	10

\*Each group comprised 20 patients.

lowest being 68 mg per 100 cc. The abnormally high values in 3 cases were found after recent intravenous dextrose or tube feeding.

As measurements of liver function, the serum bilirubin,<sup>2</sup> thymol turbidity,<sup>3, 4</sup> cephalin cholesterol flocculation<sup>5\*</sup> and plasma prothrombin concentration<sup>6\*</sup> were determined. Although these studies usually revealed evidence of severe liver disease, there were no consistent or striking changes between those made before and during coma (Table 3). The urine urobilinogen was extremely variable although in a few cases the nonurobilinogen Ehrlich-reacting substances<sup>7</sup> were increased in the urine to exceptionally high values †.

The blood alpha amino nitrogen concentration<sup>8</sup> was determined in 5 cases during coma, and values varied from 3.6 to 4.9 mg per 100 cc of serum, all within the normal range. Amino acid tolerance tests in 4 of these patients were previously reported and showed only slightly higher blood concentrations of alpha amino nitrogen four hours after the infusion than those of normal subjects.<sup>9</sup>

Blood tyrosol (free phenol) values were determined by the method of Bernhart and Schneider,<sup>10</sup> as modified by Roen,<sup>11</sup> and were found to be either normal or somewhat elevated but did not differ significantly from values obtained in the same pa-

\*Determined at the Boston City Hospital Surgical Research Laboratory. Dr. Stephen J. Maddock, director.

†These urinary chromogens are poorly understood. The general term urobilinogen is used to designate them. Their chief constituent seems to be indol acetic acid.

tients before coma or in other patients with cirrhosis not in coma. This is in contrast to a small group of patients with uremia in whom the values were consistently elevated, as reported by others.<sup>12</sup>

The spinal fluid was characteristically clear, under normal pressure and without cells. Small amounts of bilirubin (0.1 to 0.4 mg per 100 cc) appeared in the spinal fluid occasionally, with extreme jaundice (bilirubin concentration of from 13 to 20 mg per 100 cc of serum).

Admission orders for all conscious patients included a high-protein, high-calorie diet, which was supplemented with brewer's yeast (40 gm per day), oral niacin (50 to 150 mg per day) and subcu-

an eggnog\* or a mixture of milk and a liver protein preparation†. They were well tolerated.

Parenteral dextrose in amounts from 1 to 3 liters daily and in concentrations of from 5 per cent to 20 per cent was administered to 14 of the 20 patients. Vitamins C, K and the B complex (thiamine, riboflavin, nicotinamide, pyridoxine and pantothenic acid), prepared for parenteral use, were usually added to the dextrose solution. The daily intake of these vitamins was usually very high, 1 or 2 ampoules‡ being used daily. In addition, each patient received from 50 to 150 mg of thiamine, subcutaneously, daily. Six of the patients were given 10 or 20 cc of unrefined liver extract daily in the

TABLE 3 Laboratory Data in Patients Dying in Uncomplicated Liver Coma

CASE No	HEMOGLOBIN		WHITE CELL COUNT		BLOOD NON-PROTEIN NITROGEN		BLOOD CARBON DIOXIDE COMBINING POWER		BLOOD SUGAR	
	ON ADMISSION* %	DURING COMA* %	ON ADMISSION* $\times 10^3$	DURING COMA* $\times 10^3$	ON ADMISSION* mg/100 cc	DURING COMA* mg/100 cc	ON ADMISSION* vol %	DURING COMA* vol %	ON ADMISSION* mg/100 cc	DURING COMA* mg/100 cc
1	104	—	17	22	25	44	—	31	—	—
2	58	54	9	8	25	35	—	46	110	235‡
3	98	—	8	11	31	65	—	31	110	—
4	58	60	6	19	29	70	42	45	99	110
5	53	58	5	9	30	51	32	32	125	171
6	91	95	5	9	31	62	—	—	—	100
7	75	—	5	22	33	45	45	36	—	144
8	78	—	8	18	36	70	—	25	114	—
9	75	68	4	4	25	74	44	34	100	—
10	48	75	5	14	37	39	41	—	—	—
11	77	70	8	—	27	57	—	—	—	—
12	78	—	6	—	28	—	—	—	—	—
13	80	120	5	52	25	52	—	40	—	95
14	80	—	9	—	34	40	—	—	—	—
15	72	73	12	15	25	65	—	27	—	82
16	95	88	3	4	26	47	—	40	—	190‡
17	—	65	—	8	—	34	—	68	—	—
18	—	84	—	16	—	80	—	44	—	68
19	—	95	—	9	—	98	—	55	—	300‡
20	—	55	—	6	—	28	—	61	—	—

\*The intervals between the data on admission and those obtained during coma are shown in Table 1.

†Icteric index of 35.

‡Icteric index of 75.

§Shortly after intravenous administration of dextrose.

¶Icteric index of 85.

||Icteric index of 90.

taneous thiamine (50 to 150 mg per day). However, most of these patients ate poorly, and only 3 of the entire group of 20 were thought to be consuming an adequate diet at the onset of the coma.

Therapeutic measures during coma were directed toward the prevention of infection, especially bronchopneumonia, and the maintenance of the patient's nutrition.<sup>13</sup> In an effort to control infection, chemotherapeutic agents were used liberally, penicillin being administered to 14 of the patients in this group.

An adequate intake of nutrients during coma was provided either by stomach tube or parenterally, or both. Although the possibility of inducing bleeding from esophageal varices by a stomach tube (Levin type) exists, we have never seen this complication. Tube-feeding formulas made use of either

intravenous infusion mixture. Two liver-extract preparations were used, one a standard preparation§ and the other¶ prepared specifically for intravenous use.<sup>15</sup> Both preparations were well tolerated, neither flushing nor pyrogenic reactions being observed with the method of administration used. In a few patients very large amounts (50 to 100 cc) of the latter preparation were administered. No

\*One quart contains 700 cc of whole milk, 3 eggs, 40 gm of sugar and 150 gm of skimmed milk powder.

†Ledinac, is furnished by the Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York.

‡Solu B (furnished by the Upjohn Company, Kalamazoo, Michigan) containing 10 mg of thiamine, 10 mg of riboflavin, 5 mg of pyridoxine, 50 mg of calcium pantothenate and 250 mg of nicotinamide. Betasymplex (Winthrop) containing 10 mg of thiamine, 5 mg of riboflavin, 5 mg of pyridoxine, 5 mg of calcium pantothenate and 50 mg of nicotinamide.

§Solution Liver Extract crude, Lilly 2 injectable USP units per cubic centimeter provided by Eli Lilly and Co., Indianapolis, Indiana.

¶Intraheptol provided by Lederle Laboratories Division, American Cyanamid Co., Pearl River, New York.

change in clinical condition that could be attributed to this form of therapy was observed

From 45 to 100 gm of one of two protein hydrolysate solutions\* were added to the intravenous infusions of 8 of the 20 patients. No pyrogenic reactions or apparently harmful effects were observed from the administration of these preparations in the presence of severe liver disease. In fact, as mentioned above, amino acid "load tests" have given no evidence of a significantly reduced tolerance in patients with severe liver disease as compared with that in normal persons.<sup>9</sup>

Central-nervous-system stimulants and analeptics were given to many of the patients. Caffeine,

Complicated Coma

Although the 20 patients in this group all died in coma and at autopsy had severe liver disease, they are considered as a separate group because each was complicated by another major pathologic state (Table 1). Seventeen patients had severe infection. Seven patients had pneumonia, 4 tuberculosis (in 3 of whom the disease was miliary), 4 peritonitis (in 3 secondary to the insertion of a peritoneal button<sup>18</sup>), and 2 bacterial endocarditis. Two patients lapsed into coma after bleeding from esophageal varices although there was no clinical evidence of shock. One patient had a hepatoma superimposed

TABLE 3 (Continued)

CASE NO	SERUM BILIRUBIN				BLOOD PROTHROMBIN CONTENT		SERUM THYMOL TURBIDITY (BARIUM SULFATE SUSPENSION)		SERUM CEPHALIN FLOCCULATION	
	PROMPT DIRECT ON ADMISSION*	TOTAL ON ADMISSION*	PROMPT DIRECT DURING COMA*	TOTAL DURING COMA*	ON ADMISSION*	DURING COMA*	ON ADMISSION*	DURING COMA*	ON ADMISSION*	DURING COMA*
	mg/100 cc	mg/100 cc	mg/100 cc	mg/100 cc	%	%	cc	cc		
1	—	—	—	—	40	—	—	—	0	—
2	0.4	1.4	0.3	1.1	80	—	3.5	4.5	—	—
3	0.2	1.9	0.3	1.7	58	72	2.9	5.1	++	++
4	2.0	4.0	6.2	9.4	78	38	0.4	0.4	0	—
5	—	—	—	—	70	—	—	—	++	++
6	—	—	2.3	8.5	37	10	—	0.9	+	++
7	—	—	1.3	3.9	75	45	—	4.5	++	++
8	0.5	0.8	0.4	0.6	90	—	—	2.0	—	—
9	1.5	4.3	1.0	2.5	48	42	3.2	2.5	++	++
10	0.4	1.2	0.7	2.3	75	75	1.5	1.5	++	++
11	0.4	1.0	0.8	1.9	87	—	—	2.4	++	++
12	0.2	0.5	0.5	1.8	43	8	1.8	3.0	0	—
13	1.5	3.4	0.6	5.8	49	48	1.7	3.0	++	++
14	0.3	1.4	0.3	1.6	65	90	2.2	2.4	++	++
15	1.9	3.8	1.3	2.7	43	95	4.9	2.8	++	++
16	0.3	1.1	0.9	2.4	75	60	4.5	4.5	++	++
17	—	—	5.7	17.3	—	40	—	2.5	—	++
18	—	—	18.5	25.2	—	25	—	1.6	—	0
19	—	—	4.7	7.4	—	10	—	2.6	—	—
20	—	—	8.2	17.5	—	65	—	4.4	—	++

benzedrine (amphetamine) sulfate and picrotoxin in moderate amounts subcutaneously or intravenously did not induce a response. In view of the reported effectiveness of sodium succinate in barbiturate narcosis<sup>16, 17</sup> 30 gm of this substance† was administered intravenously over a period of one hour to each of 2 patients. Marked flushing and tachypnea occurred, but no therapeutic effect was observed. Rapidly infused concentrated dextrose solution (usually 100 cc of a 50 per cent solution) failed to alter the state of coma in all but 1 patient. In this patient the coma became temporarily lighter but was then refractory to the further administration of dextrose.

on Laënnec's cirrhosis. The mental symptoms in this case may have been due to cerebral metastases. The historical data and physical findings concerning this group of patients are presented in Table 2. The lesser incidence of ascites, edema and collateral abdominal veins in the complicated group is evident.

The development of coma in these patients was an accelerated version of that seen in the uncomplicated group. In 8 patients the liver disease was far advanced and clinically indistinguishable from that encountered in the uncomplicated group. In the remaining 12 there was severe liver disease, but the complicating infection or hemorrhage was obviously the chief difficulty. It appeared as though the complicating factor had precipitated the terminal coma before it would have occurred in the natural course of the liver disease alone.

\*"Amgen" furnished by the Mead Johnson Company, Evansville, Indiana; "parenamine" furnished by Frederick Stearns and Company, Detroit, Michigan.  
† "Sodaxon," furnished by Brewer and Company, Incorporated, Worcester, Massachusetts.

The laboratory data were essentially the same as those in the uncomplicated group except for the presence of bacteremia in 6 cases. The white-cell count was not a reliable index of infection, being above 12,000 in only 6 patients and below 5000 in 5. Moreover, the white-cell count was frequently high in the uncomplicated cases.

Hypnotics and analgesics were administered to 8 patients in this group, and in some cases undoubtedly contributed to the development of coma. Paraldehyde was used in 7 patients in amounts of 6 to 96 cc over a period of a few hours to several days. Demerol was combined with paraldehyde in 1 case, as was morphine sulfate in another. One patient became comatose after 225 mg of demerol given in three doses over a period of twelve hours.

In addition to the therapeutic measures used for the patients with "uncomplicated" coma, vigorous treatment of the complicating factor was undertaken. Appropriate chemotherapeutic agents were administered. Sulfonamides (usually sulfadiazine) were not withheld because of liver disease if their use was indicated but were administered cautiously as recommended by Peterson, Deutsch and Finland.<sup>19</sup> Blood transfusions were used after acute blood loss from bleeding varices. That these therapeutic measures are occasionally effective is suggested by the fact that in the two years covered by this study, 4 patients with cirrhosis, not included in this study, recovered from coma. The coma in 2 was accompanied by severe infection and in 2 was associated with sedation.

### DISCUSSION

Since Frerichs's description, presented above, many attempts have been made to define both clinically and etiologically the coma in patients with liver disease. Leyden,<sup>20</sup> in 1866, noted a clinical resemblance of liver coma to kidney failure and suggested the term "cholemia," ascribing the coma to a retention of bile acids in the blood. This terminology has persisted, although the underlying concept has been generally discredited. Indeed, complete biliary obstruction is compatible with long periods of comparatively good health, and, in contrast, liver disease may terminate in coma with only minimal bile retention (Tables 2 and 3). Spence and Ogilvie,<sup>21</sup> in 1927, reported terminal "cholemia" in 21 cases of acute yellow atrophy of the liver, but were unable to elucidate the etiology on the basis of their clinical findings.

No specific clinical finding other than coma served to distinguish the comatose state in our patients. The patients appeared to be sleeping but could not be aroused. The presence of liver disease was usually obvious from the history and physical examination, although jaundice was not always present. Respirations were usually regular although commonly increased in depth and rate. Neurologic findings were likewise nonspecific.

The results of the usual laboratory tests were neither characteristic nor of help in elucidating the pathogenesis of the condition. Greene<sup>22</sup> similarly noted the lack of significant blood chemical changes. The terminal rise in blood nonprotein nitrogen observed could be correlated with oliguria, which was usually present in spite of an adequate fluid intake.<sup>22-26</sup> Our results do not indicate which fraction of the blood nonprotein nitrogen rises, except that it is not alpha amino nitrogen. Maddock<sup>17</sup> found a high undetermined fraction of blood nitrogen in hepatectomized monkeys. Croftan<sup>23</sup> suggested, in 1906, and others have subsequently concurred, that after liver damage the blood is flooded with "toxic" products of incomplete protein breakdown. The occurrence of mental symptoms and coma in Eck-fistula dogs fed high meat rations supports the toxin theory,<sup>29</sup> although others believe the cause in this instance to be an incidental infectious encephalitis.<sup>30</sup> The possibility that a toxic compound from altered protein breakdown, especially from the aromatic amino acids, might be found in the blood phenol fraction led us to measure the free phenol concentration. As with other blood constituents, any abnormality found (a rise in this case) was no greater in liver coma than in patients with severe liver disease not in coma. Thus, in spite of a long-continued search for a metabolic toxin in liver coma none has been demonstrated. In fact, Greene<sup>22</sup> has suggested that it is unnecessary to postulate a "toxin" to explain coma in disease of an organ with as profound biochemical importance as the liver.

Our patients failed to show significant hypoglycemia, however, most of them were given carbohydrate by mouth or glucose parenterally, both before and during coma. In only 1 case did the coma become significantly lighter in response to rapidly infused concentrated dextrose, and then the response was only transitory. Thus, the coma in these patients is not analogous to the hypoglycemic coma that develops in hepatectomized dogs and responds dramatically to the parenteral administration of glucose.<sup>29, 31</sup>

Recently, Snell and Butt<sup>32</sup> observed increased amounts of lactic and pyruvic acids in the blood of patients with liver coma and noted a clinical response to administration of parenteral glucose, niacin and thiamine. They postulated that coma in hepatic disease is due to an abnormality of carbohydrate metabolism related to deficiencies of these vitamins. Patek<sup>33</sup> has confirmed the beneficial effect of the administration of glucose and vitamins. Simple vitamin deficiencies did not appear to be responsible for the coma in our patients since large supplements were given to all, both before and during coma. However, the observation of Williams and Bissell<sup>34</sup> that in patients with liver disease the formation of cocarboxylase from thiamine is impaired indicates a metabolic abnormality in these pa-

tients that may explain the high blood pyruvate found by Snell and Butt<sup>32</sup>. It seems likely that this and other biochemical abnormalities exist in patients with liver disease and may play an important role in the genesis of coma.

Although the metabolic defects responsible for coma in liver disease have not been explored, the etiologic importance of infection, hemorrhage and sedatives is clear, the first two at least, may be amenable to specific treatment.

Infection was the single most common known factor in the precipitation of coma in our series, being considered of major importance in 17 patients. The coma so produced was indistinguishable from that developing spontaneously. The exact nature of the influence of infection upon the metabolic processes of the liver is not known. Fever itself may cause hepatic necrosis, which is evidenced clinically by jaundice and bromsulfalein retention<sup>33, 36</sup>. Furthermore, jaundice occurs in a small percentage of patients with pneumococcal pneumonia, especially in pneumonia complicated by septicemia, and is thought to be due, at least in part, to liver damage<sup>37</sup>. Beeson et al<sup>35</sup> have demonstrated that the hepatic-vein blood in cases of endocarditis contains strikingly fewer bacteria than either peripheral venous or arterial blood, suggesting that the liver is a major site of removal of circulating bacteria. The possibility of concentration of bacterial toxins in the liver thus exists. The pneumococcus, tubercle bacillus, and gram-negative organisms from the gastrointestinal tract were the bacterial agents responsible for the infections encountered in our patients, however, little is known of the effect upon the liver of the toxins elaborated by these organisms.

In patients with "medical shock" due to severe infections, indications of damage to the liver have been observed both clinically and pathologically<sup>39</sup>. The profound circulatory changes that occur with infections and fever<sup>40</sup> may diminish the oxygen supply to the liver and may thus be comparable to the situation following hemorrhage, as pointed out below.

Acute hemorrhage from ruptured esophageal varices precipitated coma in 2 of our patients. Recent studies on the effect of acute blood loss have shown a greater reduction in portal blood flow than is suggested by changes in the systemic blood pressures, and further that the oxygen content of the portal blood is also markedly decreased<sup>41-44</sup>. Since the liver receives from 75 to 80 per cent of its oxygen from the portal system, marked hepatic anoxia might be expected from severe hemorrhage, and, according to the observations of LePage,<sup>45</sup> depletion of adenosine di-phosphate and triphosphate would occur.

In addition to infection and hemorrhage, the injudicious use of sedatives was a factor in the production of coma in our patients. In some cases it

was clearly the major factor, whereas in others it appeared only to be contributory, being given during the phase of excitement and serving to hasten the appearance of coma. Most forms of sedatives seem to be poorly tolerated by patients with liver disease. This is especially true of morphine and other alkaloids<sup>46</sup>. Fagin and Thompson<sup>47</sup> observed that of 15 patients dying in liver coma, the coma in 6 followed the administration of morphine by a few hours. In fact, as little as 10 mg of morphine sulfate may induce coma lasting up to three days or until death supervenes. There is little or no evidence that small doses of morphine actually damage the liver, but it is probable that with liver disease the body is less able to get rid of the drug, since a portion of administered morphine is conjugated in the liver with glucuronic acid<sup>48-50</sup>. After experimental liver damage the excretion of free morphine is increased and that of the glucuronide decreased<sup>51, 52</sup>.

Many of the barbiturates are likewise poorly tolerated in patients with liver disease<sup>53</sup>. Like morphine, most are in part, if not largely destroyed, conjugated or excreted by the liver (especially amytal, pentobarbital, seconal and evipal).<sup>54-56</sup> Barbitol and phenobarbital are to a greater extent eliminated by the kidney but, although probably safer than the others, are not without danger. Paraldehyde has been a favorite hypnotic for use in alcoholism and, because of the frequent concurrence of the two conditions, has often been used in patients with liver disease. In our experience, however, it may be highly dangerous. Levine<sup>57</sup> has shown in animals that the drug is metabolized largely by the liver and that it persists in the blood of both men and animals for long periods when liver damage is present. The problem of providing adequate sedation or analgesia in patients with severe liver disease is, indeed, a difficult one, and at present there does not appear to be a satisfactory solution. Although the danger of sedatives in liver disease must not be overlooked, it should be pointed out that patients to whom sedatives have not been administered also develop coma.

#### SUMMARY

The clinical and laboratory studies on 40 patients with severe primary liver disease who died in coma are presented. Liver coma is a distinct clinical syndrome characterized by a progression from lethargy to noisy confusion, to coma and usually to death. The syndrome occurs in patients with severe liver disease, either spontaneously or as the result of infection, hemorrhage or sedation. In half the patients, the coma was precipitated by infection (17 patients), acute hemorrhage (2 patients) or cerebral metastases (1 patient). Central-nervous-system depressants have a prolonged action in patients with liver disease and in this way are believed to play an important role in the genesis

of liver coma. Aside from evidence of severe liver disease, the physical examination and laboratory findings during coma are not distinctive nor are they significantly different from precoma findings. Treatment, which is generally unsatisfactory, is directed at maintenance of nutrition, control of infection or hemorrhage and avoidance of sedatives. Analeptics, including glucose, sodium succinate, caffeine, and benzedrine, are without effect upon the comatose state.

## REFERENCES

- French, F. T. *A Clinical Treatise on Diseases of the Liver*. Translated by C. Murchison. 2 vol. London: New Sydenham Society, 1860. Vol. 1, p. 241.
- Ducci, H., and Watson, C. J. Quantitative determination of serum bilirubin with special reference to prompt-reacting and chloroform-soluble types. *J. Lab. & Clin. Med.* 30: 293-300, 1945.
- MacLagan, N. F. Thymol turbidity test as indicator of liver dysfunction. *Brit. J. Exper. Path.* 25: 234-241, 1944.
- Ley, A. B., Lewis, J. H., and Davidson, C. S. Quantitative determination of thymol turbidity reaction of serum. *J. Lab. & Clin. Med.* 31: 910-913, 1946.
- Hanger, F. M. Serological differentiation of obstructive from hepatogenous jaundice by flocculation of cephalin-cholesterol emulsions. *J. Clin. Investigation* 18: 261-269, 1939.
- Souter, A. W., and Kark, R. Quick prothrombin time simplified by use of stable thromboplastin. *Am. J. M. Sc.* 200: 603-607, 1940.
- Kelly, W. D., Lewis, J. H., and Davidson, C. S. Determination of urine urobilinogen: interpretation of rate of color development of Ehrlich reaction. *J. Lab. & Clin. Med.* 31: 1045-1049, 1946.
- Hamilton, P. B., and Van Slyke, D. D. Gasometric determination of free amino acids in blood filtrates by ninhydrin-carbon dioxide method. *J. Biol. Chem.* 150: 231-250, 1943.
- Lewis, J. H., Taylor, F. H. L., and Davidson, C. S. Tolerance to intravenously administered protein hydrolysate in severe human liver cirrhosis. *Am. J. M. Sc.* 214: 656-661, 1947.
- Bernhart, F. W., and Schneider, R. W. New test of liver function — tyrosine tolerance test. *Am. J. M. Sc.* 205: 636-643, 1943.
- Roen, P. R. Chemical basis of uremia: blood phenol. *J. Urol.* 51: 110-116, 1944.
- Neabur, R. M., Burk, L. B., and Olsen, N. S. Level of blood phenol in uremia. *Arch. Surg.* 53: 483-488, 1946.
- Davidson, C. S., Chalmers, T. C., Paboon, W. W., Murphy, T. L., and Eckhardt, R. D. Treatment of chronic liver disease. *Univ. West Ontario M. J.* 18: 47-54, 1948.
- Lewis, J. H., Taylor, F. H. L., and Davidson, C. S. Protein nutrition: therapeutic use of digest of liver protein, especially in patients with cirrhosis of liver. *New Eng. J. Med.* 236: 351-359, 1947.
- Labby, D. H., Shank, R. E., Kunkel, H. G., and Hoagland, C. L. Intravenous therapy of cirrhosis of liver. *J. A. M. A.* 133: 1181-1190, 1947.
- Soslin, S., and Taubenhaus, M. Sodium succinate as antidote for barbiturate poisoning and in control of duration of barbiturate anesthesia (including its successful use in case of barbiturate poisoning in human). *J. Pharmacol. & Exper. Therap.* 78: 49-55, 1943.
- Barrett, R. H. Analeptic effect of sodium succinate on barbiturate depression in man. *Anesth. & Analg.* 26: 74-81 and 105-113, 1947.
- Crosby, R. C., and Cooney, E. A. Surgical treatment of ascites. *New Eng. J. Med.* 235: 581-585, 1946.
- Peterson, O. L., Deutsch, E., and Finland, M. Therapy with sulfonamide compounds for patients with damage to liver. *Arch. Int. Med.* 72: 594-612, 1943.
- Leyden, E. *Beiträge zur Pathologie des Icterus*. 210 pp. Berlin: A. Hirschwald, 1866.
- Spence, J. C., and Ogilvie, A. G. Cholaemia. Clinical study of nervous symptoms in liver atrophy. *Arch. Dis. Child.* 24: 1-8, 1927.
- Greene, C. H. Liver and biliary tract: review for 1940. *Arch. Int. Med.* 67: 867-888, 1941.
- Neshitt, S. Excretion of porphyrin in urine in alcoholic cirrhosis and after episodes of hepatic coma. *J. A. M. A.* 116: 2534, 1941.
- Idem*. Excretion of coproporphyrin in hepatic disease. III. Urinary excretion of coproporphyrin in hepatic insufficiency during episodes characterized by neurologic manifestations. *Arch. Int. Med.* 71: 62-67, 1943.
- Rall, E. P., Rohson, J. S., Clarke, D., and Hoagland, C. L. Factors influencing ascites in patients with cirrhosis of liver. *J. Clin. Investigation* 24: 316-325, 1945.
- Meyer, K. A., Popper, H., and Steigmann, F. Significance of rise of nonprotein nitrogen in medical and surgical jaundice. *J. A. M. A.* 117: 847-850, 1941.
- Maddock, S. J., and Svedberg, A. Effect of total removal of liver in monkey. *Am. J. Physiol.* 121: 203-208, 1938.
- Croftan, A. C. Hepatic insufficiency: its causes, recognition by significance and treatment. *Med. Rec.* 69: 653-656, 1906.
- Bollman, J. L., and Mann, F. C. Physiology of impaired liver. *Exp. & Physiol.* 38: 445-492, 1936.
- Bald, J. L., and Korpaay, B. Encephalitis of dogs with Eck fistula fed on meat. *Arch. Path.* 13: 80-87, 1932.
- Mann, F. C. Studies on dehepated animals: review. *J. Mt. Sin. Hosp.* 11: 1-22, 1944.
- Snell, A. M., and Butt, H. R. Hepatic coma: observations bearing on its nature and treatment. *Tr. A. Am. Physicians* 54: 321-327, 1941.
- Patek, A. J., Jr. Dietary treatment of Laennec's cirrhosis. *N. Y. State J. Med.* 46: 2519-2522, 1946.
- Williams, R. H., and Bissell, G. W. Thiamine metabolism with particular reference to role of liver and kidneys. *Arch. Int. Med.* 73: 203-211, 1944.
- Braddon, J. H. Hepatitis of hyperthermia: report of fatal case. *New Eng. J. Med.* 237: 765-769, 1947.
- Machella, T. E. Relationship of bromaulphalein retention to liver of natural *P. falciparum* malaria. *Am. J. M. Sc.* 213: 81-86, 1947.
- Ottenberg, R., and Spiegel, R. Present status of non-obstructive jaundice due to infectious and chemical agents: causative agents, pathogenesis, interrelationships, clinical characteristics. *Midwest J.* 22: 27-71, 1943.
- Beeson, P. B., Brannon, E. S., and Warren, J. V. Observations on sites of removal of bacteria from blood in patients with bacterial endocarditis. *J. Exper. Med.* 81: 9-23, 1945.
- Davidson, C. S., Lewis, J. H., Tagnon, H. J., Adams, M. A., and Taylor, F. H. L. Medical shock: abnormal biochemical changes in patients with severe acute medical illnesses with and without peripheral vascular failure. *New Eng. J. Med.* 234: 279-288, 1946.
- Altschule, M. D., and Freedberg, A. S. Circulation and respiration in fever. *Medicine* 24: 403-440, 1945.
- Wiggers, C. J., Opdyke, D. F., and Johnson, I. R. Portal pressure gradients under experimental conditions including hemorrhagic shock. *Am. J. Physiol.* 146: 192-206, 1946.
- Hoff, H. E. Physiology. *New Eng. J. Med.* 235: 855-862, 1946.
- Engel, F. L., Harrison, H. C., and Long, C. N. H. Biochemical studies on shock. III. Role of liver and hepatic circulation in metabolic changes during hemorrhagic shock in rat and cat. *J. Exper. Med.* 79: 9-22, 1944.
- McMichael, J. Oxygen supply of liver. *Quart. J. Exper. Physiol.* 27: 73-87, 1937.
- LePage, G. A. Effects of hemorrhage on tissue metabolites. *Am. J. Physiol.* 147: 446-453, 1946.
- Jones, C. M. Liver intoxication. *New Eng. J. Med.* 230: 766-774, 1944.
- Fagin, I. D., and Thompson, F. M. Cirrhosis of liver: analysis of 71 cases. *Ann. Int. Med.* 21: 285-297, 1944.
- Oberst, F. W. Studies on fate of morphine. *J. Pharmacol. & Exper. Therap.* 74: 37-41, 1942.
- Idem*. Relationship of chemical structure of morphine derivatives to their urinary excretion in free and bound forms. *J. Pharmacol. & Exper. Therap.* 73: 401-404, 1941.
- Bernheim, F., and Bernheim, M. L. C. Note on in vitro insensitivity of morphine by liver. *J. Pharmacol. & Exper. Therap.* 83: 85, 1945.
- Gross, E. G., Plant, O. H., and Thompson, V. Urinary excretion of morphine after liver injury by chloroform in tolerant and non-tolerant dogs. *J. Pharmacol. & Exper. Therap.* 63: 13, 1938.
- Gross, E. G. Effect of liver damage on urinary morphine excretion. *Proc. Soc. Exper. Biol. & Med.* 51: 61-63, 1942.
- Richards, R. K., and Appel, M. Barbiturates and liver. *Curr. Res. Anesth. & Analg.* 20: 64-77, 1941.
- Cameron, G. R., and deSaram, G. S. W. Effect of liver damage on action of some barbiturates. *J. Path. & Bact.* 48: 49-54, 1939.
- Pratt, T. W. Comparison of action of pentobarbital (nembutal) and sodium barbital in rabbits as related to detoxicating power of liver. *J. Pharmacol. & Exper. Therap.* 48: 285, 1933.
- Koppanyi, T., Dillie, J. M., and Linggar, C. R. Studies on barbiturates. XVII. Effect of prolonged chloroform anesthesia on duration of action of barbiturates. *J. Pharmacol. & Exper. Therap.* 58: 119-127, 1936.
- Levine, H., Gilbert, A. J., and Bodansky, M. Pulmonary and urinary excretion of paraldehyde in normal dogs and in dogs with liver damage. *J. Pharmacol. & Exper. Therap.* 69: 316-323, 1940.

## THE USE OF BRILLIANT GREEN IN THE TREATMENT OF CHRONIC ULCERS OF THE SKIN

ARTHUR W FEINBERG M D \*

GREAT NECK, NEW YORK

THE multiplicity of treatments reported in the literature on the subject of chronic ulcers of the skin is evidence that no one treatment has adequately met the required standards of being bactericidal, nontoxic, stimulating to the growth of epithelium and granulation tissue, giving prompt, effective and uniform results and being cheap and easy to use. During a tour of duty with the Army in the Pacific Theater of Operations, I had occasion to see a number of cases of chronic skin ulcerations, of varied etiologies. Each of these cases was treated with the rosaniline dye, brilliant green, and the results obtained indicate that this drug is the one that most nearly meets the stated requirements.

Chemically, brilliant green, like gentian violet, crystal violet and methyl violet, is a derivative of triphenylmethane. These rosaniline dyes are inhibitory to the gram-positive micro-organisms, particularly staphylococci, *Corynebacterium diphtheriae* and *Pseudomonas aeruginosa*. Brilliant green, though employed sporadically for many years because of its sterilizing properties, is not an official drug as yet. It has received trials in the treatment of erysipelas and leprosy, and, in recent years, Aldrich<sup>1</sup> has combined it with gentian violet and acriviolet in his triple-dye treatment of burns. The dye has been used most frequently in bacteriologic staining and can be obtained in the form of a green powder, which is readily soluble in water and alcohol.<sup>2,3</sup> Narat,<sup>2,3</sup> who has written extensively about brilliant green, claims that the aqueous solution is not stable, but in my experience this is not true, inasmuch as stock aqueous solutions continued to give excellent clinical results months after their preparation.

Brilliant green was used in over 20 cases of chronic ulceration of the skin. It is realized that this series is too small to justify extensive conclusions, but the results were so uniform and so excellent in all cases that it was decided to present them in the form of a preliminary report in the hope of stimulating further investigations regarding its use. In all cases the dye was used as a 2 per cent solution in distilled water. After thorough cleansing of the ulcer with hydrogen peroxide and alcohol, the dye was painted on daily until healing was progressing well — generally about seven to ten days. It was then applied every other day until healing was complete. The ulcer was covered with a dry sterile dressing after each treatment. The patient was advised to rest as much as

possible and to sleep with the affected extremity elevated. Otherwise no instructions or treatments were given.

### CASE REPORTS

CASE 1 M J R., a 25-year-old Filipino merchant seaman, was first seen in November, 1947, complaining of a large, rapidly progressing ulcer on the dorsum of the right foot (Fig 1). About 1 month prior to his first visit his foot had



FIGURE 1 A Chronic Ulcer of One Month's Duration before Treatment

been bruised by a steel cable, and the resulting small wound became infected and quickly broke down. Upon examination the ulcer measured 3.8 by 5.3 cm, the base was deep and was covered with dirty, evil-smelling necrotic tissue. No evidence of healing was seen. Pain was moderate. The patient was



FIGURE 2 Ulcer after Five Applications of Brilliant Green

placed on hot soaks, bed rest and elevation of the leg for a 2-day period, with no change in the appearance of the lesion except that the size of the wound had increased slightly. Brilliant green was applied. After one treatment with the dye, the necrotic exudate had lessened considerably, the odor had practically disappeared, and evidences of healing were already present. The pain and discomfort in the wound were completely gone. After only five applications of the dye, the necrotic exudate had disappeared, the base of the wound was level with the surrounding skin and was composed of clean

\*Intern in medicine, Maimonides Hospital (Israel Zion Division) Brooklyn, New York.

†Manufactured by National Aniline Division, Allied Chemical and Dye Corporation, New York City.

healthy granulation tissue, and epithelium was growing rapidly at the edges. The wound now measured 3.3 by 2.6 cm, having closed 5 to 7 mm in less than 1 week (Fig. 2). Healing progressed rapidly and steadily so that on the 26th day of treatment, after eighteen applications of brilliant green, heal-



FIGURE 3 Ulcer Completely Healed on the Twenty-Sixth Day of Therapy, after Eighteen Applications of the Dye

ing was complete and the skin surface intact (Fig. 3). Follow-up examination 1 month later showed no evidence of recurrence.

CASE 2 L. R., a 10-year-old Filipina, first appeared early in December, 1947, with a large, deeply excavated tropical ulcer over the medial malleolus of the left leg (Fig. 4). It had started 3 months before as a slight scratch, which had become infected and had grown progressively larger and deeper. She had received intensive treatment with hydrogen peroxide soaks, sulfanilamide crystals and locally applied neosarsphenamine before coming to the clinic, without retarding the progress of the lesion. Upon examination, the



FIGURE 4 A Tropical Ulcer of Three Months' Duration before Treatment

wound measured 3.4 by 3.0 cm, and the edges were markedly indurated. The base was 4 mm below the skin surface and was covered with the same type of slimy, malodorous, necrotic discharge as that in Case 1. Pain was marked, especially at night. After one application of the dye, the pain was gone, the swelling and induration about the ulcer had lessened, the base of the wound was starting to fill in, and the exudate, though still profuse, was no longer foul smelling. After eleven applications of brilliant green, the surface of the ulcer was completely level with healthy granulations, and epithelization was progressing rapidly. The ulcer now measured 1.5 by 1.8 cm, a closure of more than 70 per cent of the surface area. There was no exudate (Fig. 5). Healing continued to be rapid, and after 29 days of treatment, which comprised 17 applications of the dye, the patient was discharged with the ulcer healed (Fig. 6). Six weeks later, she returned for a follow-up visit. The ankle looked perfectly normal, and there was no evidence of regression (Fig. 7).

CASE 3 C. D., a 53-year-old man employed as a merchant seaman, appeared in the clinic in August, 1947, for the first time, complaining of an infected ulcer over the anterior surface of the left tibia of 1 week's duration. The patient gave a



FIGURE 5 Progress of Healing after Eleven Applications of Brilliant Green

history of mild diabetes mellitus, which was kept under control by dietary measures. His cardiovascular history was completely negative. He had struck his shin 1 week before, received an abrasion that refused to heal, rapidly became infected and then ulcerated. Physical examination revealed



FIGURE 6 Healing of the Ulcer on the Twenty-Ninth Day of Therapy, after Seventeen Treatments with the Dye

the heart to be normal, and there was no glycosuria on repeated examinations. On his left leg he had a circular wound, 2.5 cm in diameter, covered with a scab. Removal of the scab exposed a shallow, dirty, infected ulcer showing no signs of healing. Both legs were covered with numerous scars, the



FIGURE 7 Follow-up Photograph, Six Weeks after Completion of Treatment, Showing a Normal Ankle

results of previous leg ulcers similar to the present complaint. None of these had healed in less than 3 months' time. The patient was treated with hot soaks, thorough daily cleansing, zinc oxide ointment and sterile dressings for 1 week. At the end of this period, the infection had subsided somewhat, but

the size of the wound was unchanged and no healing tendency was noted. Brilliant green applications were then started, and other treatments suspended. Improvement was noted almost immediately and the ulcer was completely healed 16 days later, after fourteen applications of the dye.

CASE 4 S L, a 32-year-old Filipino man employed as a clerk, was first seen in September, 1947. Almost 4 months before, he had developed a carbuncle on the left side of his abdomen. He received no medical attention, and the carbuncle gradually emptied of itself. One month after onset, it had become an indolent, nonhealing ulcer. On first examination, the ulcer measured 2.5 by 2.4 cm and was moderately infected. It was shallow, but the base showed no clean granulations. Brilliant green applications were started at once, and 1 day later, evidences of healing could be noted. In 11 days after only seven dye applications, the ulcer was completely healed, and the patient discharged. Follow-up examination 2 months later showed no recurrence.

### DISCUSSION

Brilliant green, a rosaniline dye of the triphenylmethane series, seems to offer many advantages in the treatment of chronic, indolent ulcers of the skin. It is bactericidal for many of the common pathogenic bacteria, has a high stimulating effect on the growth of epithelium and granulation tissues and counteracts the malodorous discharge common to this type of case. It is completely nontoxic, does not

irritate tissues and has the added advantage of being low in cost. It can be as easily used in the doctor's office or the patient's home as in the hospital clinic. The staining of normal skin that occurs incident to its use can be removed readily by washing with alcohol.

### SUMMARY

Experiences in a limited series of cases of chronic skin ulcers with a 2 per cent aqueous solution of the rosaniline dye, brilliant green are presented.

The advantages of brilliant green — its bactericidal action, its stimulative effect on epithelium and granulation tissue, its nontoxicity, cheap cost and ease of application — are cited.

It is believed that the use of brilliant green merits further trials in the treatment of all types of chronic ulcers of the skin.

### REFERENCES

1. Aldrich R. H. Treatment of burns with compound of aniline dyes. *New Eng J Med* 217 911-914 1937
2. Narat J. K. Brilliant green: clinical study of its value as local antiseptic. *Ann Surg* 94 1007-1012 1931
3. Idem. Brilliantgreen als locales antiseptikum. *Zentralbl f Chir* 61 2871-287 1934

## THE RELATION BETWEEN THE INDUSTRIAL PHYSICIAN AND THE FAMILY DOCTOR\*

THOMAS L. SHIPMAN, M.D.

WEST LYNN, MASSACHUSETTS

DURING the decade from 1911 to 1920 all but a handful of states enacted workmen's compensation acts and thereby brought into being that peculiarly hybrid creature, the industrial physician. Back in those early days the propriety of entering such a low-born specialty was questionable, and there can be no doubt that a number of poorly qualified doctors entered this field. There were in addition, however, men of unquestioned ability and integrity, and as pioneers in a new and uncharted field they endured the scorn and insults of other doctors, and at the same time they evolved the fundamental knowledge and procedures that now form the basis of industrial medicine, a specialty today in its own right. In general the relations between the industrial physician and the general practitioner are now harmonious, but there is still room for improvement, and there are probably justifiable complaints on both sides.

I should like to pause here for a moment to define roughly my own ideas of what constitutes an industrial physician and his job. An industrial physician should in the first place be a well trained, capable and honest doctor. As Professor Philip Drinker has

often expressed it, a doctor is not good enough to care for the employees of a plant unless he is also good enough to care for the boss and the boss's family. The industrial physician must in addition have an interest in the employees in health as well as in sickness. Far too common is the self-styled industrial doctor who is nothing but a "patcher-upper", this man usually knows nothing about the workings of the plant, the materials employed, the procedures carried out or the nature of the actual jobs performed by the workers. How can a doctor carry out a routine pre-employment physical examination if he doesn't know intimately the demands and requirements of the job in question? In the year or so following the war I had the opportunity of talking with a large number of young doctors just out of the service who were looking for industrial jobs. Actually all but a tiny minority were looking only for a sort of insurance job, bits of traumatic surgery with fees guaranteed. They had not the slightest interest in supervising the well-being of the healthy worker and in trying to keep him that way.

Last year at the Atlantic City meeting of the American Medical Association Dr. Poole,† of the Lockheed Aircraft Corporation gave a paper on this

\*Presented at the annual meeting of the Massachusetts Medical Society on May 25, 1949.

†Instructor in industrial hygiene, Harvard School of Public Health; assistant in medicine, Massachusetts General Hospital; consultant in industrial medicine, Salem Hospital; works physician, Lynn plants of General Electric Company.

†Poole E. E. General practitioner as adjunct to industrial surgeon. *Occup Med* 4 293-304 1947.

same general subject. Without any question he stole much of my thunder, but running in second position I have the opportunity of re-emphasizing many of his points. In one particular I shall undertake to split a hair. Dr. Poole chose as his title, "The General Practitioner as an Adjunct to the Industrial Surgeon." I should prefer to put the shoe on the other foot and state that the industrial physician—or surgeon—is more properly an adjunct to the general practitioner. Regardless of who gets top billing, the aim of both is exactly the same, and they must be regarded as collaborators. Let us briefly consider this point. The family doctor, or any physician in private practice for that matter, ordinarily sees his patients only when they are sick or ailing. When he does see them his natural desire, unless he is a charlatan, is to restore them to health as quickly as possible. In other words, he wants to get the patient back to a normal productive life as soon as it is safe and proper. This is naturally of particular importance if the patient is the wage-earner for a family. The industrial physician has exactly the same idea, he is perhaps more concerned with keeping the well person healthy and in protecting the handicapped person from further damage. His purpose, his *raison d'être*, therefore, is to keep the human element in industry efficient and productive. Naturally this is advantageous to the industry and its management, but it is even more of a boon to the individual.

Only 10 per cent of the total time lost in industry because of sickness is the result of occupational disease or industrial injury. The industrial physician who interests himself solely in the care of injuries is no more than nibbling at the corner of the problem. He is obligated to consider all phases of the employees' make-up just as much as the family doctor must give thought to the occupational aspects of his patients' histories. Your work and mine, therefore, overlap, and where they do not overlap, they supplement one another. Let us consider a few specific situations in which general medicine and industrial medicine do overlap and in which apparent differences of opinion arise.

First of all there is the problem of the preplacement physical examination. This is one of the first contacts that a new worker makes with his future employer. The examining physician assumes that the man is healthy—at least he walked in under his own steam ready to go to work. Unlike the hospital physical examination, abnormal findings here come usually as a surprise. The preplacement examination is brief but more searching than one might think. The findings are considered not as pathologic entities but as they relate to the specific job the man is to do, the requirements for a draftsman and an outdoor laborer obviously are not the same. Occasionally it will become apparent that a man's physical condition and his job do not go together, and the doctor has to say, "No, it would be a serious mistake

to permit this man to do this type of work—he might be able to do some other job, but he can't do this one." In many cases the man himself is unaware of the significance of his disability, and he feels hurt, not to say insulted.

Nobody wins if a man is permitted to go to work on a job for which he is unsuited, it is the responsibility of the examining physician to keep the square pegs out of the round holes. Frequently, a disappointed worker goes straight to his family doctor, and that is just where he should go, more often than not it has been suggested by the examining doctor that he make the visit. You would be astonished at the number of perfectly reputable physicians who disregard entirely the warnings of the plant physician and argue heatedly that the man is able to go to work, even though they have little or no idea of the precise nature of the work and its demands.

Physicians doing a good deal of examining for large industries become fairly proficient in discovering the elusive hernia. One would think that most doctors would be somewhat guarded in flatly contradicting the statement of an experienced examiner that a definite hernia has been found, and yet that is done repeatedly. It might be mentioned that the outpatient departments of the large hospitals, where the examinations are performed by relatively inexperienced house officers, are particularly frequent offenders in this regard. I am frank to admit that at no time in my hospital experience have I ever learned how to find hernia except one visible at ten paces.

The pre-employment—or preplacement—examination is an ideal opportunity to discover pathology in its earliest stages. I can think of no more common-sense form of preventive medicine, and I have enough faith in the profession to believe that every doctor would prefer to have one of his own patients come to him with a condition easily correctible rather than something neglected and beyond repair. Sometimes one wonders even about that, we recently sent a man back to his family doctor after a chest x-ray film had revealed a suspicious apical shadow. This doctor was utterly scornful and said that the patient could not have tuberculosis, since he had neither cough nor loss of weight.

Local practitioners are frequently critical in claiming that industrial clinics offer treatment for non-industrial conditions. In my own clinic approximately 20 per cent of our total visits are listed as being for nonindustrial complaints, and this seems to bear out the criticism. However, most of these visits are for heartburn, runny noses, headaches, hangovers, nosebleeds, diarrhea and similar trivialities. These are not problems that send a person to his family doctor—they are the conditions that send the child to and are treated by its mother (not the hangovers, perhaps). If we should deny attention to these people they would not go to their doctors—they would go if anywhere to the corner drugstore. I contend that it is distinctly within the

province of the industrial physician to see and treat these minor problems if they are of such nature that the patient can be given relief and returned to finish his day's work in safety. It is also this doctor's responsibility to make as certain as possible that the bellyache is not appendicitis, that the headache is not a brain tumor and that the diarrhea is not a cancer of the rectum. All the patients whose problems seem to demand a bit more than simple first aid are automatically referred to their family doctors for further consideration. The old complaint that the industrial doctor is stealing the bread from the mouth of the family doctor is definitely not justified.

Acutely sick patients, of course, are seen in every industrial clinic. Coronary-artery attacks, renal colic, appendicitis and bleeding or perforated peptic ulcer turn up in industrial practice not infrequently, and the disposition of the case is usually decided on after a telephone conversation with the family doctor. The early observations made in the case, together with simple laboratory work, will usually be of material assistance in making the diagnosis promptly and in saving the patient much time and discomfort. The industrial doctor does not want to take care of these patients, however, he wants to get rid of them, to see them placed in proper hands just as soon as possible.

In addition to the acutely sick persons many men with serious but noncritical conditions come to the industrial clinic. This group includes patients with diabetes, cardiac disease, ulcers, asthma, varicose veins, hemorrhoids, arthritis and a host of other conditions. Some of these men realize that all is not well with them and come to the company doctor seeking advice. They want to know where to go for proper treatment, or for relief. They may be sent to the dispensary by their foremen, who have noticed some indication of failing health, they may even come at the suggestion of the family doctor. Such situations call for a certain amount of diagnostic procedure before one can intelligently advise a man regarding the course to follow. It is important to know whether the problem is serious or trivial, and whether it needs prompt attention or elective treatment. Every large industrial clinic today has x-ray facilities, an electrocardiograph and a laboratory. The use of these diagnostic aids in industry is no attempt to supplant similar facilities elsewhere; it is simply to provide a preliminary survey that, it is hoped, will be of value and help in the ultimate solution of the patient's problem. The thoughtful wharf owner does not object to the placing of channel buoys to guide ships into the harbor.

There is, I should point out, an increasing willingness on the part of large industries to provide this preliminary diagnostic service for more and more people. Periodic physical examinations are required for certain workers in hazardous trades, and the same service is being offered on a voluntary

basis to larger and larger groups. In every case the information is available for the family doctor, and frequently it is sent to him whether he wants it or not.

A man came to my office some time ago complaining of a lump in his groin. He was a laborer, foreign-born, and spoke English only with difficulty. Instead of a lump in one groin he had lumps in both—large, egg-sized lymph nodes. The axillary lymph nodes were also involved. He was referred to his family doctor and returned a day or so later with a note from the doctor stating that he was suffering from chronic bronchitis and was able to do his work. I sent him back a second time with firmer instructions. A second note from the doctor admitted the presence of an enlarged inguinal lymph node on one side, and suggested that the man be changed to another job. This time I took no chances and wrote to the doctor urging biopsy and appropriate treatment. My letter was ignored and so was the patient's disease. Some time later the man reappeared with a letter from another doctor. This stated that the man had a generalized rash, occupational in nature, and that he should have a different job. It also stated that night-shift work seemed to be bad for the man. By this time there was massive enlargement of the inguinal, axillary and subclavicular lymph nodes, easily visible from a considerable distance. It might be said that I forced the issue this time, and the patient has received adequate treatment for Hodgkin's disease.

Another man, a leading engineer, came in for a routine physical examination. Both of two urine specimens showed large amounts of sugar. At my suggestion he went to a doctor of his own choice, an eminent internist in this city. Here he was given a clean bill of health and told not to worry. A year later he returned to me saying that he had lost 25 pounds and that he seemed to have developed an uncontrollable thirst. He is now taking insulin. Here I think that both doctors were at fault,—I for feeling that a physician of his eminence could not make a mistake, and he for feeling that anything coming out of an industrial clinic was probably unreliable.

In no situation is the need for co-operation greater than in that of the man returning to work after an illness. Almost every industry, certainly all the large ones, have certain rules and regulations concerning time away from work because of illness. It is common practice for industry to request from the attending physician a note stating that the patient is in his opinion ready to return to his job, and this also provides an opportunity to suggest any limitations or suggestions about the man's work that might be necessary. You would be amazed at the number of notes of this sort which are absolutely insincere and dishonest. No, I am not the only one who has been disgusted with this

situation Let me quote from Dr Poole's paper, which touches on the same problem in California

These letters are commonly referred to by personnel men and foremen as "S2 letters" I frequently hear scornful remarks from plant supervisors who believe that the ethics of the profession can be winked at for small fees and that a physician can be induced to write anything I must confess that after reading thousands of these letters I have many times shared their opinions

It is a sordid bit of business and I doubt if even the so-called patient can have much respect for the doctor who would stoop so low The industrial physician or personnel director must be pardoned, I think, if he refuses to accept as gospel a note that says that a patient has been ill and under a doctor's care, unable to work for two or four or six months because of hypotension or secondary anemia, nervousness or general debility The pattern is unmistakable, and the authors only too well known

There is a brighter side to this problem, however, and nothing gives a plant doctor more pleasure than to work together with the family physician in arranging suitable hours and conditions of work for the patient who is recuperating from severe illness Many physicians fail to remember what a bad enemy the clock is to the patient who is scarcely out of his convalescent stage Just sitting at a desk until the clock points to five is fatiguing to the person who is "out of training" Not infrequently the industrial doctor must apply the brakes in such a situation, sometimes even insisting that the patient remain away from work entirely for a week or so longer than his own doctor has advised

Quite a different situation arises when a doctor in all good faith requests that one of his patients be granted a leave of absence from work, or be given a different job, or be changed to a different shift Frequently the necessity for the recommendation is obvious, and appropriate action will be taken *if this is possible* Please note those words, "if this is possible" Sometimes it is not possible to carry out the proposed measures Every industry has definite rules and regulations regarding leaves of absence, for example, and these must be adhered to if the rights of all are to be protected In addition, nearly every industry has a complicated system of rules regarding job seniority, these rules are usually not of industry's seeking or choice, but they must be followed Ordinarily it is not possible, for example, to have a short-service man on a night shift displace a longer service employee on the day shift, even though the former's peptic ulcer makes it impossible or inadvisable to continue to work at night Here is a perfect stalemate, and the poor family doctor doubtless feels that the industry or its doctor is failing to co-operate in the care of the patient Actually the desire to co-operate is there but successfully blocked by conditions quite beyond the doctor's control

So far I have talked very glibly about industrial medicine as though all workers had available the same highly organized medical departments as those existing in the large corporations We all know that this is not so Actually, many of the workers in Massachusetts have available little or nothing in the way of competent medical supervision There is no industry so small that it should not and cannot have this medical supervision, but only a handful seem to recognize the fact The management of a small plant usually believes that it has done everything necessary if it has a nurse and a first-aid room, forgetting that this nurse needs a doctor's supervision No nurse should be asked or expected to work unless her duties and procedures are outlined and followed by a physician Simply having a doctor on call for emergencies does not constitute adequate supervision

This, however, is a situation that cannot be corrected overnight If a real problem exists and the family doctor wishes to make specific recommendations about a man's work, there are certain procedures that may be employed First of all, let me join with Dr Poole in condemning the note that starts off, "To whom it may concern" If no medical supervision for the patient exists at his place of work, one should find out the name of the ultimate boss, the manager, the president or owner, who should be addressed directly either by sealed letter or by telephone If the patient is entrusted with the note he should be told to see that it gets to the person to whom it is addressed and not to anyone else It may take an extra day to have the patient find the name of the proper person, but this delay is justified A letter sent by mail or a telephone call will permit far greater frankness and emphasis than is ever possible in an open note that is handed to the patient

The average doctor when taking his patient's present and past history usually exhibits a reasonable and healthy skepticism In considering an occupational history his attitude can only be described as gullible If a patient says that his job is dusty the doctor more often than not screams "silicosis" before he considers either the patient's symptoms or the nature of the dust He criticizes a job on the grounds of overfatigue and advises a leave of absence without considering the fact that the man is spending his leisure time building a house or tending a bar He deplores the heavy work a man does without finding out what that work consists of An unbelievable number of cases of scabies have been diagnosed as occupational dermatitis, and there appears to be a total inability in the medical profession to discriminate between a toxic hazard and a bad smell Let me assure you that industry welcomes inquiries on these subjects It is a pity that it is not more practical for doctors

actually to visit the places where their patients work, to see for themselves what the conditions are, and to find out what the working environment is

Every patient is affected either directly or indirectly by jobs and wages. Sitting at a desk in a bank is a job just as surely as standing at a lathe or a boring mill. The effect of poor adjustment to a job may be even more damaging to a wife or child than to the worker in question. You, therefore, have a stake in industrial medicine whether you want it or not. Where industrial medicine is practiced well it deserves your support. Where it is practiced poorly and improperly it deserves your constructive criticism more than your condemnation. Where medical supervision of workers is non-

existent your scorn of management that is unwilling to provide it should be followed by your help in showing how it can be obtained. The working man spends forty or more of the one hundred and sixty-eight hours in a week at his job. You cannot disregard this period, and your patient cannot afford to have you do so. Where good industrial medicine exists, cultivate it, get in the habit of using it, learn the ways in which it can help you to get your patients well and keep them that way. Accept the challenge of the missionary work needed to improve industrial medicine and extend its benefits to an ever-increasing number of working men and women, who, incidentally, are your own patients.

## FENESTRATION SURGERY FOR DEAFNESS

### Present Status

CHARLES I. JOHNSON, M.D.\*

BOSTON

THE general practitioner is being increasingly plagued by newspaper and magazine publicity describing new technics in medical and surgical therapy. Too often he finds himself confronted with the unpleasant chore of blasting the hopes falsely raised by some garbled or, at best, premature report of a "cure" for high blood pressure, arthritis, asthma, sinusitis, deafness and so forth. The situation takes on the proportions of a real problem, moreover, when the doctor must decide what answer to give a patient who asks about a technic that has really proved to be effective but only under certain conditions and for certain types of sufferers.

A particularly good example of a therapeutic technic that can tremendously improve a bodily defect and, at the same time, remove its ill effects on the personality is the novovalis fenestration operation. There has been a good deal of publicity about this operation in the decade since Lempert developed the one-stage technic for the cure of deafness due to otosclerosis, and more and more patients are coming to their physicians for information and advice about their chances of benefiting from it.

The first point the physician must determine in deciding whether the patient should consult a surgeon skilled in this technic is the cause of deafness in the particular case with which he is dealing. The fenestration operation is successful only for deafness of otosclerotic origin. Otosclerosis is a histologic lesion in the bone of the inner ear and

takes the form of circumscribed, sharply defined inlaid areas of new bone formation of unknown etiology and microscopically somewhat like Paget's disease or osteitis fibrosa. In otosclerosis the piling up of new bone formation is usually about the foot plate of the stapes, and the deafness progresses as the fixation of the stapes increases. The fenestration technic consists in making a new fenestra in the inner ear so that sound waves can by-pass the obstructed middle-ear circuit.

The general practitioner can make at least a tentative diagnosis of otosclerosis on the basis of history and symptomatology. The patient usually gives a history of bilateral deafness beginning in adolescence or early adult life and, as a rule, becoming progressively worse. Although in some cases deafness does not develop beyond the point where practical hearing is possible, most patients suffer progressive impairment to a degree where hearing loss is incapacitating. Many of them ultimately show nerve degeneration. There may be found a past history of acute otitis media, but this finding does not preclude a window operation if the eardrum membrane is intact. A chronic sup-purulation of the middle ear on the other hand, is a contraindication.

As part of his general information about this disease, the physician may find it helpful to know that a hereditary factor has been found in 53 per cent of cases. Also, about six times as many women as men have otosclerosis, and in about half the female patients impairment of hearing increases during pregnancy.

\*Fellow to the Winthrop Foundation, surgeon, Massachusetts Eye and Ear Infirmary, Massachusetts General Hospital, assistant surgeon, Children's Hospital, chief of otolaryngology, Faulkner Hospital.

It is characteristic of the otosclerotic patient to hear well over the telephone and in noisy places such as a subway or railroad train. Good hearing over the telephone, it is true, may be found in chronic catarrhal or chronic adhesive deafness, but here one can elicit a history of nasal allergy or chronic upper respiratory infections and ear-aches with or without discharge. Examination provides another differentiating point in otosclerosis: the eardrum is normal, without perforation or discharge, and gray or pink in color unless complicated by an isolated attack of otitis media. In the other type of deafness mentioned, the eardrum may be thickened, atrophic, scarred and possibly perforated anteriorly.

Tuning-fork tests will show the otosclerotic patient to have prolonged bone conduction and diminished air conduction. He characteristically hears well with a hearing aid of either the air-conduction or bone-conduction type. In fact, this type of patient does not have to rely solely on the fenestration operation for help, even if he proves eligible for it by all the various criteria used by the surgeon in advising operation: he can always fall back on a hearing aid instead of submitting to surgery. The decision about undergoing surgery actually rests with him, but many of these patients are not willing to use a mechanical device despite its effectiveness.

Certain other factors must be taken into consideration in judging a patient's chances of benefiting from a fenestration operation. One of them is age. Persons between eighteen and fifty are the most eligible, although younger and older patients have been operated upon with good results. Another factor is emotional stability. Since not every operation can be guaranteed to be an unqualified success, and the aftertreatment, in every case, is necessary and since a few patients occasionally develop post-operative vertigo, the emotionally unstable person is a poor psychologic risk.

When a patient is referred to an otologist for study preliminary to possible fenestration surgery, a number of devices designed to gauge cochlear-nerve function help the surgeon make his decision. He will use air and bone audiograms, tuning-fork tests, the speaking tube and word tests played on a recording machine.

Although the fenestration does not give perfect hearing, it does make possible practical hearing that enables the patient to carry on a conversation, attend lectures or church and otherwise live a normal life. For properly selected patients, the chance of bringing the hearing to a permanently serviceable level is about 50 per cent. By permanent is meant a period longer than two years, after which period no patients with successful cases have lost their hearing. I performed my permanently successful cases of oldest standing in December, 1941, and these patients have lost none of their hearing gains. Of 64 operations performed between December, 1941, and April, 1946, 31 were successful — or 48.5 per cent.

Patients who have undergone successful operations say that their hearing has none of the distortion produced by the hearing aids they formerly had recourse to and also that they can be more selective in their hearing. In other words, the hearing made possible by the fenestration operation is more satisfactory than that effected by a hearing aid because it is more natural.

What to me is the most striking effect produced by a successful fenestration operation is the extraordinary change for the better in the patient's personality. The self-conscious, dejected, hypersensitive person with inferiority feelings living a life circumscribed by the limitations put on his activities by deafness emerges from this operation a more self-confident, happy and better adjusted man or woman possessed of an energy, enthusiasm and joy in living that is tremendously rewarding to see.

## MEDICAL PROGRESS

### RENAL DISEASE\*

ALASTAIR D HALL M D,† AND JOHN A LUETSCHER, JR, M D‡

MONTREAL, CANADA, AND SAN FRANCISCO, CALIFORNIA

WE ASK the reader's indulgence for some liberties in the selection and presentation of recent developments in renal disease. The literature on the kidney is too large to permit any complete description in these few pages. We have therefore chosen a few subjects of current interest for discussion. These include some studies of the earlier stages of glomerular nephritis and a glimpse of the gradually evolving cardiovascular-renal relations. The curious effects of large doses of vitamin D on the kidney are mentioned. The acute renal tubular injury that accompanies many types of bodily injury is now recognized as one of the commonest and most important forms of renal disease. Its etiology is discussed and related to the novel studies of Trueta on the renal circulation. Finally, some new methods for the treatment of acute renal insufficiency are described.

#### GLOMERULAR NEPHRITIS

Two important new books on nephritis have appeared this year. In his scholarly work on Bright's disease, Christian<sup>1</sup> presents a well organized, detailed description of the present state of knowledge of renal disease. The author follows his well known system of classification of renal disease. Clinical descriptions include numerous case histories, charts, and pathological descriptions. A large bibliography offers opportunities for further study.

Addis<sup>2</sup> has published a thoughtful, personal account of his studies on glomerular nephritis, and of much related experimental work. His book contains a detailed consideration of the clinical features and laboratory evidences of glomerular nephritis, as well as a unique presentation of treatment as applied to an individual patient. In contrast to the usual textbook, the author probes with obvious relish into vast areas of present ignorance about the causation and treatment of nephritis. A number of current physiologic and therapeutic principles emerge somewhat battered from the encounter.

A large part of Addis's book is devoted to the argument for a diet of minimal protein content

throughout the course of glomerular nephritis. "Renal work" in secreting urine consists largely in concentrating urea from a low level in the blood to a high level in the urine. Of course, the kidney does much work of other sorts but the work imposed by a high-protein diet has been repeatedly shown experimentally to be injurious to a damaged kidney. The normal or damaged kidney hypertrophies when the dietary protein is increased. However, when the capacity for urea excretion is exceeded by dietary nitrogen, signs of further renal injury appear in the form of protein, red blood cells and casts in the urine, together with a rising blood pressure and a progressive anemia. These animals die in uremia, which is readily avoidable by the use of a low-protein diet. The same general principle may apply to patients with limited renal function and perhaps to patients who have had an attack of acute glomerular nephritis.

Addis also emphasizes an adequate fluid intake at all times. This serves two purposes: the minimizing of renal work, and the prevention of protein precipitation in the renal tubules. He regards dehydration as dangerous to the patient with proteinuria, a thought to consider before ordering a test of urinary concentrating power. A daily intake sufficient to yield 2 or 3 liters of urine is considered adequate. Above these levels, increases in the fluid intake become less efficient as well as difficult to maintain.

#### Acute Stage

The etiology of acute nephritis is known in general outline, but the specific mechanism remains obscure. The occurrence of several cases in the same family has suggested a "constitutional" predisposition. Addis reports 4 cases of nephritis occurring in only 1 of identical twins. In 1 of these cases the children lived under apparently identical conditions, sleeping in the same room, and each was recovering from a mild attack of scarlet fever when 1 of the twins developed acute nephritis. An essential, nonhereditary factor is strongly suggested by such observations.

Cardozo<sup>3</sup> has recently described an increased volume of the blood in acute nephritis. Addis had suggested that the sudden development of mild anemia and hypoproteinemia, and their reversion to normal levels with diuresis, were due to changes in plasma volume. We have examined this point

\*From the Department of Medicine, Johns Hopkins University School of Medicine and Johns Hopkins Hospital.

Some original work reported here was supported by a research grant from the Division of Research Grants and Fellowships of the National Institute of Health, United States Public Health Service.

†Teaching fellow in medicine, Montreal General Hospital, Montreal, Canada; formerly research fellow in medicine, Johns Hopkins Hospital, Baltimore, Maryland.

‡Associate professor of medicine, Stanford University School of Medicine, San Francisco, California; formerly assistant professor of medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland.

in some detail.<sup>4</sup> During the initial stage, with or without oliguria, the excretion of sodium is greatly depressed. If gastrointestinal symptoms do not block the intake of water and salt, edema develops rapidly. At this stage, the plasma volume is usually increased far above the expected figure. The venous pressure is frequently as high as in cardiac failure, and yet symptoms of failure are not necessarily present. With the onset of diuresis, all these changes may be reversed with astonishing speed. Sodium and water pour out through the kidneys, edema disappears, the plasma volume contracts rapidly, and the plasma protein concentration mounts, sometimes overshooting the mark to a level of 9 or 10 gm per 100 cc. The proportion of albumin is usually unchanged during diuresis, suggesting that there has been a simple concentration of the plasma proteins. When the venous pressure has been elevated, it falls as the edema is eliminated. These findings suggest that retention of salt and water accounts for many of the changes observed in acute nephritis, although doubtless other factors play important roles.

The excellent prognosis in acute nephritis has been emphasized by recent reports.<sup>5-7</sup> Treatment is currently directed at minimizing the physiologic disturbances as they appear. The recently developed antihistaminic drugs suggest the possibility of blocking some effects of the hypothetical antigen-antibody reaction responsible for glomerular nephritis, but only preliminary reports<sup>8</sup> of their successful use have been forthcoming. Penicillin has been very useful in controlling the preliminary infection, and preliminary reports indicate that it may reduce the severity of the ensuing nephritis.<sup>9</sup>

### *Nephrotic Stage*

A comprehensive review of the nephrotic syndrome by Bradley and Tyson<sup>10</sup> recently appeared. The following discussion covers only certain new information in its relation to the nephrotic syndrome.

Many students of the nephrotic syndrome believe that hypoproteinemia can no longer be considered the sole cause of edema.<sup>2, 10, 11</sup> Perhaps the most revealing data came from the studies of treatment of the nephrotic stage with concentrated human serum albumin.<sup>12-15</sup> Albumin has proved to be a safe and frequently effective diuretic, but in most cases, the serum protein concentration is not increased above so-called "critical levels" for edema. The increased circulating albumin draws in fluid to produce a large increase in the plasma volume, clearly demonstrating the Starling effect.<sup>16</sup> When fluid is mobilized from the periphery, however, the excess fluid is not necessarily excreted. The patient may be left with the anomalous combination of a normal total amount of albumin and globulins circulating in his blood, but with double the normal plasma volume and with only half the normal protein concentration. This situation throws

the responsibility for the hydremia and edema directly on the kidney's failure to excrete sodium and water.<sup>17</sup>

The specific difficulty in sodium excretion in the nephrotic syndrome is well recognized. An attempt to reproduce this defect by the classic methods of protein depletion in dogs has been made.<sup>4</sup> Acute plasmapheresis to plasma protein levels around 2.5 gm per 100 cc does not appreciably impair the dog's ability to excrete sodium or water. Chronic protein depletion causes some diminution in excretory function, involving sodium and water to a limited degree. In general, the results do not resemble those found in the nephrotic syndrome, and one is forced to assume that the nephrotic patient's difficulty in the excretion of sodium and water is not due to hypoproteinemia per se. This conclusion is supported by the observation of spontaneous diuresis in nephrosis without a preceding increase in the plasma protein concentration. The depression of sodium excretion in the edematous nephrotic patient may be related to the failure of sodium excretion in acute glomerular nephritis, and may represent a response to this form of renal injury.

Chemical changes preceding a diuresis in a cyclic form of nephrosis have recently been described by Rytand.<sup>18</sup> A rise in urinary alkalinity was the first sign of impending diuresis. Excretion of water preceded the release of sodium and chloride into the urine. We have observed a group of patients with nephrosis who showed a similar lag in the appearance of sodium in the urine, with a corresponding rise in the serum sodium concentration. Excretion of water without sodium may also occur for brief periods at the beginning of albumin treatment in severe nephrosis.<sup>4</sup>

The various forms of treatment of nephrotic edema are critically examined by Thorn<sup>19</sup> in a recent review. The basic measure is the low-sodium diet, abetted by acid-ash diet, acidifying diuretics or potassium salts if renal function permits. If signs of circulatory failure appear, digitalis is indicated. The mercurial diuretics are avoided as potentially dangerous. If renal function is adequate, urea may be given in large amounts by mouth to eliminate fluid from the body, but the fluid intake must be restricted. Amino acids or a high-protein diet is helpful if there has been a prolonged dietary deficit in protein or if the physician wishes to take advantage of the resulting high output of urea, but it requires careful planning to keep the sodium intake low when much protein or amino acids are given. Concentrated human serum albumin for intravenous use has advantages over plasma in its lower sodium content and its freedom from risk of homologous serum jaundice.\* Other

\*Concentrated human serum albumin is now scarce and expensive and one can only hope that voluntary blood donation through the American Red Cross and local programs will furnish adequate supplies of this valuable agent.

protein products are more readily available than albumin, but there are some reservations concerning their use. Southey's tubes remain a very effective means of removing accumulated edema without appreciable risk if careful sterile technic and penicillin therapy are used to eliminate infection. The induction of measles in nonimmune children may initiate a diuresis.<sup>20</sup>

### *Varieties of the Nephrotic Syndrome*

To the difficult differentiation of lipoid nephrosis from the nephrotic stage of glomerular nephritis, Addis<sup>2</sup> adds a third possible choice—a benign, cyclic form of nephrosis. Occurring at any age, a suddenly developing proteinuria is followed by most of the features of the nephrotic syndrome, which may subsequently disappear completely. Recurrences and remissions are seen. Death may rarely occur in the edematous stage, and a few post-mortem studies have shown no glomerulitis. The urinary sediment is not distinctive until after prolonged proteinuria. The urine may return to normal during remission, a finding that Addis regards as incompatible with a diagnosis of glomerular nephritis.

Rytand<sup>18</sup> has observed a cyclic nephrosis following bee sting. Tridione has been implicated as a cause of the nephrotic syndrome.<sup>21</sup> Early syphilis<sup>22</sup> and amyloidosis<sup>23, 24</sup> as causes of nephrosis are the subject of recent reviews.

## CARDIOVASCULAR-RENAL RELATIONS

### *Renal Failure*

The kidney occupies a strategic position in the regulation of the fluid and electrolytes on which the cardiovascular system depends for its normal function. Hypotension and collapse may occur in the "salt-losing nephritis," as well as in Addison's disease, when excessive amounts of sodium and water are lost in the urine.<sup>25</sup> In acute nephritis, the retention of sodium and water is associated with edema, an increased venous pressure and a dilated heart, as well as hypertension. Although the terminal stage of nephritis usually includes hypertension, cardiac embarrassment and retinal-artery disease, the patient with "salt-losing nephritis" usually escapes these complications until the last stages of his illness, when edema may also appear.<sup>25</sup> These observations strongly suggest that the kidney's handling of salt and water may affect the cardiovascular system.

### *Cardiac Failure*

Studies of cardiac failure indicate that the kidney is equally sensitive to failure of its normal cardiovascular support. Warren and Stead<sup>26</sup> have shown that in congestive heart failure, the kidneys fail to excrete salt and water in the normal manner, with resultant edema. They have further demonstrated that this salt retention is due to diminished cardiac

output, and not to venous engorgement of the kidneys or to increased venous pressure, as has long been the accepted view. They point out that the retention of salt and water takes place before there is any demonstrable increase in venous pressure. Merrill<sup>27</sup> states that the decreased volume of glomerular filtrate, combined with normal reabsorption of salt by the tubules, leads to salt retention. Mokotoff, Ross and Leiter<sup>28</sup> have also emphasized the relative constancy of the tubular reabsorptive mechanism for sodium despite variations in glomerular filtration rate. The acute sensitivity of the kidney to shock is described below. It seems quite possible that there is a common, central, regulatory mechanism that is stimulated to conserve sodium and water in an effort to sustain blood volume and cardiac output during cardiovascular emergencies.<sup>29-31</sup>

### *Hypertension*

The renal handling of sodium and water may play a role in "essential" hypertension. Perera and Blood<sup>31</sup> believe that hypertensive patients excrete sodium with some difficulty, owing to abnormal activity of the adrenal cortex. This is based on experiments with a comparative study of normal and hypertensive patients from whose diet salt was withdrawn for twenty-four hours. There was weight loss and diuresis in the control group, but these changes were not observed in the hypertensive patients. Landis and Abrams<sup>32</sup> report that hypertensive rats have an aversion for sodium chloride and bicarbonate, and when desoxycorticosterone is given this aversion is increased. These hypertensive rats did not show any particular appetite for ions supposed to reduce hypertension, such as ammonium, magnesium, thiocyanate and nitrite. These findings support an important role attributed to sodium chloride and the adrenal cortex by Selye,<sup>33</sup> in his general adaptation syndrome and in other observations by Selye and Stone.<sup>34</sup> These developments furnish some foundation for the use of low-salt diets in the treatment of hypertension.<sup>35, 36</sup> It seems likely that the success of Kempner's<sup>36</sup> rice diet is dependent on its low-salt and low-protein content. In this connection, it is interesting to note further observations by Selye's group<sup>37</sup> in which they have shown that the nephrosclerosis induced by the injection of anterior pituitary substance in rats is accompanied by hypertension, and that a low-casein diet is effective in preventing both. They also observed a significant increase in the weight and size of the adrenal glands in animals fed the high-protein diet.

The role of the kidney in the causation of hypertension is still unsettled. It seems clear that renal ischemia can cause hypertension,<sup>38-40</sup> but in the majority of patients, hypertension is not associated with a demonstrable, primary, renal lesion.<sup>41, 42</sup> There is still a real problem in the selection of the

hypertensive patients with unilateral renal disease for nephrectomy. In a recent review of the subject, Smith<sup>43</sup> has analyzed 242 reported cases in which nephrectomy was performed. In assessing the value of operation, only 47 of these met the criteria, which included a clear demonstration of, first, pre-existing hypertension, secondly, reduction of blood pressure to normal levels (140 systolic, 90 diastolic or below) and, thirdly, persistence of blood pressure at this level for a year or longer. Smith considered the operation successful in 19 per cent of the cases. Sabin<sup>44</sup> has reviewed 106 cases in which nephrectomy was performed for hypertension associated with unilateral renal disease. Pyelonephritis was the commonest offending pathologic lesion (45 per cent of the total), as in Smith's series. In Sabin's group, the blood pressure became normal in 51 patients, reduced in 23 and unchanged in 26—a more successful result than that in the cases reported by Smith, largely because of variations in criteria. Landley and Platt<sup>45</sup> have evaluated a similar group of patients. Smith concludes that the advisability of nephrectomy must rest upon conservative and recognized surgical indications, and not upon the hope of reducing blood pressure. If bilateral disease is present (and it usually is present in advanced hypertension), as a result of the hypertensive process itself, nephrectomy may shorten life by removing an important fraction of total available renal function.

#### RENAL DISEASE IN DIABETES MELLITUS

Robbins<sup>46</sup> discusses a group of conditions of frequent occurrence in diabetes, including glycogen nephrosis, nephrosclerosis, intercapillary glomerulosclerosis, pyelonephritis and necrotizing papillitis.

Glycogen nephrosis is a benign renal change limited to diabetic patients and those with von Gierke's disease (glycogenosis). In general, the presence of this finding at autopsy is dependent upon terminal control of the diabetes and not so much on the severity of the diabetes.

"Benign nephrosclerosis" is a frequent finding especially in older patients with hypertension. It occurs in a relatively younger age group and runs a more serious course in patients with diabetes.

Intercapillary glomerulosclerosis as defined by Robbins occurs only in diabetes, although closely allied pathological changes are found in nondiabetic persons. Kimmelstiel and Wilson's<sup>47</sup> cases were examples of the nodular type, which probably does not occur without diabetes.<sup>48</sup> A similar glomerular lesion occurring in diabetes mellitus is the diffuse type, which bears a close resemblance to changes seen in chronic glomerulonephritis and in nephrosclerosis.

Most recent observers agree that it is not easy to make the diagnosis clinically.<sup>46, 48-50</sup> Long duration of diabetes predisposes to the renal change, although the diabetes need not be severe. Hyper-

tension is of little diagnostic significance in an older diabetic patient. Albuminuria is also a common finding, but profuse albuminuria indicates a probable glomerular lesion. Hypoproteinemia and edema favor intercapillary glomerulosclerosis, but occur in only a small proportion of cases. Slowly developing renal insufficiency and a mixed vascular and diabetic retinopathy may be present. Robbins<sup>46</sup> suggests that a correct diagnosis can be made clinically in 60 per cent of the cases. In a recent report, Adams<sup>50</sup> discusses 5 interesting cases in young diabetic patients that fit the clinical criteria, but the pathologic lesions were found to be a combined inflammation and vascular hyaline degeneration.

Acute pyelonephritis is four and a half times more common a cause of death in diabetic than in nondiabetic patients, and 1 in 5 diabetic patients at autopsy shows some acute pyelonephritis.

Necrotizing renal papillitis is a peculiar form of pyelonephritis with massive necrosis of the renal pyramids, frequently involving all pyramids of both kidneys. Edmondson, Martin and Evans,<sup>51</sup> in a series of 859 diabetic patients, discovered 29 patients with renal papillitis, an incidence of 3.4 per cent. The organisms most commonly noted were *Escherichia coli* and *Staphylococcus aureus*, but *Mycobacterium tuberculosis* and actinomycetes were each found once. In the same series of 32,000 autopsies, these workers observed pyelonephritis in 1023 nondiabetic patients, of whom 21 had lesions characteristic of papillary necrosis. In 20 of these it was a complication of urinary-tract obstruction. Robbins, Mallory and Kinney<sup>52</sup> discussed 26 cases, 19 of the patients had diabetes, and all except 1 of the seven nondiabetic patients had an associated urinary-tract obstruction. Mallory, Crane and Edwards<sup>53</sup> have produced similar lesions in rabbits by ligating one ureter and injecting suitable pathogenic organisms into a vein. The lesions appeared only in the obstructed kidney.

The symptoms of necrotizing renal papillitis may be acute, with sudden onset of prostration, septic type of fever, tachycardia, leukocytosis, pyuria, oliguria, azotemia and a fulminating course ending in death within three or four days. In other cases, a subacute, protracted type appears, characterized by weeks or months of purulent pyelonephritis, with a terminal exacerbation resembling the acute form of necrotizing papillitis. Richfield<sup>54</sup> and Stevens et al.<sup>55</sup> have reported cases, the latter group including an interesting review of the subject.

Edmondson and his co-workers<sup>51</sup> suggest that criteria for diagnosis of necrotizing papillitis in diabetes should include hematuria, renal colic, sudden appearance or aggravation of pyelonephritis and signs of sepsis or unexplained coma. Earlier, Mellgren and Redell<sup>56</sup> also described colic, explained by obstruction of the ureter by a sloughed papilla.

Characteristic roentgenographic signs have been reported by Allen,<sup>57</sup> who describes a cavity-like enlargement and deformity of the calyces in the pvelogram, resembling the findings in some types of renal tuberculosis. Edmondson<sup>51</sup> has more recently emphasized this point.

The early recognition of this serious complication, and the prompt institution of therapy may give the patient some chance of recovery.

#### IRRADIATED STEROL POISONING

This type of renal injury must be considered in any cases of uremia of obscure origin, and a history of joint pains and vitamin treatment should be sought. The widespread use of large doses of potent irradiated sterols for arthritis has made hypercalcemic renal insufficiency no longer a rarity.<sup>55, 59</sup> There is a wide individual variation in susceptibility to these products. Anorexia, nausea, abdominal pain and muscular weakness may give warning of a rising serum calcium. Prolonged hypercalcemia may lead to metastatic calcification of many tissues. Walsh and Howard<sup>60</sup> have recently described glistening deposits in the conjunctiva and cornea, visible under the slit-lamp, developing soon after a rise of the serum calcium.

Polyuria is often the first symptom of renal involvement. The urine is usually dilute and may contain no trace of albumin. Microscopical examination of urine may show casts containing black granules, which dissolve in acid. The finding of a grossly elevated blood urea may come as a surprise with such a benign urinalysis. If Sulzowitch's<sup>61</sup> simple test is applied to the urine, the hypercalciuria is at once apparent. The mystery is quickly solved when the patient is questioned specifically about vitamin D ingestion. Hyperparathyroidism must be considered if no history of medication can be obtained, and may raise a difficult diagnostic problem, since the serum calcium subsides very slowly in some patients when vitamin D is withdrawn. The normal condition of the bones and the high level of serum phosphate after vitamin D administration may be helpful.

#### RARE RENAL LESIONS

Interesting cases of renal involvement by poly-cystic disease,<sup>62-64</sup> periarteritis nodosa,<sup>65</sup> sarcoidosis<sup>66</sup> and sickle-cell disease<sup>67</sup> have been reported.

#### ACUTE RENAL-TUBULE INJURY

Lower-nephron nephrosis is the term designated by Lucké<sup>68</sup> to describe the renal lesions produced by a wide variety of traumatizing conditions that have in common the main feature of shock. Harkins<sup>69</sup> has listed more than 30 causes of shock, including trauma, burns, freezing, vascular occlusion, intestinal strangulation, bile peritonitis, visceral perforation, toxic drugs, venoms, anaphylaxis, transfusion reactions and fulminating infec-

tions. It is possible for renal lesions to develop secondarily to any one of these. Indeed, numerous recent reports<sup>70-74</sup> indicate the diversity of the etiologic factors, including many of those listed above.

Harman<sup>71</sup> has reviewed 1065 autopsies of battle casualties and found evidences of lower-nephron nephrosis in 152, or 14.2 per cent. Of these, 70 patients had died of renal insufficiency. The exciting causes included vascular damage, muscle trauma, crush, transfusion reaction, hemorrhage, burns, gas gangrene and shock. He also observed that the administration of sulfonamides had not increased the incidence or severity of the nephrosis.

Tagnon and his co-workers<sup>72</sup> have reviewed the situation regarding burns. They report 450 patients who lived more than two weeks after the burn and showed no evidence of lasting kidney dysfunction. On the other hand, of 35 patients who died less than two weeks after the burn, 14 had definite clinical and pathological evidence of renal injury. Martineau and Hartman,<sup>73</sup> in a combined experimental and clinical study of burns, conclude there is a close relation between the "burn" kidney and the renal findings of other conditions characterized by intravascular hemolysis.

In relation to shock from trauma and burns, Fox and Baer<sup>75</sup> have correlated death with extrusion of considerable potassium from injured cells and their acquisition of an equivalent amount of sodium. They believe that this exchange results in swelling of uninjured tissue cells throughout the body, leading to additional reduction in extracellular fluid and blood volumes.

Sanderson<sup>74</sup> has reported 4 cases of renal insufficiency following abdominal catastrophe in which he believed that dehydration played a dominant role.

Corcoran, Taylor and Page<sup>76</sup> and, more recently, Kugel<sup>77</sup> have used the term "acute toxic nephrosis" to apply to cases that are primarily the result of poisoning or from hemolytic transfusion reaction. Many such cases have been reported. Bock et al.<sup>78</sup> have reported a case due to sulfadiazine; Woods<sup>79</sup> and Kugel<sup>77</sup> cases due to carbon tetrachloride, Anderson<sup>80</sup> a case of renal damage resulting from sensitivity to neoarsphenamine, and Corcoran, Taylor and Page<sup>81</sup> cases of vitamin D intoxication and mercuric bichloride poisoning.

The renal lesions occur in a similar region in all these cases, with selective tubular damage to the ascending loops of Henle and the distal tubules. The glomeruli and proximal tubules are only indirectly affected. These pathological findings have been described by Lucké,<sup>68</sup> Mallory,<sup>82</sup> Bywaters<sup>83</sup> and others. Woods<sup>79</sup> has remarked on the similarity of the renal changes in the crush syndrome and carbon tetrachloride poisoning.

The mechanism of the production of this renal injury has been the subject of much experimental

work Corcoran and Page<sup>84</sup> showed that shock and early hypotension from bleeding resulted in renal vasoconstriction, and that subsequent raising of the arterial blood pressure and blood volume by transfusion failed to restore the indirectly determined renal blood flow to more than 50 per cent of normal. In an earlier work, Page<sup>85</sup> suggested that the vasoconstrictive ischemia is of humoral origin. In this connection, Little, Green and Hawkins,<sup>86</sup> in crossed-transfusion experiments with shocked and normal dogs, were unable to observe any impairment in urine formation that could be attributed to the operation of a humoral factor and concluded that it was probably due to a lowering of the mean arterial pressure together with homeostatically induced renal vasoconstriction.

Corcoran and Page<sup>84</sup> summarize the sequence of events as follows: vasoconstrictive renal ischemia occurs with onset of shock or injury and more or less myoglobin diffuses into the blood from the crushed area and is filtered into the renal tubules; pigmentary precipitation may then occur and is facilitated by the presence of a urine that is acid and of small volume. Bywaters<sup>83</sup> and Mallory<sup>82</sup> agree that the formation of precipitated material in the tubules may contribute to the progress of the lesions once they are initiated by renal ischemia, though they do not believe that mechanical obstruction is the cause of renal failure. Lucké<sup>88</sup> states that in many of his cases he found few pigment casts and points out that in the anuria of shock the urine is of low specific gravity and small volume, indicating a more general renal lesion. In this connection, Yuile, Gold and Hinds<sup>87</sup> conclude that the precipitation of hemoglobin in the renal tubules is primarily dependent on antecedent damage to the tubules and not on the acidity or alkalinity of the urine or the amount of hemoglobin in the blood.

The similarity of the lesions produced by nephrotoxic substances and shock has led Lucké to suggest that the cause of renal insufficiency is the same in both conditions. It is generally agreed that renal ischemia is the first step.<sup>88, 89</sup>

#### NEURAL CONTROL OF THE RENAL CIRCULATION

An important new description of the renal circulation promises to shed light on some of these obscure problems in renal dysfunction. Trueta et al.<sup>90</sup> present convincing evidence of a dual circulation to the kidney under the control of the autonomic nervous system. The work began with arteriograms of the hind limbs of rabbits after a simulated crushing injury. Arterial spasm was demonstrated not only at the level of the injury but also extending proximally and sometimes into the opposite limb. The renal arteries were found to be singularly sensitive to this reflex spasm, which persisted for hours after the injury. The blood pressure did not fall enough to account for such a compensatory vasoconstriction. It was found that

stimulation of afferent sciatic-nerve fibers, of efferent splanchnic-nerve components or of fibers about the renal artery caused renal-artery spasm. Other effective stimuli were rapid hemorrhage, large doses of epinephrine or pitressin and the injection of staphylococcus toxin.

In an excellent series of radiographs and pigment injections, Trueta and his co-workers demonstrated a striking diversion of intrarenal blood flow from the cortex to the medulla of the kidney during the various procedures used to excite the renal-artery spasm. The blanching of the cortex was observed directly on the exposed kidney. The renal blood flow did not stop, but the renal vein sometimes took on a bright-red color and a pulsatile flow. The rapid renal-circulation time as measured by dyes suggested that an actual shunt of blood through the medullary circuit might occur.

The arterial spasm affecting the outer two thirds of the cortex failed to impair the circulation to the innermost glomeruli. These juxtamedullary glomeruli were dilated, and supplied the first link in the medullary shunt, which then continued through the vasa recta deep into the medulla. The vasa recta mingled freely with the long loops of Henle arising from the deeper glomeruli. It is suggested that this is an ideal site for water reabsorption, and that the diversion of circulation to the medulla may lead to oliguria or even to anuria.

Most of these experiments were done in rabbits, which are known to have a very labile renal circulation, but the work has now been extended to several other mammals and doubtless will soon be tested in man. Normal men have a very steady rate of glomerular filtration, but there is evidence that disease may modify this picture. In particular, hemorrhagic shock is known to affect renal clearances out of all proportion to the fall in blood pressure.<sup>88</sup> In dogs, the clearance of para-amino hippuric acid, which usually measures renal blood flow, may be depressed well below the actual renal flow for prolonged periods, even after blood transfusion has increased the blood pressure to normal levels.<sup>84</sup> Collateral evidence<sup>84, 88, 89</sup> points strongly to a redistribution of circulation through the kidney in hemorrhagic shock and may indicate the presence in man of a shunt such as Trueta and his co-workers have demonstrated. It also seems likely that reflex and hysterical anuria may depend on renal vasoconstriction. The importance of ischemia of the renal cortex in the development of the crush syndrome and allied states has already been pointed out.

Diseased kidneys may contain juxtamedullary glomeruli that have degenerated into little more than direct passages for the escape of blood from the arteries to the vasa recta. Trueta and his co-workers suggest that these are produced in some cases by repeated reflex diversion of the blood through the medullary circuit. If such changes could follow emotional stress, a possible explanation

tion for the development of cortical ischemia and of a chronic hypertension might be imagined. Endless fields for speculation on the possible effects of the reflex control of the renal circulation are opened up, and further experimental studies are eagerly awaited.

#### TREATMENT OF ACUTE RENAL INSUFFICIENCY

Therapy is considered in three stages: immediate, specific treatment to minimize damage, regulation of fluid and electrolyte balance, and dialyzing procedures to reduce azotemia.

##### Initial Measures

The first aim of therapy is to limit the extent of damage as far as possible. The first measure is replacement of lost blood and fluid in cases of severe shock, and pressure bandaging of the affected part before removal of the tourniquet in cases of trauma.<sup>84</sup> It is during this period of the first few hours that renal ischemia is present and renal blood flow and renal function are reduced.<sup>88, 89</sup> Dogs can tolerate complete renal-artery occlusion for as long as two or three hours without irreversible damage.<sup>91, 92</sup> The timing of blood replacement is of utmost importance to the ultimate outcome, since in the earliest stages serious renal injury may be avoided.

In the nephrotoxic cases, the immediate exclusion or neutralization of the offending agent is of prime importance. Alkalinization of the urine is valuable in the prevention of renal injury by sulfonamides, and may be useful in transfusion reaction, although there is still difference of opinion about the efficacy of this. Thus, Flink<sup>93</sup> reports that in dogs the excretion of hemoglobin proceeds at about the same rate and produces approximately the same renal damage whether the urine is acid or alkaline. On the other hand, Fox et al.,<sup>94</sup> Corcoran and Page<sup>84</sup> and others recommend the alkalinization of the urine after transfusion reactions. Clinically, the use of alkali appears of limited value unless given early and in adequate dosage.

BAL<sup>95</sup> may be life saving in mercuric bichloride poisoning, but prompt institution of therapy is important. Most patients have recovered despite very large doses of mercuric chloride, when BAL was given in adequate dosage within four or five hours after poisoning. When treatment is delayed for six hours, the effectiveness of BAL is much less striking. Sodium formaldehyde sulfoxylate is recommended for lavage of the stomach, to inactivate unabsorbed mercuric chloride.

##### Fluid and Electrolyte Balance

When a patient is found to be passing no urine, and when obstruction of the urinary tract has been ruled out, there is a natural impulse to force fluids to "open up the kidneys." Dehydration and shock are strong indications for immediate parenteral therapy, but often the treatment is continued too

long and too vigorously when no urine is excreted. After some days of heavy intravenous fluid therapy, the patient is edematous, circulatory failure may be imminent, and frequently the concentration of sodium and chloride in the plasma is depressed to dangerous levels.

The error in treatment arises from failure to recognize the elementary fact that *the anuric patient cannot excrete water* except in very limited amounts in breath, sweat and stools. There is every reason to establish a normal circulation and state of hydration, but there are equally cogent reasons for not exceeding the normal range of fluid volume. Another liability of the anuric patient is his inability to excrete potassium, which slowly increases in concentration in the plasma until dangerous or fatal levels are reached.

Hope must not be lost even when the outlook seems darkest, for diuresis may begin at any time if the patient is kept in good condition. Since the renal injury is usually self-limited, a remarkable restoration of function occurs if the patient can be tided over the critical period.

Thorn<sup>19</sup> has outlined a program to be followed during this phase.

The careful restriction of fluids so that no gain in body weight is observed during the period of anuria. In most patients 1000 to 1500 cc of fluid for twenty-four hours is adequate in the absence of fever or fluid loss from vomiting, diarrhea or other causes.

The provision of as high a caloric intake as possible during the early stage of anorexia and vomiting, 15 per cent glucose solution as an infusion will reduce endogenous protein breakdown.

The use of small quantities of plasma ( $\frac{1}{2}$  unit) or normal human serum albumin (10 to 15 gm daily) in the glucose solution to maintain blood volume and to prevent to some extent excessive fluid dissipation into the extracellular spaces. Intravenous albumin and plasma may reduce endogenous nitrogen breakdown somewhat.

Digitalization at the first evidence of cardiac enlargement or pulmonary congestion.

The quantity of sodium chloride to be given each day should be planned to keep a normal concentration of these electrolytes in the plasma. Kugel<sup>77</sup> suggests 5 or 6 gm per day to supply the approximate amount required daily by the normal person and that this amount be increased or decreased according to the state of hydration. He also points out that marked tissue weight loss occurring during this period may release a large volume of intracellular fluid, which aggravates the edema.

By this conservative routine, spontaneous diuresis may be effected on the tenth to the twelfth day in many cases, especially the less severe ones, and the

patients will go on to recover Thorn<sup>19</sup> and Kugel<sup>77</sup> have reported cases in which such recoveries have taken place

In the severe cases such an outcome may occur, but resort to more radical means of correcting the azotemia and electrolyte unbalance may become necessary These procedures are discussed below

### *Phase of Diuresis*

Burwell, Kinney and Finch<sup>96</sup> point out that the second peak in the mortality rate in cases of intravascular hemolytic crises occurs on the tenth day regardless of the fact that many of the patients had shown a spontaneous diuresis at that time Thorn<sup>19</sup> suggests that this is related to the development of hypochloremia and subsequent dehydration at a time when the renal lesion is actually improving but normal function has not been completely established Large amounts of sodium chloride and water may be required during this period, or, in rare cases, water without salt must be given<sup>97</sup> The amount can only be determined by close examination of the serum chloride and bicarbonate levels until the kidney has recovered its normal regulatory functions

### *Artificial Kidney*

With the increased incidence and recognition of lower-nephron nephrosis and toxic nephrosis during recent years, there has been a strong impetus to further the clinical application of the original work done by Abel, Rowntree and Turner<sup>98</sup> in the removal of diffusible substances from the blood by dialysis Several methods have been evolved by different investigators and applied clinically with varying degrees of success

Kolff,<sup>99</sup> Alwall<sup>100</sup> and Murray<sup>101</sup> have developed "artificial kidneys" and applied them successfully in many cases of renal failure They differ in some respects, but all use cellophane as the membrane to remove diffusible crystalloids from the blood to the exterior as well as to maintain the normal concentration of the essential components of the blood

Kolff<sup>99</sup> has recently reviewed some of his results Of the first 15 patients on whom the artificial kidney was used, 14 died, and of the next 16, 10 died These apparently disastrous results were due to the high percentage of chronic renal disease, in which any improvement could be only temporary On the other hand, he cited several cases of successful treatment of uremia in patients with acute glomerulonephritis and mercuric bichloride poisoning

Alwall<sup>100</sup> claims that his dialyser is superior to that of Kolff and lists advantages to support his view the apparatus is small, all the cellophane is in contact with saline solution, the blood does not have to pass the rotation cylinder, arterial pressure is the driving force lessening the incidence of hemolysis, there is less risk of coagulation, heparin

dosage is reduced, and there is therefore less tendency to hemorrhage, and the blood pressure does not fall, and therefore there is no shock Certainly, the reduction of hemorrhage and shock would be important advances Alwall has reported successful cases in which his apparatus was used, both experimentally and clinically

Murray<sup>101</sup> has had good results with his artificial kidney in experimental work One of his clinical cases with renal shutdown secondary to an induced abortion is particularly enlightening Repeated use of the artificial kidney kept the patient alive until the kidneys were able to secrete urine, and progressive recovery ensued As much as 66 gm of nonprotein nitrogen was removed with a single period of dialysis

In contrast to these generally successful reports, Muirhead and Vanatta<sup>104</sup> have tested the artificial kidney experimentally on dogs, and, after disastrous results, concluded that in its present form it is not ready for clinical application

At present, the artificial kidney appears to be a promising therapeutic instrument for treatment of acute renal insufficiency, but its use is not without risk It requires a trained medical and technical team for effective performance

### *Peritoneal Dialysis*

Suggested many years ago by Ganter,<sup>105</sup> peritoneal dialysis has recently been reintroduced by Seligman, Frank and Fine<sup>106, 107</sup> in the treatment of acute renal failure Fine, Frank and Seligman<sup>106</sup>, Goodyear and Beard<sup>108</sup> and Muirhead et al,<sup>109</sup> to mention a few, have reported successful application of this method to the treatment of uremia following incompatible blood transfusion Bloxson and Powell<sup>110</sup> have successfully treated a case of uremia concomitant with acute glomerulonephritis, and Pearson<sup>111</sup> reports its trial in a case of carbon tetrachloride poisoning Marsden<sup>112</sup> has reported its use in an interesting case of eclampsia Odel and Ferris<sup>113</sup> give an excellent review of 27 cases collected from the literature and report 1 case of their own

The clinical application of this form of treatment is becoming a widely accepted procedure, but it requires careful planning to avoid the pitfalls of water and electrolyte unbalance, of infection, and of poor timing The dialyzing fluid must be prepared in great volume The addition of sodium bicarbonate and antibiotics just before the fluid is used is clumsy and increases the possibility of contamination The composition of the fluid must be carefully planned to contain all the ingredients of the plasma, but its composition may have to be changed to meet individual needs Glucose is added to prevent the loss of blood sugar, and as an osmotic balance to avoid undue absorption of water The best method of use of antibiotics is still unsettled, and peritonitis is a definite risk Heparin is usually added to the fluid to slow the deposition of fibrin,

but the efficiency of dialysis falls off rapidly after three or four days

Muirhead, Small et al<sup>114</sup> report 3 cases in which they encountered one or another of these complications. In 1 case too much sodium chloride was absorbed, and the edema increased until distilled water was substituted and 70 gm sodium chloride subsequently removed in this way with copious diuresis following. In another case, after a transfusion reaction, peritoneal irrigation was begun early in hopes of preventing the development of azotemia. This condition was not avoided, however, and the renal lesion progressed in spite of irrigation, and edema and acidosis were continuous worries. A third case was also complicated by severe acidosis and edema. Rob and Richardson<sup>115</sup> have likewise emphasized these points. Robertson and Rutherford<sup>116</sup> have encountered pulmonary edema in a patient dying on the eighth day.

To combat some of these complications, Reid, Penfold and Jones<sup>117</sup> have successfully used intermittent peritoneal irrigation. This may prevent the formation of a channel between entrance and exit tubes, which often takes place with continuous irrigation.

For control of peritonitis, most authors recommend the addition of penicillin, streptomycin or sulfonamides to the fluid, but Reid<sup>117</sup> has discarded penicillin as having an irritating effect on the peritoneum, which, by causing exudation, might interfere with free osmosis.

In summary, it may be said that peritoneal irrigation should be reserved for cases of acute renal insufficiency in which the process is likely to be reversible and only after more conservative measures have failed.

### *Intestinal Lavage*

In an effort to find a safe, effective means of dialyzing water and crystalloids across a membranous surface of the body, numerous investigators have used various segments of the gastrointestinal tract.

Kolff<sup>118</sup> and Daugherty, Odel and Ferris<sup>119</sup> have concluded that the colon is unsuitable as a dialyzing membrane in the treatment of uremia, but an isolated loop of small intestine can be used with more success. Seligman, Frank and Fine,<sup>120</sup> after comparative studies in animals, concluded that the jejunum is probably the most suitable segment of the intestine for dialysis.

Most of these authors<sup>106, 118-121</sup> have perfused various segments of the gastrointestinal tract in treating patients with uremia. The results do not seem to be as encouraging as those with peritoneal lavage, but the procedure has not been so widely applied and many technical difficulties have to be overcome.

### *Renal Decapsulation*

One of the numerous theories proposed to explain renal failure in toxic nephrosis is a decrease of the effective filtration pressure as a result of increased intrarenal pressure. Peters<sup>70</sup> recommends early decapsulation in severe cases and states that this procedure reduces the intrarenal pressure by 50 per cent. One point against this theory is that it does not explain the spontaneous diuresis on the tenth to the twelfth day when fluid retention is maximum. A more reasonable relation to the onset of the diuresis appears to be the fact that the tubular epithelium begins to regenerate soon after injury and is often adequately healed by the fourteenth day. Reports of a few cases successfully treated by this method have recently appeared in the literature including one by Reid, Penfold and Jones<sup>122</sup> in which peritoneal irrigation was combined with renal decapsulation.

Culpepper and Findley,<sup>123</sup> in an excellent review of the subject, discuss numerous cases of decapsulation and report an over-all mortality of about 50 per cent. They suggest that decapsulation of one kidney is as effective and less dangerous than a bilateral operation.

### *Spinal Anesthesia or Splanchnic Block*

Trueta and his co-workers<sup>90</sup> have clearly demonstrated that reflex stimulation of the splanchnic nerves can divert the renal circulation from the cortical glomeruli. After section of the splanchnic nerves, this effect is reversed, and injury leads to a dilated cortical circulation. It is suggested that renal failure in the crush syndrome and allied conditions are of neurogenic origin and that they should be treated by spinal anesthesia or splanchnic block.

Several recent reports describe successful use of these methods in the treatment of acute renal shutdown. O'Sullivan and Spitzer<sup>124</sup> have successfully treated 2 cases of postabortion anuria with spinal anesthesia. Williams<sup>125</sup> reports a case of renal failure due to Weil's disease, in which diuresis continued after the effects of spinal anesthesia had worn off. This patient went on to recover. Robertson<sup>126</sup> has reported 3 cases of renal failure secondary to Weil's disease treated by this method, with 1 recovery and 2 deaths. In the fatal cases, the spinal anesthesia was carried out very late in the course of the disease.

Hingson and his co-workers<sup>127</sup> have had some interesting results with continuous caudal and spinal anesthesia, 35 patients suffering from anuria due to various causes, including eclampsia and acute vascular accidents, were treated. There were 8 deaths, 2 being among eclamptic patients, and in 2 it is possible that the splanchnic block contributed to the fatal outcome. It seems possible to keep up a continuous block for ten days, — that

is, to the crucial period, — after which the kidneys may resume normal function

\* \* \*

These observations bring out the important interdependence of the cardiovascular system, the autonomic nervous system and the kidney, and emphasize the need of consideration of the whole group of organs in renal malfunction or injury. Only rarely can an established renal injury be modified, but, guided by chemical and physiologic data, one can tide some patients over a critical period of renal insufficiency.

## REFERENCES

- Christian, H. A. *Bright's Disease* 385 pp New York Oxford University Press 1948
- Addis T. *Glomerular Nephritis Diagnosis and treatment* 338 pp New York Macmillan Co 1948
- Lopez Cardozo E. Hydræmia in acute nephritis *Acta med Scandinav* 125 333 338 1946
- Luetscher, J. A., Jr., and Hall A. D. Unpublished data
- Burke, F. M., and Ross S. Acute glomerulonephritis: review of ninety cases *J Pediatr* 30 157-170 1947
- Rapoport, M. Some thoughts on management of acute hemorrhagic nephritis in children *Pennsylvania M J* 50 1342-1344 1947
- Rudebeck J. Clinical and prognostic aspects of acute glomerulonephritis *Acta med Scandinav Supp* 173 pp 1-184 1946
- Steinmann B. and Reuhl F. Beitrag zur antiallergischen Behandlung der Nephritis *Helvet med acta* 13 456-459 1946
- Sen S. Penicillin in acute nephritis in children *Am J M Sc* 211 289 292 1946
- Bradley S. E., and Tyson C. J. 'Nephrotic syndrome' *New Eng J Med* 238 223 227 1948
- Combined Staff Clinics. Nephrotic syndrome *Am J Med* 2 386-401 1947
- Janeway C. A. et al. Chemical clinical and immunological studies on products of human plasma fractionation VIII Concentrated human serum albumin *J Clin Investigation* 23 465-490 1944
- Thorn G. W. Armstrong S. H. Jr. Dickerson U. C. Woodruff L. M. and Tyler, F. H. Chemical clinical and immunological studies on products of human plasma fractionation XXX Use of salt poor concentrated human serum albumin solution in treatment of chronic Bright's disease *J Clin Investigation* 24 802-828 1945
- Roth O. Concentrated human plasma albumin in treatment of nephrotic edema: report of four cases *Connecticut M J* 11 514-519 1947
- DeSanctis A. G. and Sullivan A. M. Nephrosis case treated with concentrated low salt human serum albumin *J Pediatr* 30 91-95 1947
- Luetscher J. A. Jr. Effect of single injection of concentrated human serum albumin on circulating proteins and proteinuria in nephrosis *J Clin Investigation* 23 365 371 1944
- Idem. Study of mechanism of nephrotic edema *J Clin Investigation* 26 1189 1947
- Rytand D. A. Chronologic separation of water and chloride diuresis in nephrotic syndrome *Am J Med* 4 624 1948
- Thorn, G. W. Treatment of renal insufficiency *J Urol* 59 119 1948
- Hutchins G. and Janeway C. A. Observations on relationship of measles and remissions in nephrotic syndrome *Am J Dis Child* 73 242 1947
- Barnett H. L. Simons D. G. and Wells R. E. Jr. Nephrotic syndrome occurring during triadone therapy *Am J Med* 4 760 764 1948
- Thomas E. W. and Schur M. Clinical nephropathies in early syphilis *Arch Int Med* 78 679-686 1946
- Reiselman, S. D. Early amyloid nephrosis in complicated trauma of bone sustained during war *Arch Int Med* 80 165-174 1947
- Lindsay S. Primary systemic amyloidosis with nephrosis *Am J Med* 4 765-772 1948
- Thorn G. W. Koepf G. F. and Clinton, M. Jr. Renal failure simulating adrenocortical insufficiency *New Eng J Med* 231 76-85 1944
- Warren J. V. and Stead E. A. Jr. Fluid dynamics in chronic congestive heart failure: interpretation of mechanisms producing edema increased plasma volume and elevated venous pressure in certain patients with prolonged congestive failure *Arch Int Med* 73 138-147 1944
- Merrill A. J. Mechanism of salt excretion in congestive heart failure: preliminary report. *Proc Am Federation Clin Research* 2 8 1945
- Mokotoff R. Ross, G. and Leiter L. Renal plasma flow and sodium reabsorption and excretion in congestive heart failure *J Clin Investigation* 27 1-9 1948
- Smith H. W. *The Physiology of the Kidney* 310 pp New York Oxford University Press 1937
- Verney E. B. Absorption and excretion of water antidiuretic hormone *Lancet* 2 739 1946
- Perera, G. A., and Blood D. W. Disturbance in salt and water metabolism in hypertension *Am. J Med* 1 602-606, 1946.
- Landis E. M. and Ahrens, H. Choices of salts and water by normal and hypertensive rats with and without desoxycorticosterone *Federation Proc* 6 147, 1947
- Selye H. General adaptation syndrome and diseases of adaptation *J Clin Endocrinol* 6 117-230 1946
- Selye, H. and Stone, H. Pathogenesis of cardiovascular and renal changes which usually accompany hypertension *J Urol* 56 399-419, 1946.
- Perera G. A. and Blood D. W. Relationship of sodium chloride to hypertension *J Clin Investigation* 26 1109 1118 1947
- Kempner W. Treatment of hypertensive vascular disease with rice diet. *Am J Med* 4 545-577 1948
- Dontigny P. Hay, E. D. Prado J. L. and Selye H. Hormonal hypertension and nephrosclerosis as influenced by diet. *Am. J M Sc* 215 442-447 1948
- Goldblatt H. Lynch, J. Hanzal R. F., and Summerville W. W. Studies on experimental hypertension I Production of persistent elevation of systolic blood pressure by means of renal ischemia *J Exper Med* 59 347-380 1934
- Goldblatt H. Experimental renal hypertension *Am J Med* 4 100-119 1948
- Braun-Menendez, E. Fasciolo J. C. Leloir L. P. Minoz, J. M., and Taquini A. C. *Renal Hypertension* 451 pp Springfield, Ill., Charles C Thomas 1946
- Castleman B. and Smithwick R. H. Relation of vascular disease to hypertensive state based on study of renal biopsies from 100 hypertensive patients *J A M A* 121 1256-1261 1943
- Golding W. Consideration of human hypertension with respect to its renal origin and therapy *Am J Med* 4 875-885 1948.
- Smith H. W. Hypertension and urologic disease *Am. J Med* 4 724-743 1948
- Sahin H. S. Hypertension in unilateral renal disease *J Urol* 59 820 1948
- Landley G. J. and Platt, R. Hypertension and unilateral kidney disease. *Quart J Med* 16 143 155 1947
- Robbins S. L. Renal lesions in diabetes mellitus *Bull Nrs Ex M Center* 10 78-83 1948
- Kummelstiel P. and Wilson C. Inter-capillary lesions in glomeruli of kidney *Am J Path* 12 83 98 1936
- Bell, E. T. *Renal Disease* 434 pp Philadelphia Lea & Febiger 1946
- Henderson L. L. Sprau R. G. and Wagener H. P. Inter-capillary glomerulosclerosis *Am J Med* 3 131-144 1947
- Adams L. J. Renal complications in young diabetics. *Casual M A J* 57 540-543 1947
- Edmondson H. A. Marun H. E. and Evans N. Necrosis of renal papillae and acute pyelonephritis in diabetes mellitus. *Arch Int Med* 79 148-175 1947
- Robbins S. L. Mallory G. K. and Kinney T. D. Necrotizing renal papillitis form of acute pyelonephritis *New Eng J Med* 235 885 893 1946
- Mallory G. K., Crane A. R. and Edwards J. E. Pathology of acute and of healed experimental pyelonephritis *Arch Path* 30 330-347 1940
- Richfield D. F. Chronic interstitial pancreatitis with diabetes mellitus and terminal necrotizing renal papillitis. *Ohio W J* 44 59 1948
- Stevens R. J. Wertbammer S. and Pearson J. S. Renal papillary necrosis complicating diabetes mellitus (review of literature with case report) *West Virginia M J* 44 12 15 1948
- Mellgren J. and Redell G. Zur Pathologie und Klinik der Papillitis necroticans renalis *Acta chir Scandinav* 84 439-457 1941
- Alken C. E. Die Papillennekrose *Ztschr f Urol* 32 433-438 1938
- Tumulty P. A. and Howard J. E. Irradiated ergosterol poisoning: report of two cases *J A M A* 119 233 236 1942
- Kaufman P. Beck, R. D. and Wiseman R. D. Vitamin D ('ertrol') therapy in arthritis: treatment followed by massive metastatic calcification renal damage and death *J A M A* 134-688-690, 1947
- Walsh F. B. and Howard J. E. Conjunctival and corneal lesions in hypercalcemia *J Clin Endocrinol* 7 644-652 1947
- Barney J. D. and Sulkowitch H. W. Progress in management of urinary calculus *J Urol* 37 746-762 1937
- Burkholder, T. M. and Braund R. R. Massive calcinosis with chronic insufficiency due to polycystic kidneys: case report *J Urol* 57 1001 1009 1947
- Mayers M. M. Polycystic kidney disease *J Urol* 59 471-476 1948
- Rieger C. O. F. Polycystic kidneys *M J Australia* 1 216 1948
- Womack R. K. and Matthews W. R. Renal manifestations of periarthritis nodosa *J Urol* 59 733 747, 1948
- Klinefelter H. F. Jr. and Salley S. M. Sarcoidosis simulating glomerulonephritis *Bull Johns Hopkins Hosp* 79 333 341 1946
- Abel M. S. and Brown C. R. Sickle cell disease with severe hematuria simulating renal neoplasm. *J A M A* 136 624 1948
- Lucké B. Lower nephron nephrosis: renal lesions of crush syndrome of burns transfusions and other conditions affecting lower segments of nephrons *Mil Surgeon* 99 371 396 1946.

69 Harkins H. Recent advances in study and management of traumatic shock. *Surveys* 9:231 1941

70 Peters J T. Oliguria and anuria due to increased intrarenal pressure. *Ann Int Med* 23:221-236 1945

71 Harman J W. Lower nephron nephrosis. *Irish J Med Sc* (No 259) 480-486 1947

72 Taghon H J, Levenson S W, Goodpasture W E and Taylor F H. L. Clinico-pathological correlation of kidneys in patients with thermal burns. *Proc Am Federation Clin Research* 2:24 1945

73 Martineau P C and Hartman F W. Renal lesions in extensive cutaneous burns. *J A M A* 134:429-436 1947

74 Sanderson P H. Renal failure following abdominal catastrophe and alkalosis. *Clin Sc* 6:207-222 1948

75 Fox, C. L. Jr and Baer H. Redistribution of potassium, sodium and water in burns and trauma and its relation to phenomena of shock. *Am J Physiol* 151:153-167 1947

76 Corcoran A C, Taylor R D and Page I H. Acute toxic nephrosis: clinical and laboratory study based on case of carbon tetrachloride poisoning. *J A M A* 123:81-85 1943

77 Kugel V H. Management of acute toxic nephrosis. *Am J Med* 3:188-205 1947

78 Bock, A. V. et al. Case records from medical grand rounds of Massachusetts General Hospital (Case 34). *Am Practitioner* 2:344-348 1948

79 Woods W W. Changes in kidneys in carbon tetrachloride poisoning, and their resemblance to those in crush syndrome. *J Path & Bact* 58:767-773, 1946

80 Anderson R H. Renal damage resulting from idiosyncrasy to neocarsphenamine. *Am J Med* 2:121-125 1947

81 Corcoran A. C., Taylor R. D. and Page I. H. Functional patterns in renal disease. *Ann. Int Med* 28:560-582 1948

82 Mallory T B. Hemoglobinuria nephrosis in traumatic shock. *Am J Clin Path* 17:427-443 1947

83 Bywaters E G L. Ischemic muscle necrosis crushing injury, traumatic edema crush syndrome, traumatic anuria, compression syndrome type of injury seen in air raid casualties following burial beneath debris. *J A M A* 124:1103-1109 1944

84 Corcoran A. C. and Page I H. Crush syndrome post-traumatic anuria: observations on genesis and treatment. *J A M A* 134:436-441 1947

85 Page I H. Occurrence of vasoconstrictor substance in blood during shock induced by trauma, hemorrhage and burns. *Am J Physiol* 139:386-398 1943

86 Little J M, Green H D and Hawkins, J E. Jr. Evidence from crosstransfusion experiments that diminished urine flow accompanying ischemic compression shock is not due to humoral factors. *Am. J Physiol* 151:554-563 1947

87 Yule C L, Gold M A and Hinds E C. Hemoglobin precipitation in renal tubules: study of its causes and effects. *J Exper Med* 82:361-374 1945

88 Lauson H. D., Bradley S E and Connard A. Renal circulation in shock. *J Clin Investigation* 23:381-402 1944

89 Phillips R. A. et al. Effects of acute hemorrhagic and traumatic shock on renal function of dogs. *Am J Physiol* 145:314-336 1946

90 Trueta J, Barclay A. E., Franklin H J, Daniel P M. and Pritchard M. M. L. *Studies on the Renal Circulation* 187 pp Springfield Ill. Charles C Thomas 1947

91 Hamilton P B., Phillips R. A. and Hiller A. Duration of renal ischemia required to produce anuria. *Am J Physiol* 152:517-522 1948

92 Phillips R. A. and Hamilton P B. Effect of 20, 60 and 120 minutes of renal ischemia on glomerular and tubular function. *Am. J Physiol* 152:523-530 1948

93 Flink, E. B. Blood transfusion studies: relationship of hemoglobin and of pH of urine to renal damage produced by injection of hemoglobin solutions into dogs. *J Lab & Clin Med* 32:223-261 1947

94 Fox, C. L., Jensen O J., Jr and Mudge G H. Prevention of renal obstruction during sulfadiazine therapy. *J A M A* 121:1147-1150 1945

95 Longcope W T and Luetscher J A., Jr. Clinical uses of 2,3-dimercaptopropanol (BAL). VI. Treatment of acute mercury poisoning by BAL. *J Clin Investigation* 25:557-567 1946.

96 Burwell E. L., Kinney T D and Finch C. A. Renal damage following intravascular hemolysis. *New Eng J Med* 237:657-665 1947

97 Luetscher J A., Jr. and Blackman S S Jr. Severe injury to kidneys and brain following sulfatiazole administration. *Ann Int Med* 18:741-756 1943

98 Abel J J, Rowntree L G and Turner B B. On removal of diffusible substances from circulating blood of living animals by dialysis. *J Pharmacol & Exper Therap* 5:275-316 1914

99 Kolff W J and Van Noordwijk J. *The Artificial Kidney* 92 pp Kampen Holland J H Kolff, 1946

100 Alwall N. On artificial kidney. I. Apparatus for dialysis of blood in vivo. *Acta med Scandinavica* 128:317-325 1947

101 Murray G, Delorme E. and Thomas N. Development of artificial kidney: experimental and clinical experiences. *Arch Surg* 55:503-522 1947

102 Kolff W J. Artificial kidney. *J Mt Sinai Hosp* 14:71-79 1947

103 Alwall N, Norrit L. and Steins A. M. Clinical extracorporeal dialysis of blood with artificial kidney. *Lancet* 1:60-62 1948

104 Muirhead E. E. and Vanatta J C. Use of artificial kidney. *Am J Med* 4:467 1948

105 Ganter G. Über die Beseitigung giftige Stoffe aus dem Blute durch Dialyse. *München med Wchnschr* 70:1478-1480 1923

106 Seligman A. M., Frank H. A. and Fine J. Treatment of experimental uremia by means of peritoneal irrigation. *J Clin Investigation* 25:211-219 1946

107 Fine J., Frank H. A., and Seligman A. M. Treatment of acute renal failure by peritoneal irrigation. *Ann Surg* 124:877-878 1946

108 Goodyear W. E. and Beard D E. Successful treatment of acute renal failure by peritoneal irrigation. *J A M A* 133:1208-1210 1947

109 Muirhead E. E., Small A. B. and McBride R. B. Peritoneal irrigation for uremia following incompatible blood transfusion: report of case. *Arch Surg* 54:374-381 1947

110 Bloxson A. and Powell N. Treatment of acute temporary dysfunction of kidneys by peritoneal irrigation: successful treatment of ten-year-old male child. *Pediatrics* 1:52-57 1948

111 Pearson C. C. Carbon tetrachloride intoxication with acute hepatic and renal failure treated with peritoneal lavage: report of case. *Proc Staff Meet Mayo Clin* 22:314-320 1947

112 Mariden J A. Use of peritoneal dialysis in case of eclampsia. *N J Australia* 2:602, 1947

113 Odel H M. and Ferris D O. Treatment of acute renal insufficiency with peritoneal lavage. *Proc Staff Meet., Mayo Clin* 22:303-313 1947

114 Muirhead, E. E., Small A. B., Haley A. E. and Hill J M. Peritoneal irrigation for acute renal damage following incompatible blood transfusion. *J Lab & Clin Med* 32:988-1001 1947

115 Rob C. G. and Richardson J S. Peritoneal dialysis. *Lancet* 1:195 1947

116 Robertson H. R. and Rutherford P S. Peritoneal irrigation in treatment of renal failure due to transfusion reaction. *J Lab & Clin. Med.* 32:982-987 1947

117 Reid R., Penfold, J B. and Jones R. N. Peritoneal dialysis. *Lancet* 1:269 1947

118 Kolff W J. *New Ways of Treating Uremia* 113 pp London J & A. Churchill Ltd 1947

119 Daugherty G W, Odel H M. and Ferris D O. Continuous lavage of colon as means of treating renal insufficiency: report of case. *Proc Staff Meet., Mayo Clin.* 23:209-214 1948

120 Odel H M. and Ferris D O. Continuous lavage of small intestine as means of treating renal insufficiency: report of case. *Proc Staff Meet. Mayo Clin* 23:201-203 1948

121 Oppenheimer G D. and Rosenak, S. Intestinal irrigation in treatment of certain types of uremia: preliminary report. *J Mt. Sinai Hosp* 14:908-911 1948

122 Reid R., Penfold J B., and Jones R. N. Anuria treated by renal decapsulation and peritoneal dialysis. *Lancet* 2:749-753 1946.

123 Culpepper W S. and Findley T. Renal decapsulation for oliguria and anuria. *Ar J M Sc* 214:100-108 1947

124 O Sullivan J V. and Spitzer W. Acute renal failure complicating abortion. *J Obst & Gynaec Brit Emp* 54:158-176 1946.

125 Williams N. H. C. Treatment of renal failure in Weils disease by spinal anesthesia. *Lancet* 1:100 1947

126 Robertson K. Weils disease: rare condition. *Brit. M J* 2:810-815 1946

127 Hingson R. A., Whitacre F E., Hughes J G, Turner H. B. and Barnett, J G. New horizons in therapeutic nerve block in treatment of vascular and renal emergencies with continuous caudal and continuous spinal analgesia and anesthesia. *Mil Surgeon* 102:197 1948

## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

TRACY B MALLORY, M D, *Editor*

BENJAMIN CASTLEMAN, M D, *Associate Editor*

EDITH E PARRIS, *Assistant Editor*

#### CASE 34431

##### PRESENTATION OF CASE

*First admission* A seventy-six-year-old woman was admitted to the hospital because of "pains in the stomach."

For many years the patient had attacks of momentary knife-like pain in the left upper quadrant of the abdomen, which never caused her much concern. About ten months before entry, however, she was confined to bed for three days with repeated attacks, each lasting about half an hour. These began with a sharp "ball of pain" in the left upper quadrant of the abdomen, which moved toward the epigastrium, "stabbing" as it went and accompanied by much gurgling. The pain then passed off. Also at that time she had a "large, black, slimy discharge" from the rectum. She had no nausea or vomiting. She was then well except for occasional pains until one month before admission, when she again had a three-day attack of the same type of pain. One week later she passed a tarry stool. She never tried food or alkali for relief of the pain, and she did not notice any loss of strength or energy during the present illness. She noted no difference in the character of the pain upon sitting or lying down.

Her appetite had been poor for eight years before admission, the change having been noted about the time of a "nervous breakdown," which followed her husband's death. She was put on a diet at that time and ate no vegetables, raw fruits, fried or fatty foods.

Physical examination revealed a woman in no acute distress but showing some evidence of weight loss. The blood pressure was 190 systolic, 80 diastolic. The rest of the examination was essentially negative.

Examination of the blood disclosed a white-cell count of 10,800, with 71 per cent neutrophils. The hemoglobin was 13.2 gm per 100 cc. The red cells and platelets were fairly normal in appearance. The total protein was 7.1 gm, and the nonprotein nitrogen 26 mg per 100 cc. The urine specific gravity was 1.016, and the sediment contained 3 white cells per high-power field. A stool was guaiac negative.

A barium enema revealed numerous diverticula throughout the entire length of the colon but more marked in the descending and sigmoid portions. There was a redundancy of the hepatic flexure of the colon, and the cecum lay high and was directed laterally. About 5 cm from the cecal tip there was a constant constriction of the lumen over a length of about 2 cm (Fig 1). The mucosa within the lumen did not appear to be destroyed. The terminal ileum was not seen. A Graham test and an intravenous pyelogram were negative. A gastrointestinal series showed a normal esophagus with the patient in the erect position. However, with the patient in a prone position a large, readily reducible hiatus hernia was demonstrated, the cardia being situated above the diaphragm. The diaphragmatic hiatus was of good size but constricted the fundus slightly. No lesion was demonstrated within the herniated portion of the stomach, and the remainder of the stomach and duodenum was not remarkable. The small bowel was normal, the ileocecal region was not well shown.

After a stay of two and a half weeks in the hospital the patient was discharged to return in two months for another barium enema.

*Second admission* (approximately two months later). In the interval the patient had felt improved although she did not find the prescribed diet palatable. She had two attacks of crampy, sharp pain in the left upper quadrant of the abdomen, each lasting about three days and unassociated with nausea, vomiting, diarrhea or constipation. She had no tarry or bloody stools.

Physical examination showed, in addition to the findings of the first admission, slight tenderness in the left upper quadrant of the abdomen. The cecum was questionably palpable. The abdomen was protuberant and tympanitic, with hyperactive peristalsis of moderately high-pitched character.

Examination of the blood disclosed a white-cell count of 9300, with 74 per cent neutrophils. The hemoglobin was 9.7 gm. The stool was guaiac negative.

A plain film of the abdomen showed a suggestion of fullness overlying the sacrum extending somewhat to the right and about which ran a loop of small bowel. A barium enema revealed no abnormalities except diverticula until a redundant hepatic flexure was passed and the distal portion of the ascending colon entered. There the barium encountered an obstruction with narrowing of the lumen of the bowel but with many mucosal folds still apparent in that region. A gastrointestinal series confirmed the previous finding of a hiatus hernia that filled and emptied well. The remainder of the stomach was normal, as was the small bowel, with the exception of one persistent loop in the right lower quadrant, which appeared to be held in relatively constant position by an oval mass in the right lower quadrant (Fig 2). The proximal

portion of the large bowel demonstrated a constricting lesion in the ascending colon at the level of the apparent mass that fixed the small bowel

On the twelfth hospital day an operation was performed

### DIFFERENTIAL DIAGNOSIS

DR RICHARD SCHATZKI I have been given a large number of films and have selected some of them for demonstration I am in the position of the radiologist who has to rely on films of the gastrointestinal tract that somebody else has taken and somebody else has seen the fluoroscopy and taken spot films If that person did not see the actual lesion, I am out of luck because I will not have films of the lesion If he has seen it and has taken inadequate films, I am still in trouble I am probably in trouble anyhow

In summarizing the history one can say that in ten or twelve months this woman had two attacks of severe left-upper-quadrant pain, bled twice and ended up by having a slight anemia

As far as the question of bleeding is concerned, I have a spot film of the lower end of the esophagus that fails to show varices, and since I cannot see

bleeding because I am convinced that it is not a very common source of massive bleeding So for the sake of this discussion I am going to say that I do not believe that this patient bled from a hiatus hernia

The patient had numerous diverticula in the colon Diverticulosis, particularly diverticulitis of the colon, is supposed to cause hemorrhage Again, I am unhappy if I cannot find any other source of bleeding in a patient but diverticulosis or diverticulitis The recent surgical literature talks about bleeding in diverticulitis as if it were very common Personally, I am convinced that it is not common



FIGURE 2



FIGURE 1

any in the film, I am not going to think any more about them The most common source of bleeding in a patient with tarry stools is duodenal ulcer There are a few spot films of the duodenum that do not show any abnormality Although it is possible that on such films an ulcer might be missed, I am going to discard this diagnosis Hiatus hernia is a source of bleeding I am usually, however, not satisfied to accept a hiatus hernia as the source of

although it does occur I do not believe that this patient bled from diverticulosis, particularly since she had tarry stools

I would like to find something in this patient's left upper abdomen In looking through the films I have not been able to see anything there that might cause the symptoms

Some other things might be mentioned She had extensive arteriosclerosis of the abdominal aorta and its branches She had changes in the left femur that were probably due to Paget's disease

So we come to the ileocecal region — the lesion described in the record is not an area that one can understand from the films that we have The abnormal position of the ascending colon is seen The tip of the cecum, if this is the tip, is not the lowest point of the right colon but lies posteriorly

# CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

## Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

TRACY B MALLORY, M D, *Editor*

BENJAMIN CASTLEMAN, M D, *Associate Editor*

EDITH E PARRIS, *Assistant Editor*

### CASE 34431

#### PRESENTATION OF CASE

*First admission* A seventy-six-year-old woman was admitted to the hospital because of "pains in the stomach"

For many years the patient had attacks of momentary knife-like pain in the left upper quadrant of the abdomen, which never caused her much concern. About ten months before entry, however, she was confined to bed for three days with repeated attacks, each lasting about half an hour. These began with a sharp "ball of pain" in the left upper quadrant of the abdomen, which moved toward the epigastrium, "stabbing" as it went and accompanied by much gurgling. The pain then passed off. Also at that time she had a "large, black, slimy discharge" from the rectum. She had no nausea or vomiting. She was then well except for occasional pains until one month before admission, when she again had a three-day attack of the same type of pain. One week later she passed a tarry stool. She never tried food or alkali for relief of the pain, and she did not notice any loss of strength or energy during the present illness. She noted no difference in the character of the pain upon sitting or lying down.

Her appetite had been poor for eight years before admission, the change having been noted about the time of a "nervous breakdown," which followed her husband's death. She was put on a diet at that time and ate no vegetables, raw fruits, fried or fatty foods.

Physical examination revealed a woman in no acute distress but showing some evidence of weight loss. The blood pressure was 190 systolic, 80 diastolic. The rest of the examination was essentially negative.

Examination of the blood disclosed a white-cell count of 10,800, with 71 per cent neutrophils. The hemoglobin was 13.2 gm per 100 cc. The red cells and platelets were fairly normal in appearance. The total protein was 7.1 gm, and the nonprotein nitrogen 26 mg per 100 cc. The urine specific gravity was 1.016, and the sediment contained 3 white cells per high-power field. A stool was guaiac negative.

A barium enema revealed numerous diverticula throughout the entire length of the colon but more marked in the descending and sigmoid portions. There was a redundancy of the hepatic flexure of the colon, and the cecum lay high and was directed laterally. About 5 cm from the cecal tip there was a constant constriction of the lumen over a length of about 2 cm (Fig 1). The mucosa within the lumen did not appear to be destroyed. The terminal ileum was not seen. A Graham test and an intravenous pyelogram were negative. A gastrointestinal series showed a normal esophagus with the patient in the erect position. However, with the patient in a prone position a large, readily reducible hiatus hernia was demonstrated, the cardia being situated above the diaphragm. The diaphragmatic hiatus was of good size but constricted the fundus slightly. No lesion was demonstrated within the herniated portion of the stomach, and the remainder of the stomach and duodenum was not remarkable. The small bowel was normal, the ileocecal region was not well shown.

After a stay of two and a half weeks in the hospital the patient was discharged to return in two months for another barium enema.

*Second admission* (approximately two months later). In the interval the patient had felt improved although she did not find the prescribed diet palatable. She had two attacks of crampy, sharp pain in the left upper quadrant of the abdomen, each lasting about three days and unassociated with nausea, vomiting, diarrhea or constipation. She had no tarry or bloody stools.

Physical examination showed, in addition to the findings of the first admission, slight tenderness in the left upper quadrant of the abdomen. The cecum was questionably palpable. The abdomen was protuberant and tympanitic, with hyperactive peristalsis of moderately high-pitched character.

Examination of the blood disclosed a white-cell count of 9300, with 74 per cent neutrophils. The hemoglobin was 9.7 gm. The stool was guaiac negative.

A plain film of the abdomen showed a suggestion of fullness overlying the sacrum extending somewhat to the right and about which ran a loop of small bowel. A barium enema revealed no abnormalities except diverticula until a redundant hepatic flexure was passed and the distal portion of the ascending colon entered. There the barium encountered an obstruction with narrowing of the lumen of the bowel but with many mucosal folds still apparent in that region. A gastrointestinal series confirmed the previous finding of a hiatus hernia that filled and emptied well. The remainder of the stomach was normal, as was the small bowel, with the exception of one persistent loop in the right lower quadrant, which appeared to be held in relatively constant position by an oval mass in the right lower quadrant (Fig 2). The proximal

## ANATOMICAL DIAGNOSIS

*Carcinoid of ileum.*

## PATHOLOGICAL DISCUSSION

DR CLAUDE E. WELCH I must congratulate Dr Schatzki on his diagnosis. This was a very difficult problem clinically. When the patient first came to the hospital we thought that her symptoms were due to diaphragmatic hernia, accounting for the left-upper-quadrant pain and, apparently, for the gastrointestinal bleeding. She had, in addition, this defect in the cecum. Our attention was focused high on the ascending colon over this area seen in the first film, which I thought could be due to adhesions around an old diverticulitis. The question arose whether to operate on the strength of this x-ray finding or whether, at the age of seventy-six, she might be relieved by diet. We therefore sent her home for a two-month period to return for further evaluation. She modified her diet to the point where it included only water, which probably accounted for the secondary anemia, since the stools remained guaiac negative. Since at the second admission the same defect in the cecum was manifested and she did have an episode of distention, it seemed wise to explore her. At operation there were numerous adhesions in the right lower quadrant, a diaphragmatic hernia and diverticulitis. The remainder of the abdomen was normal except for the region of the ileocecal valve, where, in the midst of the adhesions, was a rather indefinite palpable mass. One definitely dilated loop of the terminal ileum was tied up in the adhesions. The rest of the small bowel was entirely normal. I did a right colectomy on her in one stage. Dr Mallory will give us the final report. It is only fair to state that we do not know yet whether or not the pains will be relieved by the operation. She is relieved of the disease in the right lower quadrant. The pain may have been due to the diaphragmatic hernia.

DR SCHATZKI How often does pain in the left upper quadrant occur with a diaphragmatic hernia?

DR WELCH The pains were repeated, postprandial attacks. It is not too uncommon to have pain of that type with diaphragmatic hernia.

DR MALLORY The lesion that Dr Welch resected was in the terminal ileum, immediately adjacent to the ileocecal valve. It was a tumor lying in the submucosal wall of the ileum. It extended through the wall into the mesenteric fat, and it had produced numerous adhesions. There was no actual tumor of the cecum. The tumor histologically was characteristic of carcinoid. There were numerous enlarged mesenteric lymph nodes, but none of them showed metastases. These carcinoids of the ileum do actually metastasize but usually not to any great distance. Not infrequently they metastasize to the immediately adjacent mesenteric lymph nodes.

DR SCHATZKI What caused the bleeding?

DR MALLORY There was no evidence of ulceration of the mucous membrane overlying the tumor, and I am not at all sure that we have an explanation for the bleeding.

DR SCHATZKI How large was the lesion?

DR MALLORY The actual tumor was 1.5 cm. in diameter — not very large.

## CASE 34432

## PRESENTATION OF CASE

*First admission* A thirteen-year-old schoolboy entered the hospital complaining of frequent bowel movements.

For about one year prior to admission he had experienced rather constant diarrhea, with up to seven evacuations daily, unassociated with pain or bleeding.

Physical examination was essentially negative.

The blood pressure was 110 systolic, 70 diastolic.

Examination of the blood disclosed a red-cell count of 3,630,000, with 40 per cent hemoglobin, and a white-cell count of 10,300, with 50 per cent neutrophils, 46 per cent lymphocytes, 2 per cent monocytes, 1 per cent eosinophils and 1 per cent basophils. The specific gravity of the urine varied from 1.008 to 1.028. The urine was negative for albumin, casts and cellular sediment. Two stool cultures were negative for pathogens, and an examination for amebas was negative. An x-ray film of the heart and lungs was noncontributory, and a barium enema showed extinction of the haustral markings with narrowing of the lumen and shortening of the bowel. On proctoscopic examination scattered pin-point, shallow ulcerations with fine hemorrhages were seen.

The serum nonprotein nitrogen was 19 mg., and the total protein 6.3 gm. per 100 cc., and the chloride 104 milliequiv. per liter. A blood Hinton test was negative.

During the patient's hospital stay of two months he was given sulfasuxidine, tincture of belladonna and two transfusions. He improved slowly and gained weight, and his bowel movements decreased to one or two a day.

*Second admission* (two and a half years later) During the interval the patient visited the Out-Patient Department regularly and gained about 20 pounds, although his diet was apparently not adequate in protein. One week before entry, following a cold, he developed slight abdominal swelling, anorexia and vomiting. He also noted swelling of the legs and scrotum. The urine was darker than previously.

On physical examination the abdomen was distended, with a well marked fluid wave. The liver edge was palpable two or three fingerbreadths below

behind the ascending colon. There are some spot films showing this constriction, which is very uncharacteristic, certainly in its shape. It does not simulate primary carcinoma of the colon. In this spot film it is conceivable that a smaller cancer is behind in the tip of the cecum, but I cannot see that in these films. The lateral view gives a better position of the cecum and ascending colon with the narrowed zone. There are many films of the small bowel. At least ten films of the small bowel were given to me. In none of them can I see the actual terminal few inches of the ileum and the actual ileocecal valve. When one looks at the loops of small bowel in the films taken at the time of the first admission and compares the pattern of the arrangement of loops of small bowel, one has the impression that the pattern does change to some degree—not quite so much, however, as it does in the average patient with a normal peritoneal cavity. This loop, for instance, is present in both these films in a similar position. In other words, I have from these films the same impression given in the reports that these loops were not freely movable but were for some reason fixed. The soft-tissue mass described in the report is not too obvious. One can see here the loop of small bowel described as running around the soft-tissue mass. There is one piece of bowel seen on only one film that I cannot explain. It looks as if it were locally dilated. If it is small bowel, it looks as if it were probably terminal ileum, and I think its proximal end was not demonstrated, this may be due to disease. Here, on another film, this might be the same loop. It is not quite so dilated, and it again ends up before it reaches the cecum. At the last examination the cecum had changed little. One still sees the constriction here, which I think is probably in the region of the ileocecal valve. On some of these films a peculiar swelling just distal to the constricted area is apparent.

To summarize the x-ray findings, after discarding the ones I decided were of no significance, I find a lesion in the region of the ileocecal valve, but I am not certain whether it started on the cecal side or on the side of the ileum. I am not certain how it looks because I am not certain I actually see the lesion. If it is in the cecum, I do see it, and it would be a very unusual type of tumor. If it starts in the ileum, I do not believe it is ileitis from the evidence we have here, but it is probably a tumor. There is, however, an outside chance that it is tuberculosis, which also might explain the changes in the peritoneal cavity. I would say first that this was a tumor of the ileocecal valve and secondly, as an outside possibility, tuberculosis. As a matter of fact, I never remember having seen a patient with tuberculosis with massive hemorrhage, but I suppose it can happen.

I looked over all the films of the stomach, and something has been worrying me for a while. The

stomach appears on these films not quite so flexible as the average stomach does when several films are taken. It does not quite fit the shape of a normal stomach. It looks as if it might be infiltrated. From the evidence at hand I do not see any way of making a diagnosis of scirrhus carcinoma of the stomach. Again, I am forced from the evidence at hand to forget about the stomach. I shall not try to go any farther histologically because I am a little uneasy about the actual shape of the lesion.

DR TRACY B. MALLORY: Would you be willing to hazard a guess whether the tumor in the region of the ileocecal valve is benign or malignant?

DR SCHATZKI: If I guess, I do so against my roentgenologic conscience because I am making a pure guess without actually seeing the lesion correctly. Statistically I should say that it is cancer. There are, however, a few things that are a little peculiar and make me think it very well may not be a straightforward cancer. One reason for my statement is the apparent good clinical condition of the patient with a history of twelve months' duration, the second reason is connected with the fact that attacks of partial obstruction lasted over such a long period. Obstruction due to cancer of the ileocecal valve usually persists once it is established. The history in this case might, therefore, be interpreted as consistent with benign tumor. If I wanted to guess further, a common benign tumor in that area would be carcinoid. Yet I do not know that a carcinoid could produce so much bleeding, but I think it could. Am I right about that?

DR MALLORY: Carcinoids almost never ulcerate the mucosa.

DR SCHATZKI: In other words, it will not bleed. The most common benign tumor in the small bowel or in the colon to bleed is an intramural, extramucosal tumor. I do not have any right to make that diagnosis unless I put more stress on the soft-tissue mass than I believe I have a right to from the evidence at hand.

DR ALLEN G. BRAILEY: How do you explain the left-upper-quadrant pain, Dr Schatzki?

DR SCHATZKI: The only possible explanation is that when the patient had pain she had partial obstruction with the hyperactive area of bowel in the left upper quadrant rather than the right. Usually, a patient with ileocecal obstruction has pain on the right side.

#### CLINICAL DIAGNOSES

Diverticulitis and diverticulosis of descending colon, with partial large-bowel obstruction  
Hiatus hernia  
Neoplasm of ascending colon?

#### DR SCHATZKI'S DIAGNOSIS

Tumor of ileocecal valve, possibly carcinoid

high white-cell count there was no obvious evidence of sepsis and the abdominal tap did not disclose peritonitis, at least in the region where the tap was made

I think that it is clear that this patient had disease involving at least three organs of the body. It is difficult, for me at least, to think of one diagnosis to explain all three conditions. I shall probably have to be content with several diagnoses and assume that there may be more than a coincidental relation among them. As you know, there are many extra-intestinal complications of so-called idiopathic chronic ulcerative colitis. Among the rarer ones are nephritis and parenchymal liver disease. Although the odds are perhaps against the coexistence of both these complications in the same patient, there is no reason why this situation should not take place. In one series of patients with ulcerative colitis, nephritis was reported in 13 per cent,<sup>1</sup> and in another, 1 per cent.<sup>2</sup> We do not know the exact nature of the renal lesion. In another series of patients with ulcerative colitis liver disease was recorded in 3 per cent,<sup>3</sup> thus making it a rare complication. There have been a few biopsies and post-mortem examinations of patients with this complication, but there has been no uniformity, as far as I can tell, in the findings. The condition is described as portal cirrhosis, chronic hepatitis and even hypertrophic biliary cirrhosis. In some cases the colitis has been mild, and the liver disease the most disabling condition.

Another possibility is that the patient had amyloidosis, secondary to long-standing chronic ulcerative colitis. This is also a rare complication of ulcerative colitis, but we have had at least 1 case in this hospital. The renal lesion could be explained on this basis. A feature against amyloidosis, but not necessarily ruling it out, is the degree of hematuria at the time of this patient's second admission. Although amyloidosis, if present, commonly involves the liver, the function of this organ is usually well preserved so that jaundice, ascites and laboratory evidence of depressed liver function are not usually recorded. There are, however, occasional exceptions, chiefly in the primary systemic type of amyloid disease. This brings me to the possibility that this patient had a primary type of amyloidosis, with amyloid infiltration of the intestinal wall simulating chronic ulcerative colitis. Diarrhea and intestinal bleeding have been described in systemic amyloidosis but never, so far as I know, a picture so closely resembling idiopathic ulcerative colitis as is seen in this patient. The terminal blood findings in this patient are of some interest. The presence of immature red cells suggests a myelophthisic anemia, with the remaining marrow overactive. Could this have been a response to amyloid infiltration in the marrow? The high white-cell count suggests sepsis, but the location is not clear. Or there could have been a venous thrombosis,

perhaps in the portal system. Although the single diagnosis of amyloidosis is appealing in explaining to us most of the picture, I have decided to reject it as far as the liver is concerned. The reason for this is that amyloidosis rarely causes liver failure, but when it does it is more on a mechanical basis, with squeezing out of the liver cells and obstruction of the bile canaliculi. Early evidence of severe liver damage would be against the diagnosis of amyloidosis of the liver in this patient.

We are left then with the diagnosis of ulcerative colitis, idiopathic type, and liver disease. In view of the persistent evidence of liver-cell damage, I think that I will call it toxic cirrhosis rather than cirrhosis of the portal or biliary types. In fact, the terminal episode may have represented severe, widespread liver necrosis. In regard to the renal lesion, although I think that it could well have been due to amyloidosis, in view of the findings in the urinary sediment at the time of the second admission, I shall put glomerulonephritis ahead of this diagnosis. I shall not try to discuss the possible relation of all three conditions. If my diagnosis is correct, I think that a relation is possible but on a rather hypothetical basis. Finally, it would be very helpful to have had some Congo-red tests on this patient.

DR TRACY B MALLORY Obviously this is an extremely difficult case. Does anyone wish to make an alternative diagnosis?

DR DANIEL S ELLIS I followed this patient, and I might say that, although he had three apparently serious diseases, at no time did he ever have any conception of how sick he was. It is of interest that he was accepted in the National Guard and did three weeks' duty at Camp Edwards within two months of the final and fatal admission. The only way they found out he was sick was that he caught a cold and went on sick call and urinalysis revealed albumin, so they sent him home. He was indignant with the armed forces and the country in general because a strapping fellow like himself should be rejected. The last year of his life was possible because of the availability of human serum albumin. No other diuretics were effective. This boy had no symptoms during this period other than anasarca, which would gradually increase until it became incapacitating. Then he would come to the hospital for a course of 300 gm of albumin and be discharged at the end of a week with a sufficient sense of well-being to go cheerfully back to school for another period.

In answer to Dr Short's question at the time the liver disease was manifested he was icteric. Those who were following him thought that he had chronic ulcerative colitis, that he developed acute hepatitis, and went on to a toxic cirrhosis, and that he probably died of acute nephritis, progressing to subacute or chronic stage.

the right costal margin. There was slight edema of the scrotum and ankles.

Examination of the blood revealed a red-cell count of 3,440,000, with 11.4 gm of hemoglobin, and a white-cell count of 8350, with a normal differential. The specific gravity of the urine was 1.030, with a +++ test for bile, and a +++ test for albumin, the sediment contained innumerable red and white cells and hyaline and granular casts. The alkaline phosphatase was 19.8 units, the thymol turbidity 7.8 units and the thymol flocculation +++. The serum total protein was 6.76 gm per 100 cc, with 3.02 gm of albumin and 3.74 gm of globulin. A cephalin flocculation test was +++ at twenty-four and forty-eight hours, and there was 36 per cent retention of bromsulfalein.

The patient remained in the hospital for about nine weeks, receiving four transfusions and therapy directed toward amelioration of kidney and liver disease. On discharge, however, the bromsulfalein retention was 52 per cent, and the serum albumin 2.98 gm per 100 cc. The urine showed a + test for albumin, with 10 to 15 red cells per high-power field and moderate hyaline and granular casts in the sediment.

*Final admission* (one and a half years later). During the interval the patient re-entered the hospital three times because of return of edema and ascites. His bowel movements had been controlled fairly well, averaging two or three a day. On these admissions he was given concentrated human albumin with satisfactory release of fluid. He also developed some swelling of the breasts during this period. He persistently showed some albuminuria, an increased cephalin and thymol flocculation and an altered albumin-globulin ratio, except following administration of concentrated albumin. About ten days prior to his final readmission he began to have anal pain and later complained of a "gassy" feeling in the stomach, followed by severe and persistent vomiting for four days.

On physical examination he retched occasionally during the interview but did not vomit. The abdomen was distended and flat to percussion throughout. There was pitting edema of the legs.

The blood pressure was 100 systolic, 50 diastolic. Examination of the blood showed 5 gm of hemoglobin and a white-cell count of 60,000, with 97 per cent neutrophils and 3 per cent myelocytes. Severe toxic granulation of the polymorphonuclear leukocytes was present. There was marked hypochromia and polychromatophilia, with 5 to 10 nucleated red cells per 100 nucleated cells. The urine specific gravity was 1.010, a  $\pm$  test for bile was present and there were 2 or 3 hyaline casts per high-power field. The serum nonprotein nitrogen was 103 mg per 100 cc, the carbon dioxide 22 milliequiv and the chloride 88 milliequiv per liter. The total protein was 3.68 gm per 100 cc, with 1.08 gm of

albumin. The prothrombin time was 39 seconds (normal, 16 seconds), and the cephalin flocculation test was +++. A van den Bergh reaction was 3.2 mg per 100 cc direct and 4.3 mg indirect.

Following admission three blood transfusions were administered. An abdominal paracentesis yielded 80 cc of clear, straw-colored fluid, showing 30 cells per cubic millimeter and no organisms on direct smear. The temperature, which was normal on admission, remained about the same. On the fourth day the patient became rather drowsy, and on the following day he became disoriented and died.

#### DIFFERENTIAL DIAGNOSIS

**DR. CHARLES L. SHORT:** At the time of this patient's first admission, at the age of thirteen, the picture certainly was that of chronic ulcerative colitis from the clinical and proctoscopic and x-ray findings. May we see the films?

**DR. JAMES J. McCORT:** X-ray examination of the colon revealed a rigid and shortened large bowel. The haustral markings are scant. In the rectosigmoid region one can see small ulcerations in the wall of the colon. Even after evacuation a normal mucosal pattern is not seen. The changes are consistent with a chronic ulcerative colitis. Examination of the chest made, I believe, before the final admission shows marked elevation of the diaphragm due to the increased intraperitoneal fluid and also a small amount of fluid in the costophrenic sinus. The lungs, so far as we can see, are clear.

**DR. SHORT:** Is there an examination of the small intestine?

**DR. McCORT:** No examination was made. There was no filling of the small bowel at the time the barium enema was performed.

**DR. SHORT:** In this patient's first admission there was no real evidence of the renal or hepatic disease that later made its appearance. Two and a half years later, just before the second admission at the age of fifteen, ascites and edema rather suddenly developed. There is nothing in the record regarding clinical jaundice or whether or not he had increased bilirubin in the blood, but at least he had bile in the urine. Liver-function tests were those indicating severe parenchymal liver disease. In addition, and I believe not accounted for on the basis of liver disease, he had marked albuminuria with casts and large numbers of red and white cells in the urinary sediment. These findings certainly point toward renal disease and fit most closely with glomerulonephritis. The colitis was apparently mild after the patient's discharge, but the evidence of liver and renal disease persisted. At the time of the last admission, at the age of seventeen, the urine showed a low specific gravity on one examination at least and absence of cellular elements in the sediment, and for the first time he developed nitrogen retention. It is interesting that with the

# The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established 1828

Official Organ of

THE MASSACHUSETTS MEDICAL SOCIETY  
and

THE NEW HAMPSHIRE MEDICAL SOCIETY

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND  
PUBLISHED WEEKLY UNDER THE JURISDICTION OF THE  
COMMITTEE ON PUBLICATIONSJames P O'Hare M.D. Richard M. Smith M.D. *Chairman*  
Oiver Cope M.D. Conrad Westelhoeft, M.D.  
John Fallon M.D.

Joseph Garland, M.D. Editor

Thomas H. Lanman M.D. Associate Editors Donald Munro M.D.

Henry Jackson, Jr., M.D.

Clara D. Davies EXECUTIVE EDITOR  
Robert O'Leary ASSISTANT EDITOR

EDITORIAL BOARD

C. Guy Lane, M.D.	Maxwell Finland, M.D.
Henry R. Viets M.D.	James M. Faulkner M.D.
Robert M. Green M.D.	Carroll B. Larson, M.D.
Dwight O'Hara M.D.	Francis D. Moore M.D.
Fletcher H. Colby M.D.	C. Stuart Welch M.D.
Robert L. Goodale, M.D.	Vernon P. Williams M.D.
Chester M. Jones M.D.	Benjamin Castleman M.D.
Harvey R. Morrison M.D.	Hugh R. Leavell M.D.

SUBSCRIPTION TERMS \$7.00 per year in advance postage paid for the  
United States (medical students \$4.00 per year) Canada, \$8.00 per year  
(Boston funds) \$9.50 per year for all foreign countries belonging to the  
Postal Union

MATERIAL should be received not later than noon on Thursday three  
weeks before date of publication

THE JOURNAL does not hold itself responsible for statements made by any  
contributor

COMMUNICATIONS including those concerning classified advertising but  
not those regarding other advertising should be addressed to the *New England  
Journal of Medicine* 8 Fenway Boston 15 Massachusetts Telephone  
KE 6-2094

NEW ENGLAND ADVERTISING REPRESENTATIVE (except for classified  
advertising) Edwin B. Tyler 89 State Street, Boston Massachusetts  
Telephone LA 3-5516.

## BOSTON UNIVERSITY SCHOOL OF MEDICINE

1848-1948

Boston University School of Medicine, in celebrating its hundredth anniversary this month, recalls with pride that its original foundation was based on the idea of higher education for women. On November 1, 1848, the Boston Female Medical College, the first of its kind in the United States and probably in the world, began its instruction in medical subjects, three years later it changed its name to New England Female Medical College. The entering wedge had been driven, and the right of women to enter the professions acknowledged.

The Massachusetts Medical Society, a bulwark of conservatism was in opposition. Nevertheless,

many of the professors of the new school were members of the Society and graduates of Harvard. The first woman professor, Dr. Marie E. Zabrzevska, appointed in 1859, became later one of the founders of the New England Hospital for Women and Children.

At first an institution that merely gave instruction in medical subjects, the new college in 1852 inaugurated its complete course leading to the degree of Doctor of Medicine. The first class of four women, graduated in 1854. Many women attended sessions without graduating, some leaving to enter practice without a degree and others to become midwives, nurses or teachers of physiology.

In 1870 the School erected a permanent building on East Concord Street that is still in use as part of Boston University School of Medicine. In 1873 the most important step was taken that the School had yet made: the joining of forces with the infant Boston University and the Massachusetts Homeopathic Medical Society, which had been organized in revolt against the drastic empiricism of "regular" medicine of the day. The School, its original function discharged, became coeducational and homeopathic. During this year, also, an amphitheater was provided that was to serve the classes for the next seventy-five years.

An optional four-year course in addition to the required three years was instituted in 1878, and in 1890 this was made obligatory — a pioneer requirement in America. In 1918, homeopathy having achieved its logical purpose of breaking down a dogma from the past, Boston University School of Medicine became nonsectarian.

The clinical teaching facilities of the School have been impressively increased. The John C. Haynes Memorial for Contagious Diseases was opened in 1909, the Robert Dawson Evans Memorial for Clinical Research and Preventive Medicine in 1911 and the Jennie M. Robinson Maternity Department in 1916. Extensive teaching affiliations have been established with the Boston City Hospital, various state hospitals, the Judge Baker Guidance Center, the James Jackson Putnam Children's Center and St. Margaret's Hospital.

May the future be as rewarding as its diversified past has been to this eminent school of medicine!

DR JACOB LERMAN I saw him on the ward during the second admission and I tried very hard to make one diagnosis fit all the findings, but it was difficult. Of course, we thought that amyloid disease would be the best bet. I do not know why it was omitted from the record but there were three or four Congo-red determinations, and all were within normal range. So we thought that he had three separate diseases: nephritis, ulcerative colitis and toxic cirrhosis.

DR EARLE M. CHAPMAN I likewise saw this patient on the service, and I had a different idea from the previous visiting man who saw the patient. He had dissociated the liver disease and thought it was not related to the ulcerative colitis. I thought of tying them together. I raise the question whether therapy had anything to do with the renal lesion, which Dr Mallory will describe. Was it related to the intensive intravenous therapy with albumin and other things that he received? I would be interested to hear Dr Mallory's comments on the possible etiology of the renal lesion.

DR ELLIS The patient developed the renal damage before he received the albumin.

DR LERMAN I agree. The albumin was given on the second admission, and the renal damage had already been established. He did have sulfadiazine, however. Do you think that may have had any etiologic relation?

DR MALLORY Were any transfusions given before the second admission? Plasma or whole blood?

DR SHORT The record states that he had one.

DR MALLORY One and a half years is too long an interval for serum hepatitis.

DR LERMAN There was a two-and-a-half-year interval between the first and the second entry.

DR ELLIS He had none during that time.

#### CLINICAL DIAGNOSES

Cirrhosis of liver, toxic  
Cholemia

#### DR SHORT'S DIAGNOSES

Chronic ulcerative colitis  
Toxic cirrhosis of liver  
Glomerulonephritis

#### ANATOMICAL DIAGNOSES

*Chronic ulcerative colitis, severe*  
*Cirrhosis of liver, toxic type*  
*Acute glomerulonephritis*  
Hemorrhage from esophageal varices  
Anasarca  
Gynecomastia

#### PATHOLOGICAL DISCUSSION

DR MALLORY Post-mortem examination confirmed the three separate lesions: chronic ulcerative colitis, a severe degree of cirrhosis of the liver, of the grossly nodular, postatrophic type that here we call toxic cirrhosis, and acute glomerulonephritis. The immediate cause of death was hemorrhage from ruptured esophageal varices. From there on I think one must pass into the realm of speculation. A large proportion of patients with severe ulcerative colitis develop fatty livers before death, and on two occasions I can remember having seen the lesion progress into a mild degree of fatty cirrhosis of the finely granular type, which we usually associate with a history of chronic alcoholism. This probably was not that type of cirrhosis. I do not know any direct way of connecting the liver and the renal disease. There is enough element of sepsis associated with ulcerative colitis to make it not unreasonable that an occasional case should develop glomerulonephritis, but I think we have to consider that a separate complication and I do not see how we can tie the liver and the kidney lesions together with one mechanism.

DR ALFRED KRANES Is there anything to account for the extreme leukocytosis?

DR MALLORY The bone marrow showed only very marked diffuse hyperplasia. There were a considerable number of small pulmonary emboli, but since there was very little infarction embolism hardly seems a good explanation for leukocytosis. The renal lesion did not progress very far. It was an intracapillary type of glomerulitis with no crescent formation and no secondary changes in the tubules; it did not appear particularly active.

DR SHORT Was the liver process very active at the time of autopsy?

DR MALLORY No, the picture was variable in the different lobules, but on the whole it looked like a healed scar and not an actively progressive process.

#### REFERENCES

1. Jankelson, I. R. Free tyrosin in blood filtrate as indication of liver disease. *Am J Digest Dis* 9:99-101, 1942.
2. Bargen, J. A., Jackman, R. J. and Kerr, J. G. Studies on life histories of patients with chronic ulcerative colitis (thrombo-ulcerative colitis) with some suggestions for treatment. *Ann Int Med* 12:339-352, 1938.
3. Tumen, H. J., Monaghan, J. F. and Jobb, E. Hepatic cirrhosis as complication of chronic ulcerative colitis. *Ann. Int. Med.* 26:44, 553, 1947.

in these pursuits. Still he is received everywhere by all conditions of men, and finds that most people are more than friendly. Men render him a rather special devotion because he is thought to be less material, less grasping, more ready than others to sacrifice his own comfort and welfare to that of those whom he serves. Presently he realizes a little sadly that this high opinion bears very little relation to his cash income.

The busy average doctor at the moment feels acutely in his pocketbook the rigors of the current inflation. He is therefore peculiarly interested in or perhaps susceptible to, economic propaganda. There is plenty of it within the profession, but he has seemingly only two choices. He may listen to the National Physicians Committee or to the Committee of Physicians for the Improvement of Medical Care or, more lately, to the Physicians Forum, and depending on his bias at the moment, may fancy that he hears the voice of red medicine or of medical fellow travelers or at least of the intellectual pinks. To confuse him further and cut down his ego, he finds that his future is being planned by Congress, sociologists and popular writers. Unpleasant comments come from almost every quarter. Some of his colleagues managing a blood bank are accused of profiting in their traffic and of being no better than vampires. He may be shocked by the statement of a wealthy elder statesman and doctor's son: "I do not fear Government taking its legitimate part in medicine any more than I fear it in education or housing. I urge the doctors to get in and pitch — not stand by on the sidelines."

Precisely what is the doctor's economic and social status? Economically he belongs to the middle class, which is being threatened from both above and below. The division of the more vocal colleagues into far-right and far-left groups is just what is happening in general society. Some name-calling is already being indulged in. Unless physicians are circumspect, they may have to face witch hunts and loyalty checks or even public trials for subversive activities. According to Townbee,\* the position of the middle class is in question now in all western countries.

\*Townbee A. J. *Civilization on Trial*. Chapter 2. Present Point in History. New York: Oxford University Press, 1948.

The middle class, really a tiny minority, has created the modern world with its technologic advances, its knowledge and its tremendous means of production. The still underprivileged majority is pressing the middle class for a fair share of the good things of life, including the "care services," of interest to all — namely, housing, social security and health. The world is caught in a conflict of ideas, and seemingly is being forced to choose between the extremes of unrestricted private enterprise, with inequalities of distribution, and unmitigated socialism, which alleges that it will divide everything equally.

Economically the physician is of the middle class but socially he is without class. His science and his art are acquired, developed and applied without regard to nation, race, creed or personal reward. In his professional life the doctor traditionally is apart from the divisions among men. If class and war have always caused the breakdown of societies, and if there is full realization that these must be eliminated now to enable the civilization to survive, may not the medical profession play a role in finding the "middle way" between apparently irreconcilable extremes?

---

#### NEW ENGLAND POSTGRADUATE ASSEMBLY

THE seventh annual postgraduate assembly of the New England state medical societies will be held at the Copley Plaza Hotel on November 3, 4 and 5. An interesting program with speakers of distinction in their special fields has been arranged and has already appeared in the *Journal* on September 30 and October 14. Particularly to be emphasized are the clinics that will be held at major Boston hospitals on the morning of November 5. The committee in charge, composed of representatives of the six New England societies, under the able chairmanship of Dr. Leroy E. Parkins, is again to be congratulated on the list of subjects and speakers that it has selected.

The New England Postgraduate Assembly, after seven years of operation in a country where events frequently succeed one another with startling rapidity, may be considered as a tradition. To be a

## THE EFFICIENCY OF MEDICAL SERVICE

FAMILY doctors have ample opportunity these days to see themselves as others see them. From such an emotional outlook as that of Ian MacLaren it was a heart-warming view, and many a patient continues to share it with those who knew the horse-and-buggy doctors at their best. In many of the mirrors held up to the physician of today, however, there is an emotional screen that removes all trace of sentiment and feeling.

The industrial or business point of view is one where efficiency sits enthroned, and where lack of efficiency is viewed with impatience. Doctors, in their daily lives, are inclined to place a higher value on the end result than they do upon the efficiency with which it is achieved. In matters seriously involving life and limb this attitude is understood and is even encouraged by thoughtless people when they tell the doctor that he is to "spare no expense" in this and that, believing that the more the service costs the better it must be. People believe this because they may have no better method of appraisal. Modern industry wants the best results too, it not only is beginning to demand them but also is aware of the fact that the efficiency with which they are achieved is a measure of their value, and to some extent of their quality as well. Although industry still employs largely the private doctor, and upon his own terms too, his methods as well as his results are being scrutinized by businessmen, by labor leaders, by engineers and by other physicians all of whom are geared to modern industry's heartless demand for efficiency as well as for good results.

How may the quality of medical service be appraised? The answer depends upon the critical capacity of the appraiser. There are probably more ways of judging medical service than there are of judging horseflesh, some are good and some are not. What is a good method for one situation may not be for another. When much is known and appreciated about the self-limitation of disease there may be created an entirely different standard of judgment. On the whole, medical service may be said to be judged by informed public opinion,

and public opinion is becoming more informed every year.

Doctors practicing in a certain locality may see themselves as the industrial physician sees them by reading Shipman's article in this issue of the *Journal*. They should remember that the author is naturally trying to emphasize the points at which friction occurs. These points are not peculiar to that industry or that region, in fact it is pointed out that similar occurrences have been noted in California. These little conflicts of opinion, of judgment and of action are rooted deep in human nature, in the competitive spirit of man and in the circumstances of the environment in which we all must live, and strive to live together.

Not only industrialists but also welfare boards, insurance carriers and compensation authorities are vividly aware of medical efficiency, or its lack, in the care of the patients in whom they are interested. When a welfare official finds that 90 per cent of the money paid in a small community goes to a single doctor (on a fee-for-service basis) and that his patients do not seem to have more serious ailments or different end results than those of the other doctors, that official is rightly suspicious of that doctor. Such doctors are scattered here and there, generally believing themselves smart in their padding activities. They are notoriously well known among people whose business it is to handle financial adjustments that involve medical services. Inefficient is a very polite adjective to describe this type of medical practice.

## HORNS OF THE DILEMMA

WITH pardonable pride, a doctor may fancy his lifework the most important in the world — especially if he is very young. When combined, as that belief usually is, with idealism and optimism and energy, it is not only pardonable but also admirable. If the youth had less regard for his profession, and less energy and idealism in its pursuit, he would not be worth his salt. Later as he measures himself against the world he finds that other activities, especially the more effective means of getting and spending, are highly esteemed, and discovers that his profession is not the most efficient

## UNITED STATES PUBLIC HEALTH SERVICE

To foster training of medical students in the mental aspects of disease, federal grants for undergraduate courses are now being offered to medical schools by the United States Public Health Service. Formerly, grants to medical schools, authorized by the National Mental Health Act, were utilized primarily for graduate training in psychiatry.

Extension of grants to the undergraduate field was recommended by the National Advisory Mental Health Council as a means of providing future physicians with basic knowledge that will help them to recognize early symptoms of mental illness, to treat cases that do not require the services of a specialist and to apply psychiatric principles in the treatment of all types of illness.

Applications must be made to the Mental Hygiene Division of the Public Health Service by October 15, 1948. Grants will cover a three-year period beginning July 1, 1949, and will be paid in annual installments.

## WATER-POLLUTION ACT

The federal Government has finally been given the power to control stream pollution under the Barkley-Taft Water Pollution Act, passed as one of the last acts of the eightieth Congress.

Under the Act, *Scientific American* reports, the Federal Works Administration is permitted to lend states and municipalities up to one third the cost of new sewage-treatment and pollution-abatement facilities. A Public Health Service research and training center on pollution control is to be located in Cincinnati, Ohio.

Eight states — Illinois, Indiana, Kentucky, New York, Ohio, Pennsylvania, Virginia and West Virginia — have meanwhile signed a regional agreement to clean up the beautiful Ohio, a stream with the reputation of being the most polluted river in the world.

## CORRESPONDENCE

## THE FAMILY PRACTITIONER

*To the Editor:* Please let me thank you for your editorial "Down East Doctor," which I enjoyed very much indeed. I also want to tell you that I find the *Journal* one of the most informative and valuable that comes to my desk among a large number of medical and general publications.

The problem that you raised concerning the preservation of the general practitioner (I think "family practitioner" is a better term) is one to which all of us should give out best attention and intelligent effort.

It appears to me that many hospital trustees, hospital administrators, certain specialists and the American College of Surgeons, unwittingly I trust, are doing much that may lead to elimination of the family physician. The problem is one not only for small communities but also for large cities. I know of hospitals in which the general practitioner is not permitted to apply splints and bandages to uncomplicated injuries or assist in short operations or open superficial abscesses, not because he is incompetent to do these things, not because he is dishonest or unethical, not because he is not a gentleman, but solely because he is not a specialist.

It seems to me that this is one of our most pressing problems today. It is only, I think, through preservation of the family practitioner, that we can prevent state medicine, and I think you will agree with me that state medicine of itself will lead to a totalitarian government, which unquestionably would soon become a slave government. That, of course, is the lesson that history teaches so clearly, and we cannot expect anything else if we follow the same dismal path.

Again let me thank you for the excellent *Journal*.  
MALCOLM THOMPSON, M.D.  
Louisville, Kentucky

## BOOK REVIEWS

*Biochemistry of Cancer*. By Jesse P. Greenstein. 8°, cloth, 359 pp., with 39 illustrations and 104 tables. New York: Academic Press, Incorporated, 1947. \$7.80.

This book is much more comprehensive and varied than the subject indicates. Oncology is the author's term for can-

cer research. The "oncologic sciences" are clinical medicine, surgery, pathology, radiation, physics, genetics, immunology, endocrinology and biochemistry — in short, the entire field of medicine. Some of the definitions used are hardly those in common use by cancer practitioners. "The term carcinoma may be applied to tumors which arise from epithelial tissue" and "the term sarcoma may be applied to tumors arising from connective and muscle tissues." The author does not distinguish between benign and malignant tumors in making these definitions although in another section he enlarges on the close margin between malignancy and benignancy. Again, "the neoplasms which ensue are known as cancers or tumors." The writer raises an interesting hypothesis regarding the capacity of tumors for autonomous growth — that a benign growth is largely dependent upon the organism and hence not truly autonomous, whereas a malignant growth is largely autonomous and independent of the organism. He suggests that a cancer of the prostate that responds to hormone therapy is relatively non-autonomous and hence benign; later, it becomes refractory to treatment and is autonomous and thus malignant.

In the chapter on the general phenomena and taxonomy of cancer Greenstein deals with the experimental induction of tumors and mentions a few of the known carcinogenic agents such as tar, polycyclic hydrocarbons, azo dyes, zinc salts, radium salts, x-rays and cysticercus. He also refers to cancerous transformation of animal tissues *in vitro*, the growth and the vascular reactions of tumors, plant tumors, the melanomas of fish and tissue-immunity reactions.

One chapter considers the extrinsic chemical factors, — the chemicals that are known to induce cancer. Among these are 1, 2, 5, 6-dibenzanthracene, and 3, 4-benzpyrene. The technique used in studying and synthesizing carcinogenic hydrocarbons is described. Much work has been done in animals to determine the types of tumors induced, the susceptibility of different strains of the hydrocarbons and the fate of the injected hydrocarbons. Many deaths have occurred from cancer of the scrotum in workers exposed to coal tar.

Intrinsic factors are defined as agents that possess a biogenic origin, including hormones and viruses. The chemistry of hormones and similar synthetic preparations and the use of these materials in experimental animals are discussed.

Chemotherapy has been of little value in the therapy of cancer. Coley's toxins when first prepared and administered by Coley seemed of some help in certain cancer patients, but later the results could not be obtained by Coley or others. Polysaccharide injections and the use of Fowler's solution and colchicine offered high hopes, but all such methods have failed.

The author is at his best in discussing the chemistry of tumors, since much of the work mentioned has been done by him or under his direction. Extensive analyses have been made of the chemical structure of normal tissues and of neoplasms, the oxygen consumption of normal and neoplastic tissues, the activity of phosphatases, the glycogen content and many other subjects. Two hundred and forty-seven references are given for the material presented in this chapter.

*Psychopathology and Education of the Brain-Injured Child*. By Alfred A. Strauss, and Laura E. Lehtinen. 8°, cloth, 206 pp., with 46 illustrations. New York: Grune and Stratton, 1947. \$5.00.

This monograph is based on research work conducted by the authors and in part previously published in various periodicals. The text is divided into two parts: psychopathology and teaching. The first part is prefaced with a historical review of the subject, followed by chapters on anatomy and function of the brain, perception and perceptual disturbances, thinking disorders, behavior disorders, testing and diagnosis of brain injury in children. The second part, on education, considers the general principles of education, and the teaching of arithmetic, reading and writing. An appendix presents a study of a deaf child with a brain injury by Mary A. Bair, an excerpt from an unpublished essay. The text is documented with a number of case histories. References to the literature are printed as footnotes on the appropriate pages. The book is well published and should prove of interest to neurologists and psychiatrists.

New England tradition is in itself a mark of distinction

Each year the Postgraduate Assembly has surpassed its previous record in attendance and — a very tangible sign of success — its attractiveness to technical exhibitors. It should be to the advantage of the New England Council of State Medical Societies some day to take over the Assembly as its own project. Present indications suggest that the Assembly might even be able to furnish the Council with those fiscal assets so necessary to existence.

## BLUE CROSS-BLUE SHIELD

### MEDICAL SECRETARY MEETINGS

As part of the Blue Shield professional relations program a series of group meetings with medical secretaries is being conducted throughout the Commonwealth.

These group discussions are designed to provide medical secretaries with current and detailed information concerning Blue Shield benefits, claim report forms, Blue Shield income limitations, rules and regulations and other pertinent information that will help to minimize or eliminate errors, thereby providing better service to participating physicians and Blue Shield patients.

These informal discussions of mutual problems have proved to be very worth while. Meetings have been scheduled for approximately forty towns and cities during the next eight months.

## MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

### REIMBURSEMENT OF PHYSICIANS UNDER EMIC PROGRAM

The Massachusetts Department of Public Health has received notification from the Children's Bureau, Washington, D. C., that all federal reimbursements for emergency maternal and infant care services, as authorized under the EMIC program, will terminate as of June 30, 1949.

That Massachusetts physicians may be assured reimbursement for such services. The Massachusetts Department of Public Health requests that all outstanding bills for care authorized under the Massachusetts EMIC program be submitted to the Division of Maternal and Child Health, Massachusetts Department of Public Health, 73 Tremont Street, Boston, not later than May 1, 1949.

Provision for maternal care under this program has been authorized for the period September 3, 1943, to April 4, 1948, for infant care such services will terminate as of April 4, 1949.

## VACCINE FOR ROCKY MOUNTAIN SPOTTED FEVER

The United States Public Health Service has announced that it is discontinuing the manufacture of vaccine for Rocky Mountain spotted fever. This vaccine is now available from commercial manufacturers so that physicians who wish to use it will have no difficulty in purchasing the product.

For many years the Rocky Mountain Laboratory was the only source from which vaccine for this disease could be obtained. The first variety of the vaccine was prepared from the bodies of infected ticks and played an important part in reducing the numbers of cases and deaths in the valleys of the Rocky Mountains, where the disease had been prevalent for many years.

The tick-tissue type of vaccine has now been superseded by the chick-embryo type. The commercial manufacturers will be supplying only the new variety. When the present supply of tick-tissue vaccine on hand is depleted, the old variety will no longer be available. The Rocky Mountain Laboratory will make the tick-tissue vaccine available as long as the present supply lasts.

## CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

The November schedule for Consultation Clinics for Crippled Children in Massachusetts under the provisions of the Social Security Act follows:

CLINIC	DATE	CLINIC CONSULTANT
Salem	November 1	Paul W. Hugenberger
Haverhill	November 3	William T. Green
Lowell	November 5	Albert H. Brewster
Gardner	November 9	Carter R. Rowe
Springfield	November 16	Garry deN. Hough, Jr.
Pittsfield	November 17	Frank A. Slowick
Brockton	November 18	George W. Van Gorder
Hyannis	November 18	Paul L. Norton
Worcester	November 19	John W. O'Meara
Fall River	November 22	David S. Grice
Greenfield	November 22	Charles L. Sturdevant

Physicians referring new patients to clinics should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

## MISCELLANY

### APPOINTMENT

Dr. Lendon Snedeker, of Brookline, has been appointed assistant administrator of the Children's Medical Center of Boston.

### BODY BLOW

Blue Cross in British Columbia, according to an Associated Medical Care Plans release, will be forced to liquidate on December 31, 1948. This will mark the first time that a well established voluntary plan has been forced out of existence in North America by the advent of compulsory health insurance.

British Columbia's Blue Cross has been unable to meet conditions imposed by the provincial Government's new hospital insurance act.

## UNITED STATES PUBLIC HEALTH SERVICE

To foster training of medical students in the mental aspects of disease, federal grants for undergraduate courses are now being offered to medical schools by the United States Public Health Service. Formerly grants to medical schools, authorized by the National Mental Health Act, were utilized primarily for graduate training in psychiatry.

Extension of grants to the undergraduate field was recommended by the National Advisory Mental Health Council as a means of providing future physicians with basic knowledge that will help them to recognize early symptoms of mental illness, to treat cases that do not require the services of a specialist and to apply psychiatric principles in the treatment of all types of illness.

Applications must be made to the Mental Hygiene Division of the Public Health Service by October 15, 1948. Grants will cover a three-year period beginning July 1, 1949, and will be paid in annual installments.

## WATER-POLLUTION ACT

The federal Government has finally been given the power to control stream pollution under the Barkley-Taft Water Pollution Act, passed as one of the last acts of the eightyeth Congress.

Under the Act, *Scientific American* reports, the Federal Works Administration is permitted to lend states and municipalities up to one third the cost of new sewage-treatment and pollution-abatement facilities. A Public Health Service research and training center on pollution control is to be located in Cincinnati, Ohio.

Eight states—Illinois, Indiana, Kentucky, New York, Ohio, Pennsylvania, Virginia and West Virginia—have meanwhile signed a regional agreement to clean up the beautiful Ohio, a stream with the reputation of being the most polluted river in the world.

## CORRESPONDENCE

## THE FAMILY PRACTITIONER

To the Editor: Please let me thank you for your editorial "Down East Doctor," which I enjoyed very much indeed. I also want to tell you that I find the *Journal* one of the most informative and valuable that comes to my desk among a large number of medical and general publications.

The problem that you raised concerning the preservation of the general practitioner (I think "family practitioner" is a better term) is one to which all of us should give out best attention and intelligent effort.

It appears to me that many hospital trustees, hospital administrators, certain specialists and the American College of Surgeons, unwittingly I trust, are doing much that may lead to elimination of the family physician. The problem is one not only for small communities but also for large cities. I know of hospitals in which the general practitioner is not permitted to apply splints and bandages to uncomplicated injuries or assist in short operations or open superficial abscesses, not because he is incompetent to do these things, not because he is dishonest or unethical, not because he is not a gentleman, but solely because he is not a specialist.

It seems to me that this is one of our most pressing problems today. It is only, I think, through preservation of the family practitioner, that we can prevent state medicine, and I think you will agree with me that state medicine of itself will lead to a totalitarian government, which unquestionably would soon become a slave government. That, of course, is the lesson that history teaches so clearly, and we cannot expect anything else if we follow the same dismal path.

Again let me thank you for the excellent *Journal*.  
Louisville, Kentucky MALCOLM THOMPSON, M.D.

## BOOK REVIEWS

*Biogenesis of Cancer*. By Jesse P. Greenstein. 8° cloth, 59 pp. with 39 illustrations and 104 tables. New York: Academic Press, Incorporated, 1947. \$7.80.

This book is much more comprehensive and varied than the subject indicates. Oncology is the author's term for can-

cer research. The "oncologic sciences" are clinical medicine, surgery, pathology, radiation, physics, genetics, immunology, endocrinology and biochemistry—in short, the entire field of medicine. Some of the definitions used are hardly those in common use by cancer practitioners. "The term carcinoma may be applied to tumors which arise from epithelial tissue" and "the term sarcoma may be applied to tumors arising from connective and muscle tissues." The author does not distinguish between benign and malignant tumors in making these definitions although in another section he enlarges on the close margin between malignancy and benignancy. Again, "and the neoplasms which ensue are known as cancers or tumors." The writer raises an interesting hypothesis regarding the capacity of tumors for autonomous growth—that a benign growth is largely dependent upon the organism and hence not truly autonomous, whereas a malignant growth is largely autonomous and independent of the organism. He suggests that a cancer of the prostate that responds to hormone therapy is relatively non-autonomous and hence benign, later, it becomes refractory to treatment and is autonomous and thus malignant.

In the chapter on the general phenomena and taxonomy of cancer Greenstein deals with the experimental induction of tumors and mentions a few of the known carcinogenic agents such as tar, polycyclic hydrocarbons, azo dyes, zinc salts, radium salts, x-rays and cysticercus. He also refers to cancerous transformation of animal tissues in vitro, the growth and the vascular reactions of tumors, plant tumors, the melanomas of fish and tissue-immunity reactions.

One chapter considers the extrinsic chemical factors,—the chemicals that are known to induce cancer. Among these are 1, 2, 5, 6-dibenzanthracene, and 3, 4-benzpyrene. The technique used in studying and synthesizing carcinogenic hydrocarbons is described. Much work has been done in animals to determine the types of tumors induced, the susceptibility of different strains of the hydrocarbons and the fate of the injected hydrocarbons. Many deaths have occurred from cancer of the scrotum in workers exposed to coal tar.

Intrinsic factors are defined as agents that possess a biogenic origin, including hormones and viruses. The chemistry of hormones and similar synthetic preparations and the use of these materials in experimental animals are discussed.

Chemotherapy has been of little value in the therapy of cancer. Coley's toxins when first prepared and administered by Coley seemed of some help in certain cancer patients, but later the results could not be obtained by Coley or others. Polysaccharide injections and the use of Fowler's solution and colchicine offered high hopes, but all such methods have failed.

The author is at his best in discussing the chemistry of tumors, since much of the work mentioned has been done by him or under his direction. Extensive analyses have been made of the chemical structure of normal tissues and of neoplasms, the oxygen consumption of normal and neoplastic tissues, the activity of phosphatases, the glycogen content and many other subjects. Two hundred and forty-seven references are given for the material presented in this chapter.

*Psychopathology and Education of the Brain-Injured Child*. By Alfred A. Strauss and Laura E. Lehtinen. 8° cloth, 206 pp. with 46 illustrations. New York: Grune and Stratton, 1947. \$5.00.

This monograph is based on research work conducted by the authors and in part previously published in various periodicals. The text is divided into two parts: psychopathology and teaching. The first part is prefaced with a historical review of the subject, followed by chapters on anatomy and function of the brain, perception and perceptual disturbances, thinking disorders, behavior disorders, testing and diagnosis of brain injury in children. The second part, on education, considers the general principles of education, and the teaching of arithmetic, reading and writing. An appendix presents a study of a deaf child with a brain injury by Mary A. Bair, an excerpt from an unpublished essay. The text is documented with a number of case histories. References to the literature are printed as footnotes on the appropriate pages. The book is well published and should prove of interest to neurologists and psychiatrists.

## BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

*Tuberculosis: A discussion of phthisiogenesis, immunology, pathologic physiology, diagnosis, and treatment.* By Francis M. Pottenger, A.M., M.D., LL.D., medical director, the Pottenger Sanatorium and Clinic for Diseases of the Chest, Monrovia, California. 8°, cloth, 597 pp., with 105 illustrations. St. Louis: The C. V. Mosby Company, 1948. \$12.00.

*The Epithelia of Woman's Reproductive Organs: A correlative study of cyclic changes.* By George N. Papanicolaou, M.D., Ph.D., professor of clinical anatomy, Cornell University Medical College; Herbert F. Traut, M.D., professor of obstetrics and gynecology, University of California Medical School; and Andrew A. Marchetti, M.D., associate professor of obstetrics and gynecology, Cornell University Medical College. 4°, cloth, 53 pp., with 22 plates. New York: The Commonwealth Fund, 1948. \$10.00.

*Atlas of Plastic Surgery.* By Morton I. Berson, M.D. 4°, cloth, 304 pp., illustrated. New York: Grune and Stratton, 1948. \$15.00.

*Diabetes Mellitus in General Practice.* By Arthur R. Colwell, M.D., associate professor of medicine and director of medical specialty training, Northwestern University Medical School, attending physician, Evanston Hospital, Evanston, Illinois, and consulting physician, Wesley Memorial Hospital, Chicago. 8°, cloth, 350 pp., with 24 illustrations. Chicago: The Year Book Publishers, Incorporated, 1947. \$5.25.

*Telepathy and Medical Psychology.* By Jan Ehrenwald, M.D. With a foreword by Gardner Murphy. 8°, cloth, 212 pp. New York: W. W. Norton and Company, Incorporated, 1948. \$3.00.

*Brief Psychotherapy: A handbook for physicians on the clinical aspects of neuroses.* By Bertrand S. Frohman, M.D. With the collaboration of Evelyn P. Frohman, and with a foreword by Walter C. Alvarez, M.D. 12°, cloth, 265 pp. Philadelphia: Lea and Febiger, 1948. \$4.00.

*Case Histories in Clinical and Abnormal Psychology.* Edited by Arthur Burton, associate professor of psychology, Willamette University; and Robert E. Harris, associate professor of medical psychology, University of California. 8°, cloth, 680 pp. New York and London: Harper and Brothers, 1947. \$4.00.

*Hormones and Behavior: A survey of interrelationships between endocrine secretions and patterns of overt response.* By Frank A. Beach, professor of psychology, Yale University. With a foreword by Earl T. Engle. 8°, cloth, 368 pp. New York: Paul B. Hoeber, Incorporated, 1948. \$6.50.

*The Treatment of Rheumatism in General Practice.* By W. S. C. Copeman, O.B.E., M.A., M.D. (Cantab.), F.R.C.P. (London), physician in charge, Department of Chronic Rheumatic Diseases, West London Hospital, physician, B.R.C.S. Clinic for Rheumatism, Peto Place, Hospital of St. John and Elizabeth and Cheyne Hospital for Children, and chairman of the Chartered Society for Physiotherapy and medical secretary, Empire Rheumatism Council. Fourth edition. 8°, cloth, 258 pp. Baltimore: The Williams and Wilkins Company, 1946. \$4.00.

*The Pathology of Nutritional Disease.* By Richard H. Follis, Jr., M.D., associate professor of pathology, Duke University School of Medicine, Durham, North Carolina. 8°, cloth, 291 pp., with 71 illustrations. Springfield, Illinois: Charles C. Thomas, 1947. \$6.75.

## NOTICES

## ANNOUNCEMENT

Dr. Lewis S. Pilcher announces the removal of his office to 1180 Beacon Street, Brookline.

## EXAMINATION FOR MEDICAL OFFICER POSITIONS

An examination has been announced by the United States Civil Service Commission for filling medical-officer positions at salaries ranging from \$4479 to \$6235 a year. The positions are located in Washington, D. C., throughout the United States and in the Panama Canal Zone, in such agencies as the Indian Service, Panama Canal Service, United States Public Health Service, Army, Veterans Administration, Civil Aeronautics Administration and Railroad Retirement Board.

No written test will be required. To qualify, applicants must be graduates of a medical school and must be currently licensed to practice medicine and surgery. (The requirement of a current license will be waived for certain persons and positions.) For positions paying \$4479 and \$5232, applicants must have completed a full internship, either general rotating or in a specialty (this requirement is waived for some positions), and for positions paying \$5232 and \$6235, they must have had professional medical experience. Maximum age limits for these positions are as follows: for Panama Canal Service, forty-five years, for Indian Service, fifty years, for other agencies, sixty-two years. For persons entitled to veteran preference, the forty-five-year and fifty-year age limits are waived to sixty-two years, and the sixty-two-year age limit is waived without limitation. Detailed information on requirements is given in the examination announcement.

Information and application forms may be obtained at most first-class and second-class post offices, from Civil Service regional offices or from the United States Civil Service Commission, Washington 25, D. C. Applications will be accepted in the Commission's Washington office until further notice.

## MIDDLESEX EAST DISTRICT MEDICAL SOCIETY

Meetings of Middlesex East District Medical Society will be held on the following dates: November 17, 1948 (Dr. Robert R. Linton will discuss the surgical and Dr. A. Stone Freedberg the medical aspect of "Thromboembolic Disease"); January 19, 1949 (discussion of medical, surgical and obstetric case, entitled "Stump the Experts"); March 23, 1949 (symposium on hypertension, with Dr. Lewis Dexter discussing the medical, Dr. J. C. White the surgical and Dr. Sanford H. Moses the obstetric aspects, and with Dr. George D. Bissell considering the general practitioner's problems); and May 11, 1949 ("Ladies' Night," with dancing and a selected speaker on a nonmedical subject).

## AMERICAN CANCER SOCIETY, INCORPORATED

A medical symposium on the cancer problem will be held by the American Cancer Society, Incorporated, at the Hotel Commodore, New York City, on November 6 and 7. The program will include discussions on the following subjects: "The Cancer Problem Today," "The Problem of Treatment—Recent Advances," "The Problem of Cancer of the Lung," and "Cancer Research, Cancer Education and the Cancer Problem in General Medical Practice."

## AMERICAN FEDERATION FOR CLINICAL RESEARCH

The annual meeting of the Eastern Section of the American Federation for Clinical Research will be held at Temple University School of Medicine, Philadelphia, on Saturday, December 4.

## INTERSTATE POSTGRADUATE MEDICAL ASSOCIATION OF NORTH AMERICA

The International Medical Assembly of the Interstate Postgraduate Medical Association of North America will be held in the Public Auditorium, Cleveland, Ohio, from November 9 to 12.

(Notices continued on page xv)

OTICES (Concluded from page 644)

## SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, OCTOBER 28

FRIDAY OCTOBER 29

\*9-00-10-00 a.m. Some special features of marked mitral stenosis Dr. Edward F. Bland Joseph H. Pratt Diagnostic Hospital

\*9-00 a.m. 12-00 m. Combined Medical and Surgical Staff Rounds Peter Bent Brigham Hospital

\*12-00 m. Clinical investigation on cancer Dr. Fred Homburger Margaret Jewett Hall Mt. Auburn Hospital Cambridge

FRIDAY NOVEMBER 2

\*12-15-1-15 p.m. Clinicorontgenological Conference Peter Bent Brigham Hospital

\*1-30-2-30 p.m. Pediatric Rounds Burnham Memorial Hospital for Children Massachusetts General Hospital

WEDNESDAY NOVEMBER 5

\*11-00 a.m. 12-00 m. Medical Rounds Amphitheater Children's Hospital

\*12-00 m. 1-00 p.m. Clinicopathological Conference (Children's Hospital) Amphitheater Peter Bent Brigham Hospital

\*2-00-3-00 p.m. Combined Clinic by the Medical Surgical and Orthopedic Services Amphitheater Children's Hospital

\*Open to the medical profession

OCTOBER 1 MAY 20 Metropolitan State Hospital Page 418 issue of September 9

OCTOBER 27 New England Obstetrical and Gynecological Society Annual Meeting Hotel Somerset, Boston

OCTOBER 27 New England Pediatric Society Page 530 issue of September 30

OCTOBER 31 and NOVEMBER 1 American Society for the Study of Atherosclerosis Page 530 issue of September 30

NOVEMBER 1-7 American Clinical and Climatological Association Page 582 issue of April 15

NOVEMBER 7 and 8 Annual Meeting of National Committee for Mental Hygiene Inc. Page 282 issue of August 12

NOVEMBER 7-8 Seventh New England Postgraduate Assembly Copley Plaza Hotel Boston

NOVEMBER 4-6 American Society of Anesthesiologists Page 418 issue of September 9

NOVEMBER 6 and 7 American Cancer Society Incorporated Page 644

NOVEMBER 8-12 American Public Health Association Page 420 issue of March 18

NOVEMBER 9-12 Interstate Postgraduate Medical Association of North America Page 644

NOVEMBER 10-13 Association of Military Surgeons of the United States Page 722 issue of May 15

NOVEMBER 12 The Use of Hormones in Breast Cancer Dr. Ira T. Velez Pentucket Association of Physicians 8:30 p.m. Haverhill

NOVEMBER 17 Middlesex East District Medical Society Page 644

NOVEMBER 20-23 American Academy of Pediatrics Annual Meeting California Haddon Hall Hotel Atlantic City New Jersey

NOVEMBER 30 Hampden District Medical Society Page 492 issue of September 23

DECEMBER 2 Suffolk Censors Meeting Page 492 issue of September 23

DECEMBER 4 American Federation for Clinical Research Page 644

DECEMBER 7-9 Southern Surgical Association Annual Meeting Page 543 issue of April 8

DECEMBER 9 and 10 New York State Society of Anesthesiologists Page 4 issue of July 1

FEBRUARY 4 1949 American Board of Obstetrics and Gynecology Page 244 issue of August 5

MARCH 28-APRIL 1 1949 American College of Physicians Page 158 issue of July 22

MAY 16-19 1949 American Urological Association Biltmore Hotel Los Angeles California

MAY 26-28 1949 American Goutier Association Hotel Lorraine Madison Wisconsin

NOVEMBER 11-17 1949 Third Inter-American Congress of Radiology Page 15 issue of July 22

## DISTRICT MEDICAL SOCIETIES

### HAMPDEN

NOVEMBER 30 8:30 p.m. Academy of Medicine Springfield Care of the Blind Dr. Grantley W. Taylor

### MIDDLESEX EAST

NOVEMBER 17

JANUARY 10

MARCH 2

MAY 11

### SUFFOLK

DECEMBER 2 Suffolk Censors Meeting

### WORCESTER NORTH

NOVEMBER 10 Henry Heywood Memorial Hospital Gardner

DECEMBER 8 Leominster Hospital Leominster

FEBRUARY 23 Northbank Hospital Fitchburg

MAY 2 Annual Meeting

Advertisement



From where I sit  
by Joe Marsh

## Now It's Neckties Made of Milk!

*Fellow in Andy Botkin's Tavern the other day was boasting about a trick necktie he was wearing made out of a by-product of milk "Took 33 pounds of milk to make this tie," he says*

Bill Webster was unimpressed "Personally," he says, "I'd rather drink the milk Just as I wouldn't change one glass of good American beer for a necktie made from thirty barrels of it!"

*Yes—modern science being what it is—seems like you can make "anything out of anything" these days. But in the case of milk, well I guess drinking it is still a whole lot better than just wearing it*

Of course there are a whole lot of other ways of abusing goods and beverages—like a fellow who doesn't appreciate a glass of beer enough to drink it slowly and in moderation

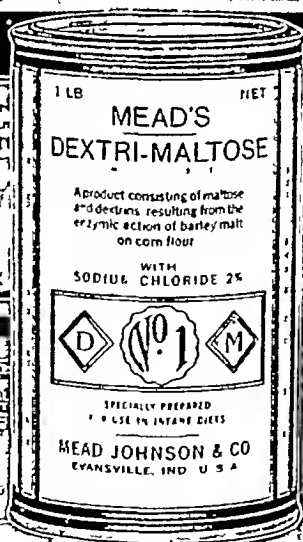
*But from where I sit, most people who enjoy a wholesome beverage like beer or ale are moderate—because beer itself is a beverage of moderation*

Joe Marsh

# BACKGROUND

The use of cow's milk, water and carbohydrate mixtures represents the one system of

infant feeding that consistently, for over three decades, has received universal pediatric



recognition No carbohydrate employed in this system of infant feeding enjoys so rich and enduring a background of authoritative clinical experience as Dextri Maltose

# The New England Journal of Medicine

Copyright, 1948 by the Massachusetts Medical Society

Volume 239

OCTOBER 28, 1948

Number 18

## INTUSSUSCEPTION IN CHILDHOOD\*

### Experiences from 610 Cases

ROBERT E. GROSS, M.D., J. AND PAUL F. WARE, M.D.†

BOSTON

INTUSSUSCEPTION is a form of intestinal obstruction that demands immediate recognition and treatment if mortality rates are to be kept at a minimum. The condition is particularly common in the first few years of life, and it must be constantly in the minds of pediatricians and the general practitioners who deal with babies and young children. Much has been written concerning the recognition and the forms of therapy for this type of mechanical obstruction. The extensive material that we have been privileged to handle prompts us to call attention again to the salient features in diagnosis of the condition and to review briefly the methods of treatment, paying particular attention to a form of therapy that has proved to be very beneficial for subjects requiring resection of an intussusception. Several previous reports have been made on the cases of intussusception at the Children's Hospital in Boston. In 1934 Ladd and Gross<sup>1</sup> studied 372 of these patients. The series has now extended to 610 cases of intussusception in infants and children; the present report including all cases treated up through 1947 by various members of the visiting staff and the house personnel. Recent years have shown a steady decline in mortality rates, particularly in the cases with a poor prognosis in which resection has been necessary.

The interval between onset of symptoms and institution of treatment is of paramount importance, and the mortality rates will more nearly approach zero the more frequently treatment is instituted within twenty-four hours of onset. Intussusception is truly an acute surgical emergency, and a heavy diagnostic responsibility is placed upon the general practitioner or pediatrician who first sees these patients. The surgeon deserves some credit for improved results in the treatment of intussusception, as is shown by comparison of the two columns

of Table 1, which lists the mortality rates for patients with similar durations of symptoms in the years 1928-1939, compared to 1940-1947. However, greatest emphasis must be attached to the facts that since 1928 in 180 patients treated in this hospital the duration of symptoms has been less than twenty-four hours and that operation has been carried out without fatality. This is a strong tribute to the physicians of the community who have

TABLE 1 *Relation between Mortality and Duration of Symptoms*

DURATION OF SYMPTOMS <i>hr</i>	MORTALITY	
	1928-1939	1940-1947
Less than 24	0	0
24-36	25	9
36-48	33	12
48-72	21	15
72-96	38	15

recognized these cases early and have referred them for treatment while the surgical problem is still a simple one.

The falling mortality rates through the years covered by this series are indicated in Figure 1, showing a gradual but steady improvement, the latest rates being 2.7 per cent.

### ETIOLOGY

When intussusception occurs in adult life, a definite mechanical cause for the telescoping can usually be found, Meckel's diverticulum, polyps and various types of bowel tumors are the inciting factors in more than half the cases in adults. Likewise, the intussusceptions that occur in late childhood are apt to have some demonstrable, underlying lesion. In striking contrast, intussusceptions in early life rarely have any mechanical factor that can be clearly identified as the cause of the invagination.

\*From the Surgical Service, The Children's Hospital and the Department of Surgery, Harvard Medical School.  
†Ladd Professor of Children's Surgery, Harvard Medical School; surgeon-in-chief of Children's Hospital.  
Resident surgeon, Children's Hospital.

Various theories have been advanced to explain the origin of intussusception in infants enlarged Peyer's patches, ileocecal neuromuscular dysfunction, enteric infections, excessive catharsis and the transition from breast or bottle feeding to a more solid diet have often been indicted as causes, but it is extremely difficult to prove that these have played an etiologic role. Discernible mechanical factors could be shown in only 5.4 per cent of the cases in this series, as follows: Meckel's diverticu-

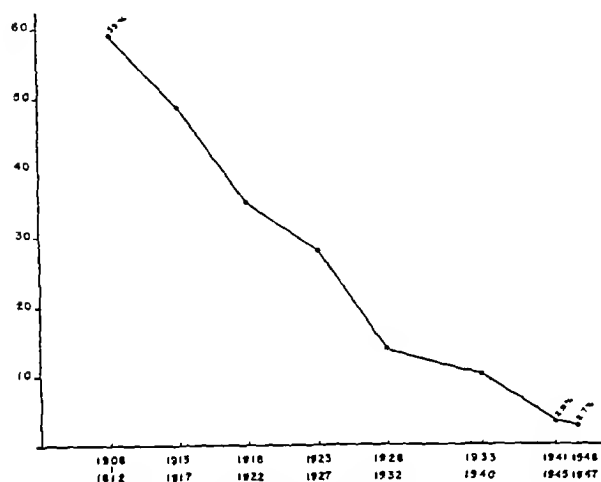


FIGURE 1 Mortality Rates in 610 Cases of Intussusception, 1908 through 1947

lum, 29 cases, intestinal polyp, 4 cases, lymphoma of bowel, 2 cases, and duplication of terminal ileum, 1 case

#### CLASSIFICATION

Invaginations are identified as involving primarily the small or the large bowel. Further classification is indicated by the portion of the alimentary system that is the leading point (intussusceptum) and is the receiving segment of intestine (intussusciptum). An "ileocolic" type describes a prolapse of the lower ileum through the ileocecal valve into the colon; it is the most commonly encountered form. A more complicated variant of this type is the ileoileocolic, in which ileum telescopes into ileum, and this entire mass passes into the colon. In the present series the types encountered were ileocolic, 76 per cent, ileoileocolic, 14 per cent, jejunoileal or ileoileal, 5 per cent, colocolic, 2.1 per cent, multiple, 0.7 per cent, and type not stated, 2.2 per cent.

#### SYMPTOMS AND SIGNS

In this series 440 cases, or 72 per cent, were found in the first year of life, with the peak of incidence between the third and eleventh months, in which 68 per cent of the cases occurred. Eighty-four per cent of the cases in the series occurred by

the age of two years, with a scattering of cases in age groups between three and twelve years. The youngest was three days of age. Sixty-five per cent of the patients were males.

The onset of intussusception is usually marked by sudden, severe, paroxysmal seizures of abdominal pain in a previously well infant of superior nutrition and development. The pain recurs at intervals of a few minutes, the colicky or recurring nature being strongly suggestive of obstruction of the small intestine. In the first few hours, the child usually appears quite comfortable and even playful between attacks of pain, but at later stages is apt to be pale and exhausted, and often sinks off into sleep between the paroxysms. The young infant usually manifests abdominal pain by forceful drawing up of the legs onto the abdomen, and holding the breath in a grunting manner or uttering an agonizing cry. Rhythmic pain was observed in more than 95 per cent of the cases in this series. Vomiting is an early symptom and is present in well over 90 per cent of the patients. With the passage of time and with the increase of obstruction, pallor, sweating and restlessness are found as the child approaches a state of shock. In neglected cases of several days' standing, the long-continued intestinal obstruction produces a moribund state in which there is collapse and severe dehydration.

The appearance of blood in the stool occurs in about 85 per cent of the cases within twenty-four hours. In about half of these the bleeding is gross and may be copious, in the remainder it is discovered by chemical tests on the stools. The first stool passed after the onset of intussusception is usually normal, but after an interval of ten or twelve hours the next stool (or enema returns) usually reveals gross or occult blood. Bleeding may be mild, moderate or almost exsanguinating. The amount of blood appearing in the stool is directly related to the degree of strangulation occurring in the intussusception.

Dr William E. Ladd frequently made the statement that "intussusception produces such a characteristic picture that it is possible to make the diagnosis over the telephone when the mother relates the story."

The importance of careful abdominal examination is evident from the fact that a mass is palpable in about 85 per cent of the cases. Small-bowel invaginations are quite mobile and only rarely palpable. More commonly an elongated tumor can be felt in the right upper quadrant or anywhere along the course of the colon. Usually, the mass is not particularly tender. An intussusception in the region of the splenic flexure or in the hepatic flexure may be difficult to feel because it lies under the costal margin or under the edge of the liver. Not infrequently a discrete mass cannot be outlined, and yet the examiner meets a definite resistance or fullness in the right upper quadrant or

in the epigastrium. On some occasions (if the baby is examined during a bout of pain) it is possible for the palpating fingers to follow the progression of an intussusception mass with each seizure and to feel

quarter of the cases, an intra-abdominal mass can be felt by rectal examination. This finding is particularly helpful if the child is straining or is so tense that palpation of the anterior abdominal wall

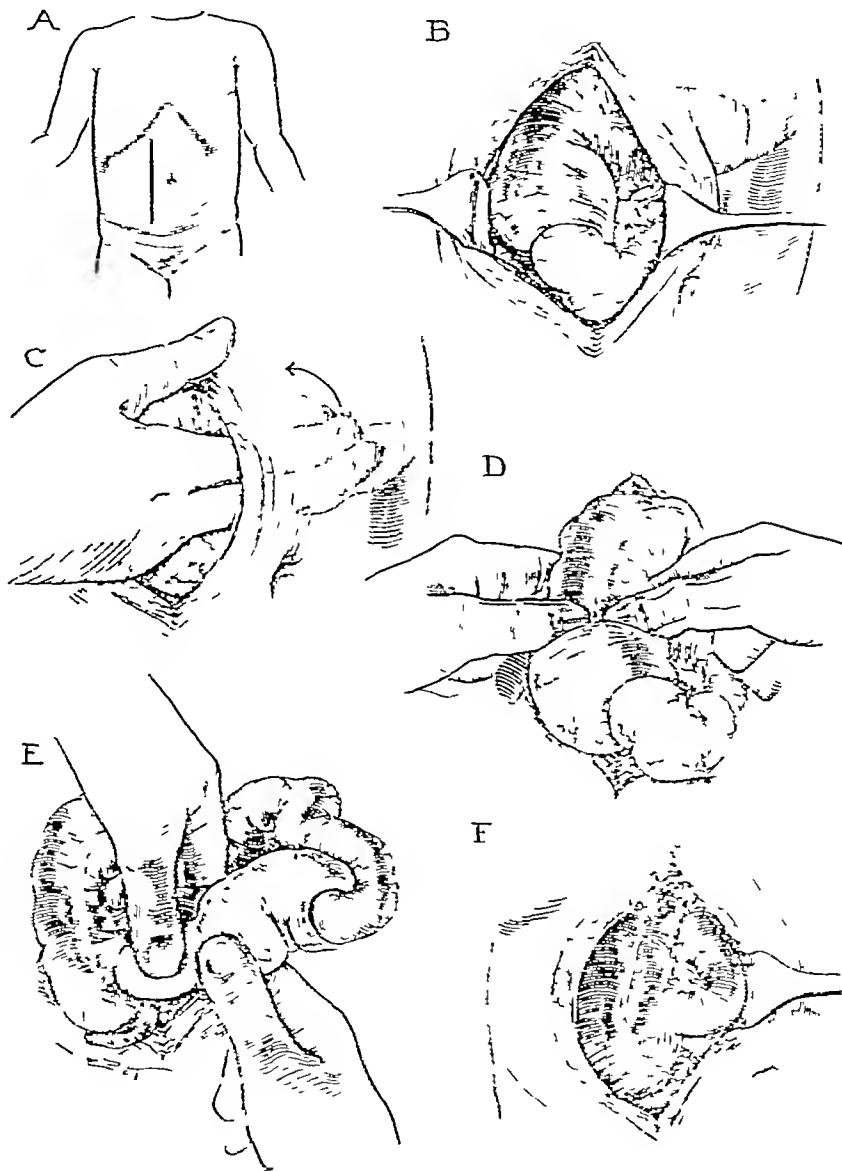


FIGURE 2. Typical Operative Reaction of Intussusception. A shows a right-rectus-muscle mass on retracting the muscle belly laterally. B retractor intussusceptum into the colon almost to the splenic flexure. C finger is retracted into the peritoneal cavity. D on the back retractor intussusceptum as far as possible by intra-abdominal manipulation. E delivery of the entire mass through the wound for correction of the reaction when retractor intussusceptum has been reduced to the ascending colon. F retractor intussusceptum being squeezed back from the terminal ileum and F the viscera returned to the abdomen (the apparatus is rarely removed).

its wall harden as its tone is increased by the peristaltic activity.

Rectal examination with bimanual palpation of the abdomen, is often informative. In about a

quarter of the cases, an intra-abdominal mass can be felt by rectal examination. This finding is particularly helpful if the child is straining or is so tense that palpation of the anterior abdominal wall

prolapsed rectum. However, differentiation from a prolapse could be quickly made by the insertion of a finger between the mass (intussusceptum) and the encircling anus—which would be impossible if the mass were a prolapse.

Roentgenologic aid is not necessary in the average case of intussusception, the diagnosis can be made without hesitation from the history and physical findings. In about a tenth of the cases the diagnosis is in doubt, and the roentgenologist's help should be sought. A film of the abdomen, without a contrast medium, may show the intussuscepting mass and some dilatation of intestine proximal to it. In the great majority of cases, the intussusceptum has progressed into the colon so that a barium enema shows a filling defect in the column of barium and a post-evacuation film demonstrates a thin shell of barium remaining around and outlining the intussusceptum.

### TREATMENT

#### *Nonoperative Measures*

Almost universally, surgical intervention has become the treatment of choice, but there are still a few advocates of therapy by colonic insufflation of air or fluid. The more recent devotees of this method suggest the rectal injection of a barium mixture, the reduction of the intussusception being watched under fluoroscopic control. We have used this on several occasions with rapid and complete reduction of the intussusception, but we believe that it should never be done except with the consent of, and in the presence of, the surgeon who must accept the responsibility of operating on the child if the reduction by hydrostatic pressure is unsuccessful. In general, there are several very sound objections to the rectal injection of fluids for the reduction of an intussusception: many of these patients later come to operative reduction because of irreducibility or because of uncertainty of complete reduction, and operation is therefore delayed, with a corresponding increase in mortality expectancy, an intestinal polyp, tumor or Meckel's diverticulum may be completely overlooked, and the method is useless when a portion of the intussusception is above the ileocecal valve—a small-bowel or an ileoileocolic intussusception will be left incompletely reduced.

#### *Operative Measures*

As a first step in hospital therapy, gastric suction should be instituted to prevent vomiting and pulmonary aspiration. Furthermore, the child should be properly covered, to reduce loss of body heat. Children and babies with intussusception present emergency situations, which should be treated by laparotomy as soon as this procedure can be safely performed. If the duration of the symptoms has been only a few hours and vomit-

ing has not been excessive, operation may be performed at once, and the fluid balance can be restored in the postoperative period. In contrast, immediate operation is dangerous when there has been excessive dehydration or blood loss, when such conditions exist, it is important to correct them partially before operation by infusion of glucose solution, plasma or whole blood. Although operation should not be delayed more than an hour or two at the most, this preoperative control of shock is of fundamental importance.

We have found open-drop ether very satisfactory for average cases of intussusception, but we believe that cyclopropane is preferable for the more seriously ill children. In extremely ill babies, the abdominal exploration is more safely done under procaine infiltration of the abdominal wall.

*Reduction of intussusception.* Regardless of the position of a presenting mass, the abdomen should be opened through a generous, right-rectus-muscle incision (Fig. 2). Lateral retraction of the rectus-muscle belly gives a stronger postoperative wound than a muscle-splitting incision. The difficult phase of reduction usually occurs in the region of the ileocecal valve or terminal ileum, hence, the incision is placed in anticipation of this. The first part of the reduction is conducted intra-abdominally, the head of the intussusceptum is milked backward along the colon as far as possible. The remaining mass can then usually be pulled outside the abdomen, where it is handled with greater facility. Excessive congestion and edema of the mass can be partially reduced if one maintains annular pressure over it with the fingers for a few minutes. Excessive drying should be avoided by the dripping of hot saline solution upon the mass from time to time. The reduction is continued by *taxis*—rather than an attempt to disengage the intussusception by traction. Serosal tears, if small, are of little consequence but constitute a warning of impending perforation, and the remainder of the reduction should be extremely gentle or else resection should be seriously considered. If serosal tears are large they should be appropriately repaired after reduction of the intussusception has been completed. In our entire series 90 per cent of the intussusceptions were manually reduced, in the last few years it has been possible to reduce about 95 per cent of them. At the completion of reduction, bowel of questionable viability can often be improved by covering for a few moments with a hot saline pack. If the intestine improves in color or if peristalsis appears on stimulation, resection is unnecessary.

Even an experienced surgeon may have difficulty in deciding when an intussusception is irreducible and should be treated by resection. Persistence in efforts at reduction will frequently be successful and will avoid resection. On the other hand, one should not persist in reduction maneuvers, only to be forced eventually to resection in an exhausted

babies. Indications for resection are threefold: if the mass is irreducible, it must obviously be excised; if the bowel is perforated or nonviable or has a doubtful viability, resection is in order, and if one is dealing with a very ill patient, no attempt should be made to reduce the intussusception — instead it should be immediately removed. In some of these critically ill babies it might be possible to reduce the intussusception and indeed to have a viable intestine, but the disengagement of the bowel releases “toxic” products into the circulation that are sufficient to produce uncontrollable shock. Hence, it is better to avoid reduction (though this might be technically feasible) and to remove quickly the entire mass so that all necrotic material can be completely removed from the body. I am sure that this decision has on several occasions helped us to save a baby who would have been lost if reduction of the intussusception had been carried out.

It is the policy of this clinic to do no more than absolutely necessary in the operative treatment of intussusception. However, this does not need to be a hard-and-fast rule. The appendix is rarely removed, this incidental procedure should be done only in the occasional case in which the general condition of the child is satisfactory and will allow an additional step. When a Meckel's diverticulum is found, it is removed if it is gangrenous or if the patient's status is completely satisfactory. Under other circumstances it is better judgment to leave removal of a polyp or diverticulum until a second operation ten days or two weeks later.

**Resection and lateral anastomosis.** For irreducible intussusception (or for gangrenous bowel) this procedure has been employed with decreasing frequency in our series of cases — and indeed has been almost abandoned. A total of 18 cases have been so treated with 3 recoveries — a mortality of 83 per cent. These primary anastomoses were all performed more than a decade ago. In our opinion, there are several reasons why primary anastomosis is not the best surgical procedure for the treatment of an intussusception that requires resection: a child with an irreducible intussusception — or with a gangrenous intestine — is invariably seriously ill, and hence, a lengthy procedure, such as completion of a primary anastomosis, may be too productive of shock, whereas, a shorter operation might be tolerated (this time factor is particularly important in younger age groups, which formed the majority of our series), open anastomosis with spillage of heavily inoculated bowel contents into a devitalized peritoneal cavity (even though this contamination is minimal) is diametrically opposed to sound surgical principles — *asepsis* is a factor of the greatest importance for survival of these children, and primary anastomoses should not be performed because one fears uncontrollable loss of fluid and electrolytes from a double-barreled en-

terostomy — present-day fluid therapy makes it quite possible to control such losses even in small babies, and furthermore, the enterostomy does not have to be left open for a long time but can be closed in six or seven days.

**Open double enterostomy.** In 23 patients a resection was performed for irreducible intussusception (or gangrenous intestine). Paul-Mixer tubes or catheters were sewed into the cut-off (open) ends of the ileum and colon, and then these entubed ends were drawn out through the abdominal wall, which was closed around them. There were 5 recoveries — a mortality of 77 per cent.

We believe that this procedure is somewhat better than direct anastomosis, chiefly because the operating time is shortened for these poor-risk patients. However, double enterostomy (cutting off the intussusception mass while the abdomen is still open) is a poor procedure because of the inevitable soiling (however slight) of the peritoneal cavity at the time of intra-abdominal resection and decompression of the obstructed bowel. Although these children frequently recovered from a rapidly executed procedure, many of them died a few days later from an overwhelming peritonitis. We believe that this type of operation should be condemned.

**Aseptic Mikulicz resection.** When resection has been necessary, the procedure of choice in our experience has been the “closed aseptic, Mikulicz resection” (Fig 3). By this, we mean that the segment to be removed is kept closed while it is freed from its mesenteric or mesocolonic attachments and is dragged out through the abdominal wound, which is then closed in layers around the bases of the two limbs, and the diseased bowel is not cut off until the skin has been completely sutured. (It is well to sew together the two limbs of ileum or colon that will remain just beneath the abdominal wall.) *By these maneuvers there is no possibility of peritoneal contamination.* If the intestine above the intussusception is so distended that it must be deflated to facilitate the abdominal-wall closure, the aspiration should not be done with a needle. Although such needling is fairly safe if the hole is immediately closed with an appropriate suture, in some cases momentary regional soiling may be sufficient to lead to a subsequent fatal peritonitis. If deflation of intestine is required, it is best to accomplish this by means of an “intestinal leech” such as that described by Swenson,<sup>2</sup> applied immediately above the intussusception, and exteriorization of the loop to which the decompression apparatus has been attached. In this way intestinal deflation can be accomplished without the slightest danger of peritoneal contamination. This type of resection has several obvious advantages: the operating time is short, shock is minimized, immediate decompression is accomplished, and asepsis is rigidly preserved.

We have not encountered difficulty in maintaining fluid and electrolyte balances during the time when ileostomies or colostomies have been open. Modern parenteral therapy makes it possible to compensate for juices that are lost from an enterostomy. Furthermore, it is important to emphasize that a crushing clamp can be applied to cut down the septum between the two spurs within a few

nine months, ten months, thirteen months, twenty months, two years and seven years.

Although this closed, aseptic, exteriorization method has given us results vastly superior to what was obtained a decade or more ago, they are not so good as the recent excellent record of Dennis,<sup>3</sup> who has performed 8 resections with primary intestinal anastomosis, all patients recover-

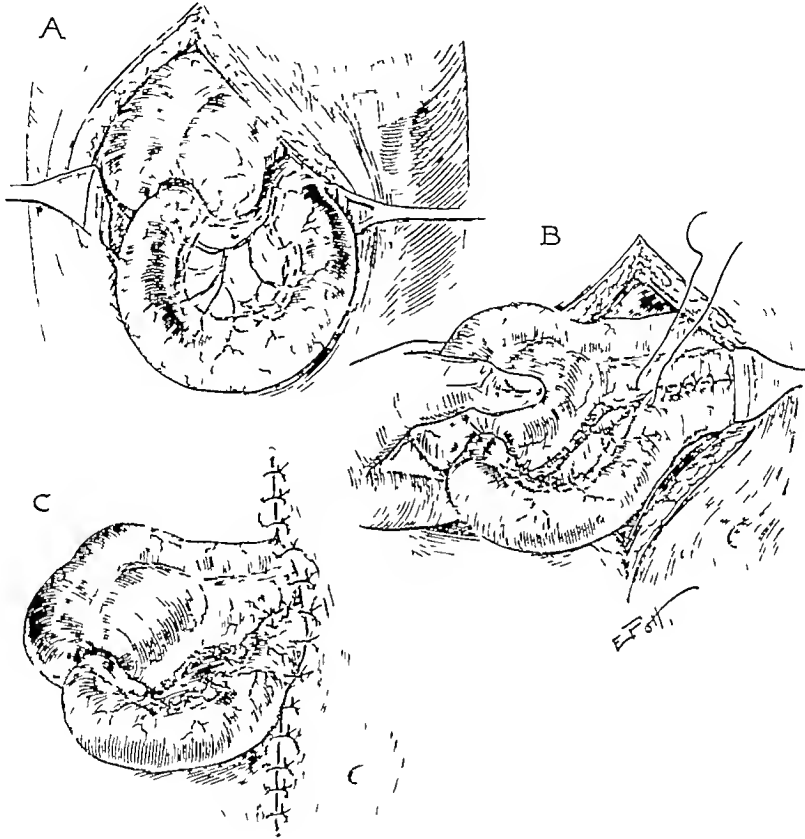


FIGURE 3 Method for Aseptic Resection of Gangrenous or Irreducible Intussusception. A shows a right-rectus-muscle incision for ileocolic intussusception (the mesentery and mesocolon will be divided along the dotted line), B the bowel freed from its mesenteric attachments, the limbs of the ileum and colon being joined by interrupted fine silk sutures, which must not pierce the mucosa, and C the intussusception being exteriorized, and the abdominal wound closed around the limbs of the ileum and colon.

days, and then the enterostomy can be closed within six or seven days of the initial operation.

In this series 14 cases in all have been treated by this method, with 11 recoveries—a mortality of 23 per cent. Eleven of these patients have been treated in the last nine years, with recovery in 10—a present-day mortality rate of 9 per cent. (The single fatal case in this latter period occurred in a four-month-old baby who, through a misunderstanding, failed to receive a postoperative blood transfusion and died in shock four hours later.) The successful resections were done in children aged three days, four months, six months, eight months,

ing. It is well to explain that all Dennis's patients were operated upon by himself—a master in intestinal surgery. In contrast, the resections in our series have been done in some cases by the senior surgeons, but most of them have been performed by the resident staff. There can be little doubt that resection and primary anastomosis is a better form of therapy, provided it is done by one who is constantly practicing intestinal or colonic surgery. However, for the surgeon who is only occasionally dealing with intestinal problems, the method of exteriorization emphasized above will probably give higher recovery rates.

## POSTOPERATIVE CARE

The aftercare of a child with an easily reducible intussusception consists mainly of gastric suction

tion eliminates the hazards of post-anesthesia vomiting and aspiration pneumonia, furthermore, it adds to the child's comfort by keeping the upper in-

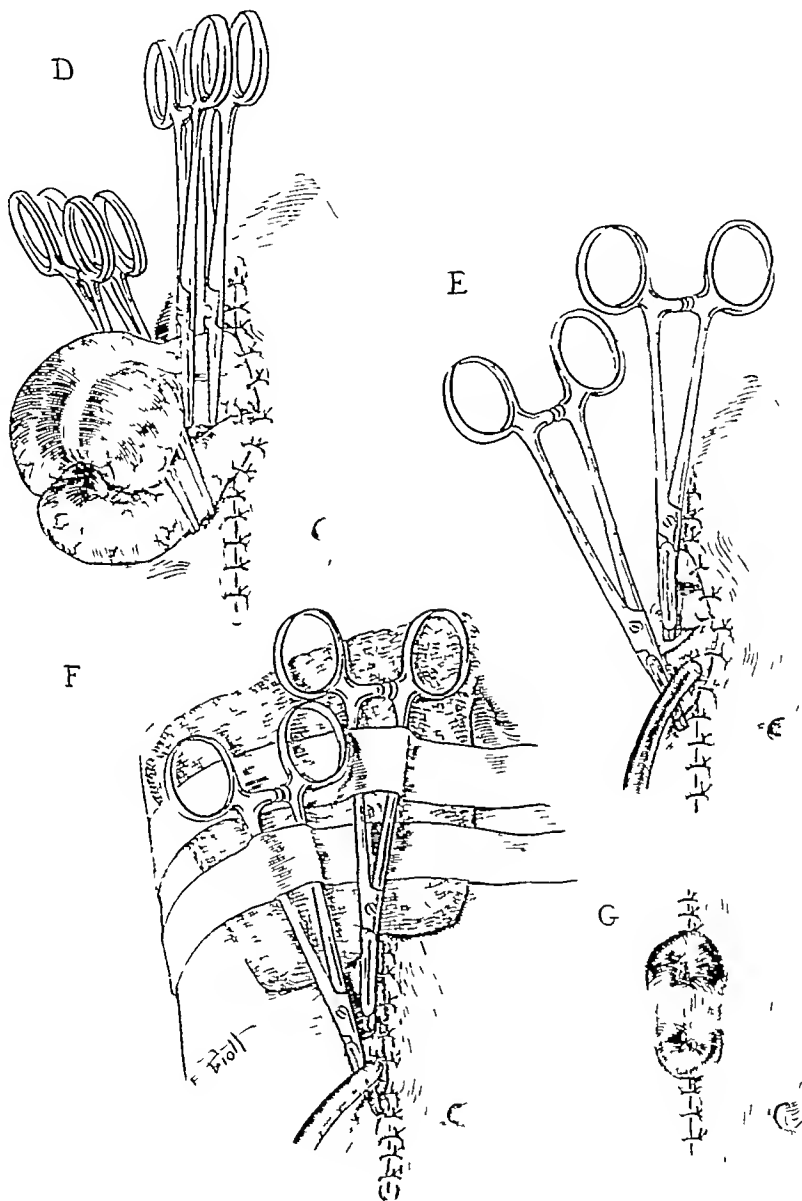


FIGURE 3 (Continued)

D demonstrates removal of intussusception deferred until the abdominal wound is completely closed (appropriate clamps are applied to the two limbs), E intussusception cut away and a catheter inserted into the ileum for immediate and continued decompression of the small intestine. F two clamps left on the limbs to anchor them for several days until the limbs become adherent to the abdominal wall, and G the appearance of the ileostomy-colostomy several days after operation and after removal of the clamps (the septum between the double-barreled spurs can now be cut down, and the remaining opening of the bowel can be turned in without entering the peritoneal cavity).

with an indwelling Levin tube or urethral catheter (in young babies) for twelve to twenty-four hours and the administration of parenteral fluids. Suc-

testinal tract decompressed. After removal of the suction tube, the child is offered sips of clear fluids, followed by more nourishing fluids as tolerated. A

fluid intake of 2 or  $2\frac{1}{2}$  ounces per pound of body weight per twenty-four hours is maintained by intravenous and subcutaneous injection of glucose and saline solutions. Parenterally administered fluids are rarely needed for more than forty-eight hours. By the fourth or fifth day the child can usually take feedings by mouth that easily meet the fluid and caloric requirements.

Successful postoperative care of the child who has had a resection requires more vigorous measures. Careful charting of temperature, pulse and respirations should be done at intervals of fifteen or thirty minutes until the patient is in a stable condition. Blood-pressure determinations in children under two years of age have little practical value. The rate and quality of the pulse are the main indexes of the child's status. An infusion of plasma, or preferably blood, should always be given at the termination of operation, and repeated if the condition of the child requires it. The size of a transfusion is determined by the severity of the blood loss and by the child's hemoglobin or red-cell count. In general, no more than 10 cc of blood per pound of body weight should be given at a time, unless blood loss has been extreme. Even if bleeding has been minimal before or during operation, strangulating obstruction always produces a decrease in the circulating plasma volume, often approaching shock proportions. Hence, repeated plasma (or albumin solution) infusions may be life saving in these critically ill children. Plasma or albumin infusion should rarely be more than 10 cc per pound of body weight, but this may be repeated in a few hours if the circulatory state requires it. Intravenous or subcutaneous injections of amigen solutions greatly aid in supporting nutrition whenever there is a long period of convalescence that is complicated by gastric suction and inadequate, oral, protein intake. The salt content of plasma (and some albumin solutions) must be borne in mind, if an excess of salt is given by injection of too much of these fluids, the baby may become edematous. If the postoperative period is prolonged for any reason, it is essential to study the plasma levels of chloride, protein and carbon dioxide combining power to guide intelligently the proper parenteral fluid or blood therapy.

Following the work of Fine and his associates,<sup>4</sup> we have frequently used high-concentration oxygen

tents for the more severely ill children, with excellent results. To keep oxygen levels at 90 to 95 per cent it is necessary to have a very tightly closed chamber, and to avoid frequent openings of the tent.

Chemotherapy has little place in the treatment of the routine case in which there is an easily reducible intussusception. It is of great value in patients who are seriously ill from peritonitis or from aspiration pneumonia.

#### SUMMARY

A series of 610 cases of intussusception treated at the Children's Hospital in Boston is presented. The etiology in 95 per cent of the cases is unknown. Intussusception is characterized by sudden onset of paroxysmal abdominal pain, vomiting, bloody stools and a palpable abdominal mass, the condition occurring usually in a well nourished baby. Roentgenologic examination by barium enema may aid in making the diagnosis in atypical cases, but it is not necessary in the majority of cases, in which the history and physical findings are sufficient to establish the proper diagnosis.

The optimum treatment of intussusception is by surgical reduction of the intussusception after rapid but important preoperative preparation. If resection is necessary, exteriorization is the method of choice, since this rigidly prevents contamination or soiling of the peritoneal cavity. Postoperative care includes the use of gastric suction, transfusion of blood or plasma, infusion of glucose or saline solution and in some cases institution of chemotherapy and placement of the child in a high-concentration oxygen tent.

The mortality rates for intussusception have improved steadily, in the last few years the mortality has been reduced to 2.7 per cent.

#### REFERENCES

- 1 Ladd W. E. and Gross R. E. Intussusception in infancy and childhood: report of three hundred and seventy-two cases. *Arch. Surg.* 29: 365-384, 1934.
- 2 Swenson O. New instrument for safely decompressing cecum during cecostomy. *J. A. M. A.* 114: 2450, 1940.
- 3 Dennis C. Resection and primary anastomosis in treatment of gangrenous or non-reducible intussusceptions in children: simple one layer silk anastomosis. *Ann. Surg.* 126: 788-796, 1947.
- 4 Fine J., Hermanson L. and Frehling S. Further clinical experiences with ninety-five per cent oxygen for absorption of air from body tissues. *Ann. Surg.* 107: 1-13, 1938.

TRENDS IN PULMONARY TUBERCULOSIS DURING FIFTY YEARS AT RUTLAND STATE SANATORIUM\*

MACEY KRONICK, M D †

RUTLAND, MASSACHUSETTS

THIS was the first state sanatorium for the treatment of pulmonary tuberculosis to be established in the United States. The project was planned in 1895 and the opening took place fifty years ago, in 1898<sup>1</sup>. Many similar institutions were modeled after this one, which was considered quite an achievement at the time.

In a review of the yearly reports<sup>2</sup> and records of the half century many interesting facts bring out certain trends in pulmonary tuberculosis, most of which apply to this sanatorium but some of which may be found elsewhere in the country.

ADMISSIONS

During the fifty-year period, this sanatorium admitted 21,304 patients. In the first decade, emphasis was placed on selecting patients who had early or incipient tuberculosis. As a policy "patients were given a trial of three or four weeks,

TABLE 1 Percentage of Patients in Various Stages of Tuberculosis Admitted to Rutland State Sanatorium\*

YEAR	MINIMAL CASES %	MODERATELY ADVANCED CASES %	FAR- ADVANCED CASES %
1898	50.0	38.2	11.5
1907†	39.0	42.0	19.0
1917	40.8	43.8	15.0
1927	12.7	33.2	49.4
1937	11.4	31.2	52.6
1947	7.0	21.0	60.5

\*The remainder of each group up to 100 per cent of the total are unclassified.

†This was the year when the cases were tabulated on the classification adopted by the National Association for the Study and Prevention of Tuberculosis. The Rutland classification used (1898-1906) was similar in most respects.

if found to have more lung trouble than could be expected to yield readily to treatment, they were asked to give up their places to those whose chances of recovery seemed to be more hopeful." Patients who resided in the Sanatorium for less than a month were classified as "not considered." In 1906, of the 1139 discharged during the year, 198 remained only about one month. During the same year the following record was made:

This institution was established by the State on the theory that incipient pulmonary tuberculosis is a curable disease. Its history, up to this time, has confirmed the theory. But the sanatorium has been so enlarged (from the original 170 to 260 beds) that not enough incipient cases apply to fill it. At present not more than one third of the patients are strictly in the incipient stage.

\*Presented at the fall meeting of the American Trudeau Society (Eastern Section) and the fiftyth anniversary meeting of the Rutland State Sanatorium, Rutland, Massachusetts, October 15, 1948.

†Assistant physician, Rutland State Sanatorium.

In 1906, of the cases under treatment 36 per cent were classified as incipient, 41 per cent as moderately advanced, and 21 per cent as advanced. Since the methods of diagnosis then were not so precise — x-ray study being used seldom if at all prior to 1919, and reliance being placed on the physical

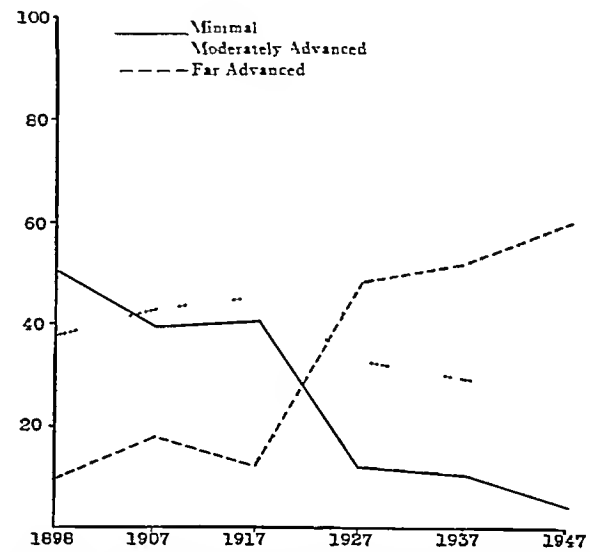


FIGURE 1 Percentages of Patients Admitted in Different Stages of Tuberculosis, Rutland State Sanatorium (1898-1947)

examination, which was of questionable value in accurately diagnosing and classifying minimal cases — it became evident within the first ten-year period that moderately advanced and advanced cases would have to receive more consideration. The changes that occurred in the last twenty-five years are striking compared to those of the first twenty-five years (Table 1). The marked increase in far advanced cases is evident in Figure 1. From 1899 to 1906, of the total number of applicants only 46 to 55 per cent were admitted each year. Forty-five per cent or more were rejected as too far advanced. Minimal cases in 1917 constituted 40.8 per cent of all patients and far-advanced cases 13 per cent, by contrast, in 1947 the minimal cases were only 7 per cent, whereas those in the far-advanced stage made up 60.5 per cent, and moderately advanced cases were 21 per cent, making a total of almost 82 per cent in the advanced stages. The noticeable decrease in the number of admissions (Table 3) began in 1911, by which time three other state sana-

fluid intake of 2 or  $2\frac{1}{2}$  ounces per pound of body weight per twenty-four hours is maintained by intravenous and subcutaneous injection of glucose and saline solutions. Parenterally administered fluids are rarely needed for more than forty-eight hours. By the fourth or fifth day the child can usually take feedings by mouth that easily meet the fluid and caloric requirements.

Successful postoperative care of the child who has had a resection requires more vigorous measures. Careful charting of temperature, pulse and respirations should be done at intervals of fifteen or thirty minutes until the patient is in a stable condition. Blood-pressure determinations in children under two years of age have little practical value. The rate and quality of the pulse are the main indexes of the child's status. An infusion of plasma, or preferably blood, should always be given at the termination of operation, and repeated if the condition of the child requires it. The size of a transfusion is determined by the severity of the blood loss and by the child's hemoglobin or red-cell count. In general, no more than 10 cc of blood per pound of body weight should be given at a time, unless blood loss has been extreme. Even if bleeding has been minimal before or during operation, strangulating obstruction always produces a decrease in the circulating plasma volume, often approaching shock proportions. Hence, repeated plasma (or albumin solution) infusions may be life saving in these critically ill children. Plasma or albumin infusion should rarely be more than 10 cc per pound of body weight, but this may be repeated in a few hours if the circulatory state requires it. Intravenous or subcutaneous injections of amigen solutions greatly aid in supporting nutrition whenever there is a long period of convalescence that is complicated by gastric suction and inadequate, oral, protein intake. The salt content of plasma (and some albumin solutions) must be borne in mind, if an excess of salt is given by injection of too much of these fluids, the baby may become edematous. If the postoperative period is prolonged for any reason, it is essential to study the plasma levels of chloride, protein and carbon dioxide combining power to guide intelligently the proper parenteral fluid or blood therapy.

Following the work of Fine and his associates,<sup>4</sup> we have frequently used high-concentration oxygen

tents for the more severely ill children, with excellent results. To keep oxygen levels at 90 to 95 per cent it is necessary to have a very tightly closed chamber, and to avoid frequent openings of the tent.

Chemotherapy has little place in the treatment of the routine case in which there is an easily reducible intussusception. It is of great value in patients who are seriously ill from peritonitis or from aspiration pneumonia.

### SUMMARY

A series of 610 cases of intussusception treated at the Children's Hospital in Boston is presented. The etiology in 95 per cent of the cases is unknown. Intussusception is characterized by sudden onset of paroxysmal abdominal pain, vomiting, bloody stools and a palpable abdominal mass, the condition occurring usually in a well nourished baby. Roentgenologic examination by barium enema may aid in making the diagnosis in atypical cases, but it is not necessary in the majority of cases, in which the history and physical findings are sufficient to establish the proper diagnosis.

The optimum treatment of intussusception is by surgical reduction of the intussusception after rapid but important preoperative preparation. If resection is necessary, exteriorization is the method of choice, since this rigidly prevents contamination or soiling of the peritoneal cavity. Postoperative care includes the use of gastric suction, transfusion of blood or plasma, infusion of glucose or saline solution and in some cases institution of chemotherapy and placement of the child in a high-concentration oxygen tent.

The mortality rates for intussusception have improved steadily, in the last few years the mortality has been reduced to 2.7 per cent.

### REFERENCES

1. Ladd W. E. and Gross R. E. Intussusception in infancy and childhood: report of three hundred and seventy-two cases. *Arch Surg* 29: 365-384, 1934.
2. Swenson O. New instrument for safely decompressing cecum during cecostomy. *J A M A* 114: 2450, 1940.
3. Dennis C. Resection and primary anastomosis in treatment of gangrenous or non reducible intussusceptions in children: simple one-layer silk anastomosis. *Ann Surg* 126: 788-796, 1947.
4. Fine J. Hermanson L. and Frehling S. Further clinical experiences with ninety-five per cent oxygen for absorption of air from body tissues. *Ann. Surg* 107: 1-13, 1938.

charges according to their classification in Table 4, one is struck by the definite decrease, in the past thirty years, of the "quiescent" group and by the increase in the combined percentages of "unimproved" and "dead." This is a natural consequence of the steadily increasing number of older patients and those with more advanced cases admitted, especially in the past decade. Another reason is that more deaths are occurring in sanatoriums, and

dropped to 36.4 in 1946, and a similar decrease occurred in the Commonwealth, it is closely paralleled by the death rate from respiratory forms of tuberculosis in Massachusetts, which decreased from 185 per 100,000 population in 1900 to 32.5 in 1947 (Fig 3). Except for a slight increase in both state and national death rates during the influenza epidemic of 1918 the decline was steady until 1939. Since then the national death rate has continued to

TABLE 4 Classification of Patients on Discharge \*

YEAR	ARRESTED OR APPARENTLY CURED		IMPROVED	UNIMPROVED		TOTAL PATIENTS	
	%		%	%			
1899	34.2		39.3	26.0		216	
1900	42.3		44.7	13.0		306	
1901	46.1		47.6	5.7		402	
1902	48.1		44.5	6.7		388	
1903	48.9		43.0	7.9		575	
1904	44.8		47.7	7.4		692	
1905	35.7		58.9	7.4		755	
1906	39.1		52.1	8.8		1139	
1907	51.5		39.5	9.2		939	
1908	54.4		34.5	10.9		804	
1909	58.7		27.5	13.9		784	
1910	62.5		28.6	9.0		758	
1911	50.5		29.5	20.1		542	
1912	37.7		52.5	21.4		522	
1913	36.7		35.1	21.4		458	
1914	39.9		32.7	20.1		476	
1915	38.8		35.0	22.2		535	
	ARRESTED	APPARENTLY ARRESTED	QUIESCENT	IMPROVED	UNIMPROVED	DEAD	
	%	%	%	%	%	%	
1916	9.6	28.6	10.5	26.2	14.9	4.5	465
1917	19.7	19.0	15.8	13.8	18.5	6.1	457
1918	5.6	8.0	50.2	20.2	17.4	9.0	510
1919	4.5	4.8	30.0	29.2	14.4	4.8	499
1920	4.5	6.1	33.9	21.4	11.7	12.2	551
1921	2.9	5.4	45.2	15.7	9.6	10.7	475
1922	2.7	4.0	45.8	15.1	12.4	12.4	465
1923	5.0	5.4	49.5	11.2	9.4	11.2	517
1924	1.5	5.2	49.0	14.4	12.2	11.6	457
1925	2.1	5.0	41.9	11.5	13.8	26.5	515
1926	1.5	2.2	40.2	11.1	13.5	22.6	450
1927	6	3.6	40.9	13.2	15.4	17.6	498
1928	2.4	2.9	38.8	14.8	15.1	22.2	404
1929	1.7	3.8	56.4	14.7	20.2	17.6	340
1930	1.7	4.4	40.1	14.0	14.0	20.6	272
1931	2.3	1.7	44.2	18.2	15.3	12.4	346
1932	91	2.7	37.8	12.1	15.4	25.9	330
1933	83	2.7	43.8	14.2	17.2	16.9	365
1934	—	3.5	41.4	15.8	13.8	16.0	398
1935	77	2.8	37.2	21.0	17.4	15.6	389
1936	—	2.3	46.5	11.5	16.1	20.1	305
1937	1.8	4.4	49.0	11.0	11.0	17.7	271
1938	2.9	10.2	28.9	16.8	15.7	22.5	273
1939	3.7	9.4	31.6	15.0	10.9	24.9	265
1940	1.2	9.7	41.1	12.0	5.6	22.0	248
1941	2.7	3.4	40.6	9.2	9.6	24.9	261
1942	1.1	10.1	28.6	13.6	12.9	24.4	287
1943	1.8	8.4	28.1	15.7	15.5	24.0	274
1944	3.7	4.5	36.7	16.1	8.3	18.5	243
1945	5.4	9.2	20.5	14.5	4.3	32.5	186
1946	8.0	16.6	18.6	14.9	8.5	27.1	188
1947	4.8	10.5	15.7	13.8	12.9	30.0	210

\*The remainder of each year totaling up to 100 per cent were nontuberculous, not considered and miscellaneous.

fewer in the community, in 1947, 795 of the 1583 deaths in Massachusetts were in sanatoriums.

Although the deaths from tuberculosis in this sanatorium have shown an increase, particularly in recent years, the death rates due to tuberculosis in the Commonwealth of Massachusetts and in the United States are definitely on the wane (Table 5). The national death rate of over 194 per 100,000 population in 1900 (all forms of tuberculosis)

fall but in Massachusetts, except for a 12 per cent increase in death rate from pulmonary tuberculosis in 1943 over the preceding year, there was no important change until 1947, when a new low record was reached.

#### LABORATORY FINDINGS

Direct smears from the sputum were used for the first thirty-five years. Concentrations were

toriums — Lakeville, North Reading and Westfield — were opened to receive tuberculous patients. Again, in 1936, there was a further decrease owing to the opening of the Worcester County and Middlesex County sanatoriums.

In 1911 Massachusetts had 1200 beds available in sanatoriums for tuberculosis. The number had expanded from a little more than 200 in 1900, and reached 3600 in 1928 and 4736 in 1938. The number in 1946 was 4471.<sup>3</sup> The slight decrease in the number of beds in recent years is attributable to the closing of private and municipal sanatoriums. The ratio of the number of beds to deaths has been considered satisfactory if it approximated 2.5:1. In 1928 it was 1.3:1, in 1938, 3:1, and in 1947, 2.8:1.

In 1925 only 35 per cent of the patients who had reported cases of tuberculosis in Massachusetts applied for hospital treatment, this increased to

TABLE 2 *Percentage of Patients in Various Age Groups Admitted (by Ten-Year Periods)*

YEAR	PATIENTS UNDER TWENTY YEARS OF AGE	PATIENTS TWENTY TO THIRTY- NINE YEARS OF AGE	PATIENTS THIRTY TO FORTY- NINE YEARS OF AGE	PATIENTS FORTY TO FIFTY- NINE YEARS OF AGE	PATIENTS OVER FIFTY YEARS OF AGE
	%	%	%	%	%
1899	12.30	42.60	23.60	21.40	
1907	17.40	44.62	28.27	8.33	1.37
1917	14.61	48.72	23.20	11.83	1.62
1927	10.24	39.35	25.41	15.37	9.63
1937	8.46	41.91	27.94	10.29	11.40
1947	4.00	23.50	20.00	25.00	27.50

55 per cent by 1929 and to 65 per cent by 1935 and is still higher at present.

The survey of the ages of all patients admitted during the half century shows that the minimum age for admission was fourteen years, which was later changed to seventeen years. During the first forty years the average age ranged from twenty-eight to thirty-three years, but from 1937 to 1947 many more of the older age group were among the admissions and the average age in 1947 was forty and two-thirds years. Table 2 presents the percentages of patients in different age groups admitted, and Figure 2 shows the decrease in patients under the age of forty with the proportionate increase in patients above that age especially during the past ten years. For the first time in fifty years, the number of patients over the age of forty now exceeds 50 per cent of all patients admitted to the sanatorium. That active tuberculosis occurs in older persons of the community with greater frequency makes it an important diagnosis to keep in mind not only because of itself but also as a differentiation from carcinoma, bronchiectasis, lung abscess and other pulmonary lesions in such patients

## DISCHARGES

Classification on discharge has changed very little during the fifty-year period. In the Rutland system of nomenclature (1899-1905) the words "apparently cured" and "arrested" were used synonymously. Either or both terms expressed practically the same idea that "apparently cured" represents in the national system except that the three-month period was not required. The official nomenclature

TABLE 3 *Admissions, Discharges and Deaths at Rutland State Sanatorium from 1898-1947*

YEAR	ADMISSIONS	DISCHARGES	DEATHS
1898*	97	0	0
1899	387	216	1
1900	317	306	5
1901	399	402	1
1902	467	388	3
1903	589	575	1
1904	687	692	4
1905	865	755	4
1906†	1113	1139	10
1907	948	939	11
1908	810	804	8
1909	783	784	11
1910	762	758	12
1911	531	542	57
1912	529	522	43
1913	449	438	36
1914	469	476	37
1915	538	535	37
1916	465	465	20
1917	431	437	27
1918	455	510	46
1919	567	499	24
1920	548	551	62
1921	483	475	51
1922	448	465	58
1923	538	517	58
1924	438	457	53
1925	513	513	82
1926	464	450	102
1927	488	498	83
1928	415	404	90
1929	333	340	60
1930	277	272	56
1931	289	346	43
1932	393	330	79
1933	357	362	62
1934	395	398	64
1935	398	389	61
1936	298	303	61
1937	272	271	48
1938	246	273	61
1939	227	265	66
1940	226	248	55
1941	268	261	65
1942	274	287	70
1943	250	274	66
1944	245	243	45
1945	168	186	60
1946	192	188	51
1947	200	210	63

\*October-December

†Fourteen months

established by the National Tuberculosis Association at Washington in May, 1905, was adopted here in 1907. From 1899 to 1910, about 90 per cent of all patients discharged were classified as improved, arrested or apparently cured, and less than 10 per cent as not improved (including deaths). In 1911 there was a sharp increase in the number of deaths (Table 3), which was attributed to the larger number of patients with more advanced cases admitted during the preceding year. In looking over the dis-

egg-nogs, and the average caloric intake was between 3500 and 5000 per day. For the last twenty years a more reasonable diet has been used consisting of 250 gm of carbohydrate, 100 gm of protein and 100 gm of fat, giving a total of 2300 calories. The omission of lunches between meals resulted in a reduction of gastrointestinal disturbances and of food complaints by patients. These patients gained weight faster than with overfeeding, and the change

smaller and more frequent. Careful judgment of the indications for starting as well as for discontinuing treatment<sup>4</sup> has been exercised, and the progress and status of the collapsed lung observed frequently by fluoroscopy and x-ray examination. The earlier experience and results with pneumothorax here were reviewed by Laroche<sup>5</sup> and Nadeau.<sup>6</sup> A total of 4236 patients have received approximately 83,000 treatments from 1927 through 1947. During this time 2176 patients, representing 37.7 per cent of the 5776 patients admitted for pulmonary tuberculosis, were started on pneumo-

TABLE 6 Summary of Procedures at Rutland State Sanatorium 1927-1947, Inclusive

DATA ON CASE	No	
Admissions	6210	
Stage I (minimal)	672	
Stage II (moderately advanced)	2057	
Stage III (far advanced)	047	
Nontuberculous hilar and not considered	454	
Pneumothoraces		
Number of patients started		
Successful	1511	(70.3%)
Unsuccessful	645	(29.7%)
Total	2176	
Percentage of admissions		37.7
Total patients treated	4236	
Total treatments given	83,000	
Pneumolyses	647	
Percentage of successful pneumothoraces started		42.2
Thoracoplasties	566	
Percentage of admissions		6
Phrenic nerve interruptions		
Temporary	178	
Permanent	217	
Total	395	
Percentage of admissions		6.8
Bronchoscopies	1294	
Percentage of admissions		22.4
Oothoraces	40	
Percentage of admissions		0.69
Extrapleural pneumothoraces	19	
Percentage of admissions		0.2
Lobectomies (15 patients)	20	
Percentage of admissions		0.26
Pneumonectomies	19	
Percentage of admissions		0.32

probably represents one of the significant improvements in treatment. In tuberculous enteritis a bland, low-roughage diet has been substituted and supplemented with cod liver oil and tomato juice since 1929. This regime, together with ultraviolet radiation to the abdomen, gives considerable relief. Tuberculin and autogenous vaccines were used about 1910, but not extensively, and were abandoned within the next few years.

From 1927 to the present time more active measures of treatment have been carried out as listed in Table 6. As early as 1911 pneumothorax was used in several cases. During the early years it was reserved mainly for advanced cases that did not respond to rest alone, for hemorrhage and for bilateral lesions if one side appeared to be not too active or extensively involved. Large refills of nitrogen at comparatively long intervals were usually given for a year or so. Since 1927 pneumothorax has been used more intensively, nitrogen has been replaced by filtered air, and refills are

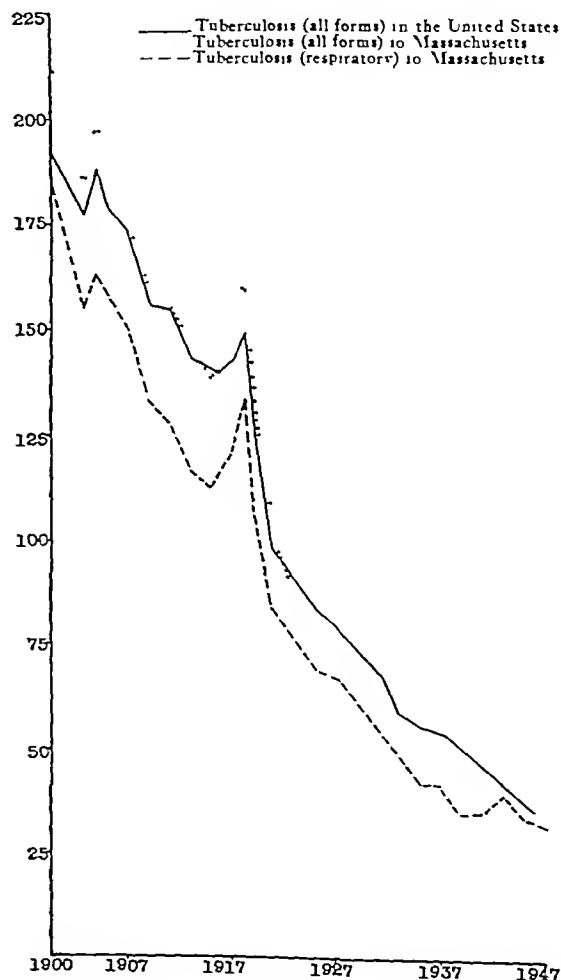


FIGURE 3 Death Rates per 100,000 Estimated Population, 1900-1947

thorax, and of these 70.3 per cent were successful and 29.7 per cent unsuccessful (Table 6). Dufault's graph showing trends of active treatment from 1927 to 1938 has been extended through 1947 (Fig. 4). The curve of total pneumothoraces initiated (in terms of percentage of admissions) during each of these twenty-one years demonstrates a steady rise from 5.8 per cent of all admissions in 1927 to the peak of 61.3 per cent in 1939. From then

begun in 1932. The culture method, started about 1936, has been used more frequently than concentrations since 1940. The original culture medium consisted of a slice of potato to which was added dye, glycerin and water. Soon this was replaced by a modified Pinner medium with a potato, water and egg base. More recently the Lowenstein medium has been substituted. The cultures may become positive in two weeks but may also require as much as six weeks to show growth. After a positive reaction has been obtained, smears are done monthly, when they turn negative, cultures are done at six-week intervals. If these are negative, or if no suitable specimen of sputum is obtained, gastric contents are examined by smear, concentration test and guinea-pig inoculation. The animals are kept for eight weeks. These methods have increased the number of "positives." When only smears from sputum were examined up to 1932, the reactions of only 67.4 per cent of all patients

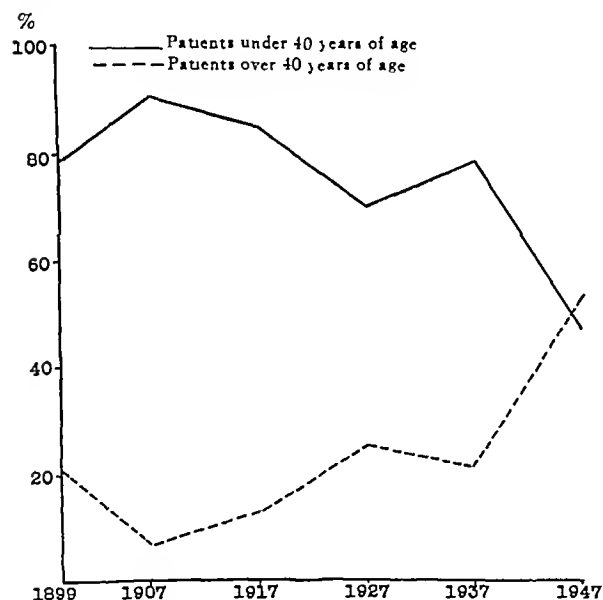


FIGURE 2 Percentages of Patients Admitted over and under Forty Years of Age

were found positive, whereas 94.5 per cent are now positive on sputum or gastric contents.

Complete blood examinations, including differential count and sedimentation rate (Rourke and Ernstene), are routinely carried out every two months and, like comparative x-ray films, are of considerable help in following the patient's progress.

An x-ray machine was installed at the sanatorium in 1919, and from a few hundred films per year, the department now averages three or four thousand

#### TREATMENT

Since the beginning of the century several changes have appeared in the treatment. The importance of fresh air was early recognized. Data concerning climatic conditions including rainfall, temperature,

humidity, sunshine and so forth were recorded during the first decade, but less attention was focused upon these factors thereafter. No longer are patients exposed to cold beyond physical comfort.

For several years, bed rest was prescribed only in the event of high temperatures or hemoptysis. Patients enjoyed moderate activity mingled with

TABLE 5 Death Rates for Tuberculosis (All Forms) for the Registration States and the Commonwealth of Massachusetts (1900-1946), and Death Rates for Pulmonary Tuberculosis for Massachusetts (1900-1947) (Rates per 100,000 Estimated Population)

YEAR	TUBERCULOSIS (ALL FORMS)*		PULMONARY TUBERCULOSIS†
	REGISTRATION STATES	MASSACHUSETTS	MASSACHUSETTS
1900	194.4	213.6	183.0
1901	189.9	206.5	177.0
1902	174.2	191.4	162.0
1903	177.2	183.1	155.0
1904	188.1	198.9	164.0
1905	179.9	191.8	156.0
1906	175.8	179.9	149.0
1907	174.2	177.6	151.0
1908	162.1	165.4	137.0
1909	156.3	160.3	133.0
1910	153.8	163.6	133.2
1911	155.1	156.4	128.2
1912	145.4	149.8	120.0
1913	143.5	144.8	116.9
1914	141.7	140.8	114.2
1915	140.1	138.6	113.3
1916	138.4	147.2	119.6
1917	143.5	145.5	121.0
1918	149.8	162.5	133.6
1919	125.6	129.5	103.1
1920	113.1	113.6	91.9
1921	97.6	97.9	83.1
1922	95.3	93.1	79.3
1923	91.7	87.9	75.7
1924	87.9	85.6	72.0
1925	84.8	82.8	69.3
1926	85.5	83.5	71.0
1927	79.6	75.8	66.2
1928	78.3	73.7	63.0
1929	75.3	69.1	60.5
1930	71.1	64.2	56.9
1931	67.8	60.3	54.2
1932	62.5	54.2	47.9
1933	59.6	53.2	48.2
1934	56.7	48.8	44.5
1935	55.1	46.1	42.3
1936	55.9	43.9	40.4
1937	53.8	43.1	41.0
1938	49.1	38.6	35.7
1939	47.1	37.6	34.9
1940	45.8	37.8	34.4
1941	44.5	38.3	35.1
1942	43.1	43.8	39.1
1943	42.6	42.5	37.0
1944	41.3	40.1	34.5
1945	40.1	36.6	34.9
1946	36.4	34.5	32.5
1947			

\*Based on data from United States Public Health Service (National Office of Vital Statistics).

†Based on data from Massachusetts Department of Public Health.

rest periods in sitting or reclining positions while fully clothed. Gradually, however, bed rest during the period of clinical activity became the rule, and graduated exercise followed when clinical and laboratory evidence indicated that the process had subsided.

In earlier years overfeeding was the rule, in addition to large meals there were lunches of milk and

egg-nogs, and the average caloric intake was between 3500 and 5000 per day. For the last twenty years a more reasonable diet has been used consisting of 250 gm of carbohydrate, 100 gm of protein and 100 gm of fat, giving a total of 2300 calories. The omission of lunches between meals resulted in a reduction of gastrointestinal disturbances and of food complaints by patients. These patients gained weight faster than with overfeeding, and the change

smaller and more frequent. Careful judgment of the indications for starting as well as for discontinuing treatment<sup>4</sup> has been exercised, and the progress and status of the collapsed lung observed frequently by fluoroscopy and x-ray examination. The earlier experience and results with pneumothorax here were reviewed by Laroche<sup>5</sup> and Nadeau.<sup>6</sup> A total of 4236 patients have received approximately 83,000 treatments from 1927 through 1947. During this time 2176 patients, representing 37.7 per cent of the 5776 patients admitted for pulmonary tuberculosis, were started on pneumo-

TABLE 6 Summary of Procedures at Rutland State Sanatorium 1927-1947 Inclusive

DATA ON CASE	No	
Admissions	6210	
Stage I (minimal)	672	
Stage II (moderately advanced)	2057	
Stage III (far advanced)	047	
Non-tuberculous hilar and not considered	414	
Pneumothoraces		
Number of patients started		
Successful	15.1	170.6%
Unsuccessful	643	29.7%
Total	2176	
Percentage of admissions		37.7
Total patients treated	47.6	
Total treatments given	83,000	
Pneumolyses	647	
Percentage of successful pneumothoraces started		42.2
Thoracoplasties	166	
Percentage of admissions		6
Phrenic nerve interruptions		
Temporary	175	
Permanent	217	
Total	392	
Percentage of admissions		6.3
Bronchoscopies	1294	
Percentage of admissions		22.4
Orethoraces	40	
Percentage of admissions		0.69
Extrapleural pneumothoraces	19	
Percentage of admissions		0.2
Lobectomies (13 patients)	20	
Percentage of admissions		0.36
Pneumonectomies	19	
Percentage of admissions		0.32

probably represents one of the significant improvements in treatment. In tuberculous enteritis a bland, low-roughage diet has been substituted and supplemented with cod liver oil and tomato juice since 1929. This regime, together with ultraviolet radiation to the abdomen, gives considerable relief. Tuberculin and autogenous vaccines were used about 1910, but not extensively, and were abandoned within the next few years.

From 1927 to the present time more active measures of treatment have been carried out as listed in Table 6. As early as 1911 pneumothorax was used in several cases. During the early years it was reserved mainly for advanced cases that did not respond to rest alone, for hemorrhage and for bilateral lesions if one side appeared to be not too active or extensively involved. Large refills of nitrogen at comparatively long intervals were usually given for a year or so. Since 1927 pneumothorax has been used more intensively; nitrogen has been replaced by filtered air, and refills are

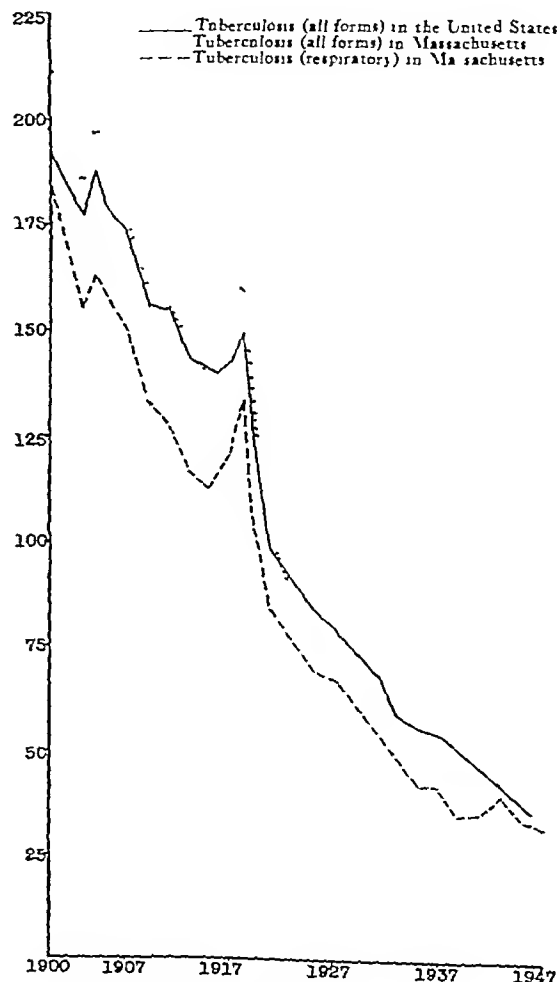


FIGURE 3 Death Rates per 100,000 Estimated Population, 1900-1947

thorax, and of these 70.3 per cent were successful and 29.7 per cent unsuccessful (Table 6). Dufault's graph showing trends of active treatment from 1927 to 1938 has been extended through 1947 (Fig. 4). The curve of total pneumothoraces initiated (in terms of percentage of admissions) during each of these twenty-one years demonstrates a steady rise from 5.8 per cent of all admissions in 1927 to the peak of 61.3 per cent in 1939. From then

begun in 1932 The culture method, started about 1936, has been used more frequently than concentrations since 1940 The original culture medium consisted of a slice of potato to which was added dye, glycerin and water Soon this was replaced by a modified Pinner medium with a potato, water and egg base More recently the Lowenstein medium has been substituted The cultures may become positive in two weeks but may also require as much as six weeks to show growth After a positive reaction has been obtained, smears are done monthly, when they turn negative, cultures are done at six-week intervals If these are negative, or if no suitable specimen of sputum is obtained, gastric contents are examined by smear, concentration test and guinea-pig inoculation The animals are kept for eight weeks These methods have increased the number of "positives" When only smears from sputum were examined up to 1932, the reactions of only 67.4 per cent of all patients

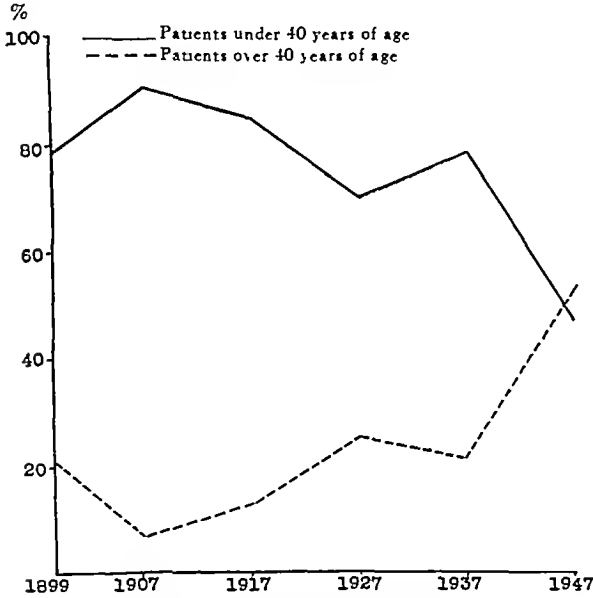


FIGURE 2 Percentages of Patients Admitted over and under Forty Years of Age

were found positive, whereas 94.5 per cent are now positive on sputum or gastric contents

Complete blood examinations, including differential count and sedimentation rate (Rourke and Ernstone), are routinely carried out every two months and, like comparative x-ray films, are of considerable help in following the patient's progress

An x-ray machine was installed at the sanatorium in 1919, and from a few hundred films per year, the department now averages three or four thousand

TREATMENT

Since the beginning of the century several changes have appeared in the treatment The importance of fresh air was early recognized Data concerning climatic conditions including rainfall, temperature,

humidity, sunshine and so forth were recorded during the first decade, but less attention was focused upon these factors thereafter No longer are patients exposed to cold beyond physical comfort

For several years, bed rest was prescribed only in the event of high temperatures or hemoptysis Patients enjoyed moderate activity mingled with

TABLE 5 Death Rates for Tuberculosis (All Forms) for the Registration States and the Commonwealth of Massachusetts (1900-1946), and Death Rates for Pulmonary Tuberculosis for Massachusetts (1900-1947) (Rates per 100,000 Estimated Population)

YEAR	TUBERCULOSIS (ALL FORMS)*		PULMONARY TUBERCULOSIS†
	REGISTRATION STATES	MASSACHUSETTS	MASSACHUSETTS
1900	194.4	213.6	185.0
1901	189.9	206.5	177.0
1902	174.2	191.4	162.0
1903	177.2	183.1	155.0
1904	188.1	198.9	164.0
1905	179.9	191.8	156.0
1906	175.8	179.9	149.0
1907	174.2	177.6	151.0
1908	162.1	165.4	137.0
1909	156.3	160.3	133.0
1910	153.8	163.6	133.2
1911	155.1	156.4	128.2
1912	145.4	149.8	120.0
1913	143.5	144.8	116.9
1914	141.7	140.8	113.3
1915	140.1	138.6	113.1
1916	138.4	147.2	119.6
1917	143.5	145.5	121.0
1918	149.8	162.5	131.6
1919	125.6	129.5	103.1
1920	113.1	113.6	91.9
1921	97.6	97.9	81.1
1922	95.3	93.1	79.3
1923	91.7	87.9	75.7
1924	87.9	85.6	72.0
1925	84.8	82.8	69.3
1926	85.5	83.5	71.0
1927	79.6	75.8	66.2
1928	78.3	73.7	63.0
1929	75.3	69.1	60.5
1930	71.1	64.2	56.9
1931	67.8	60.3	54.2
1932	62.5	54.2	47.9
1933	59.6	53.2	48.2
1934	56.7	48.8	44.5
1935	55.1	46.1	42.3
1936	55.9	43.9	40.4
1937	53.8	43.1	41.0
1938	49.1	38.6	35.7
1939	47.1	37.6	34.9
1940	45.8	37.8	34.4
1941	44.5	38.3	35.1
1942	43.1	43.8	34.6
1943	42.6	42.5	39.1
1944	41.3	40.1	37.0
1945	40.1	40.1	34.5
1946	36.4	36.6	34.9
1947		34.5	32.5

\*Based on data from United States Public Health Service (National Office of Vital Statistics)

†Based on data from Massachusetts Department of Public Health.

rest periods in sitting or reclining positions while fully clothed Gradually, however, bed rest during the period of clinical activity became the rule, and graduated exercise followed when clinical and laboratory evidence indicated that the process had subsided

In earlier years overfeeding was the rule, in addition to large meals there were lunches of milk and

## DISCUSSION

At this sanatorium during the past half century a few trends seem evident. An important one is the advanced stage of the disease in patients admitted and the older ages of these patients. This combination accounts in large measure for the increasing death rate, the decreasing number of patients suitable for collapse therapy (pneumothorax and thoracoplasty) and the prolonged length of residence. From an average stay of four to six months at the early part of the century, the length of residence increased to an average of six to ten months in the years 1910 to 1927, and for the last twenty years has ranged from ten to eighteen months. Another factor influencing length of residence has been the change in methods of treatment. There is little doubt that since the first thirty years, when almost 100 per cent of patients received only the basic rest treatment, many lives have been saved or prolonged by more active therapeutic measures. During the last twenty years, approximately 1 out of every 2 patients received rest alone, in 1 out of every 3 pneumothorax was attempted, 1 out of every 4 had successful pneumothorax, almost half the patients with successful pneumothoraces had pneumonolysis, 1 out of every 16 patients had thoracoplasty, 1 out of every 15 had phrenic-nerve surgery, and 1 out of every 60 received extrapleural pneumothorax, pneumoperitoneum, oleothorax, lobectomy or pneumonectomy. Our experience with streptomycin is still limited but agrees with the reports in the literature regarding its beneficial effects in selected cases and may prove to be

an important supplement to our other forms of therapy.

In the community the clinically significant trend in pulmonary tuberculosis that has taken place during the past fifty years is the definite and steady decline in death rates. A contributing factor in reducing the case rates and death rates, in addition to our methods of therapy, may be the isolation of active cases from the general population. In Massachusetts the case rate is now one fourth that in 1910, and the death rate only one sixth of what it was in 1900. Strides have been made in the medical and surgical methods of collapsing the lung and the closing of cavities. We seem to be approaching the ideal agent that might, by its bactericidal or bacteriostatic action in early cases, completely change our prolonged methods of treatment.

## REFERENCES

- 1 *Tuberculosis in Massachusetts*. Edited by E. A. Locke. 223 pp. Boston: Wright & Potter Printing Co. 1908.
- 2 Massachusetts Department of Public Health Reports including Yearly Reports from Rutland State Sanatorium (1897-1947).
- 3 Hospital service in the United States. *J A M A* 133:1065-1082 1947.
- 4 Dufault, P. and Laroche, A. Question of when artificial pneumothorax should be discontinued. *Am Rev Tuberc* 31:139-146 1935.
- 5 Laroche, A. Evolution of pneumothorax therapy. *New Eng J Med* 210:1013-1015 1934.
- 6 Nadeau, G. Bilateral pneumothorax. *New Eng J Med* 210:1012 1934.
- 7 Dufault, P. Evolution of treatment of pulmonary tuberculosis at Rutland State Sanatorium. *New Eng J Med* 221:374-379 1939.
- 8 *Idem*. Thoracoplasty after twenty years. *New Eng J Med* 239:660-663 1948.
- 9 Sweet, R. H. Lobectomy and pneumonectomy in treatment of pulmonary tuberculosis. *J Thoracic Surg* 15:473-483 1946.

on there was a progressive decline (except for 1943) until only 24.8 per cent in 1946 and 18.0 per cent in 1947 were started on pneumothorax.

Intrapleural pneumonolysis was carried out 647 times between 1927 and 1947. This comprises 42.4 per cent of all the patients who had successful pneumothorax. With conservative approach and careful technic the number of complications, including effusions, hemothorax and empyemas, has decreased considerably.

Bronchoscopy has assumed an important and integral role in diagnostic if not therapeutic aid in

valuable measure for suitable cases. Its application, however, has been limited. Our first 2 cases were done in 1927, and a review of the entire group from 1927 to 1938 was presented by Dufault.<sup>7</sup> A further report to bring the study to date is being prepared.<sup>8</sup> In the extension of Dufault's chart to the present (Fig. 4) it is evident that the curve reached its height in 1939, when 16.5 per cent of patients admitted came to thoracoplasty, but the incidence has dropped since then to 5.6 per cent in 1946 and 3.3 per cent in 1947. During the last twenty-one years 366 of these patients, representing

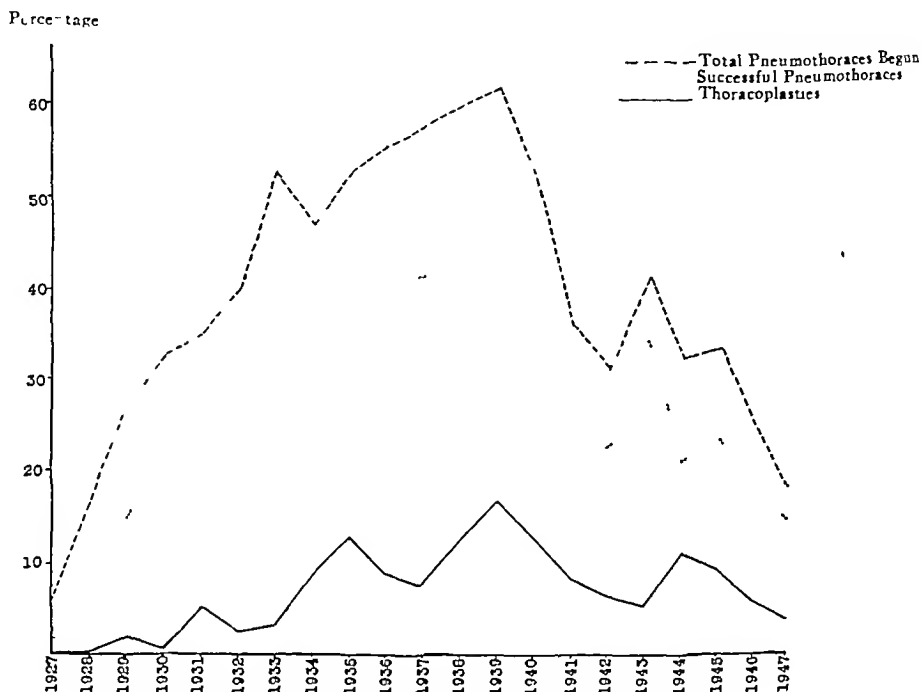


FIGURE 4 Trends of Active Treatment, 1927-1947, Inclusive (Expressed as Percentages of Admissions)

pulmonary tuberculosis. The presence of endobronchial disease may be demonstrable in more than 50 per cent of such pathologic conditions as ulceration, edema, stenosis and strictures, and may explain the persistence of positive sputum, the presence of atelectasis and of the other lesions the pathogenesis of which is obscure even with serial x-ray films and clinical data. In the 1927-1947 period, 1294 bronchoscopies were performed, mostly for diagnostic purposes. Occasionally, a patient with bronchiectasis received repeated aspirations, and in earlier years many ulcers were treated by chemical and thermal coagulation and cauterization. In recent years fewer cases have been treated actively. Bronchoscopy has been a routine preoperative procedure for all thoracoplasties during the last few years.

Thoracoplasty, as well as pneumothorax, has withstood the test of time and experience as a

6.3 per cent of those admitted, received thoracoplasty.

Extirpative surgery has been found beneficial in a small selected group. Fifteen patients had lobectomies from 1939 through 1947, and 19 patients had pneumonectomies from 1940 through 1947. Eighteen of the latter were incorporated in the 36 cases reported by Sweet.<sup>9</sup>

Other forms of active treatment have passed their peak and are now applied infrequently. Phrenic-nerve surgery, used in 381 cases in 1929-1938, was carried out in only 14 cases during the last nine years. Oleothorax, utilized in 40 cases between 1931 and 1939, has been practically abandoned. Extrapleural pneumothorax had its limited role in 1938 and 1939 with 19 cases, but has not been used since. Pneumoperitoneum has been administered to a few patients.

culous empyemas, making a total of 26 (Table 8). In 19 cases the empyema was accompanied by pulmonary tuberculosis, as evidenced by the positive sputum. That 14, or 56 per cent of them are living and well in 1947 is an agreeable surprise. As they were all operated on between the years 1931 and 1942, they have now been well from five to seventeen years. The patients with tuberculous

culosis. The current use of streptomycin before and after the operation may eliminate most postoperative deaths due to pneumonic and miliary spreads.

#### SUMMARY

Thoracoplasty was performed in 362 patients at the Rutland State Sanatorium between 1927 and 1946, inclusive.

TABLE 8 *Empyemas*

TYPE OF EMPYEMA	SPUTUM POSITIVE	SPUTUM NEGATIVE	PATIENTS WELL		PATIENTS DEAD		TOTAL
			NO	PERCENTAGE	NO	PERCENTAGE	
Mixed	11	-	7	46.7	8	55.7	16*
Tuberculous	5	2	7	70.0	3	30.0	10
Totals	19	7	14		11		26
Averages				56.0		44.0	

\*1 unknown

empyema did much better than those with mixed empyema.

#### DEATHS

Eighteen patients died postoperatively — that is, within an arbitrary time limit of two months after the operation. The time of death for the others ranged between one and nineteen years. 5 patients dying within one year, 9 after one year, 22 after two years, 19 after five years and 8 after ten years. Five deaths are attributable to heart disease, in no way related to tuberculosis so far as could be ascertained. One death was due to an accident, and another followed a cholecystectomy years after discharge. It was not always possible to determine precisely the cause of death in every case but it is assumed that it resulted from progressive tuber-

culosis. The patients who received thoracoplasty represent 63 per cent of the 5597 tuberculous persons admitted during the same period.

The clinical indications are the same today as they were twenty years ago.

As sanatorium patients are noticeably older and sicker than they were in the past, the percentage of thoracoplasties is likely to decrease rather than increase if the present trends continue.

The immediate and late results of thoracoplasty for pulmonary tuberculosis and for tuberculous and mixed empyemas are tabulated.

The 86 deaths are briefly studied.

Thoracoplasty is now a well standardized and time-tested procedure which, in properly selected cases, gives excellent results.

All thoracoplasties were done at the Massachusetts General Hospital on the services of Dr. Edward D. Churchill and Dr. Richard H. Sweet.

are well, 12 are ill, 47 are dead, and in 14 the results are unknown

LATE RESULTS

Table 7 shows the present status of 362 patients over a period of twenty years. As much of the follow-up observation was made by correspondence, it would have been too difficult to evaluate exactly

to the "well," there is a survival rate of approximately 70 per cent. Close to 90 per cent (87 per cent) of these patients showed demonstrable cavitation. The others had persistently positive sputum, with fibrotic lesions or else suffered from an empyema. Untreated cavernous pulmonary tuberculosis, as well as tuberculous and mixed empyema, ends fatally in 90 per cent of cases within a few

TABLE 6 Conversion of Sputum to Negative Reaction \*

YEAR	NEGATIVE AFTER THREE MONTHS		NEGATIVE AFTER SIX MONTHS		POSITIVE AFTER SIX MONTHS		TOTALS
	NO	PERCENTAGE	NO	PERCENTAGE	NO	PERCENTAGE	
1927-1936	68	46.5	22	15.0	56	38.3	146
1937-1946	100	50.1	31	15.6	67	33.8	198
Totals	168		53		123		344
Averages		48.8		15.4		35.7	

\*Eighteen of the 362 patients in whom thoracoplasty was performed died postoperatively and are consequently eliminated from this table.

the condition of the patient as arrested, apparently arrested, quiescent and so forth, according to the National Tuberculosis Association diagnostic standards. This tabulation is based only on one practical point: Is the patient well enough to work or is he not? If the patient is in the sanatorium or at home, but invalid or semi-invalid, he is listed

years. Allowing for a 10 per cent survival without surgery, one is left with a 50 per cent salvage to the credit of thoracoplasty. If only the period from 1927 to 1936 is considered, this salvage has already lasted from ten to twenty years. Furthermore, some of the deaths occurring over such a span of years are from causes other than tuberculosis.

TABLE 7 Results of Thoracoplasties over a Period of Twenty Years

YEAR	RESULT				TOTALS
	PATIENT WELL	PATIENT ILL	PATIENT DEAD	UNKNOWN	
1927	1		1		2
1928	1				2
1929	1			1	2
1930	2	1	4	1	8
1931	9		6		15
1932	7		1	1	9
1933	9	1	1		11
1934	18	1	7	3	31
1935	26	2	16	4	48
1936	18		7	2	27
Totals	92 (59.7%)	5 (3.2%)	43 (27.0%)	14 (9.0%)	154
1937	9		8	3	20
1938	17	2	12	1	32
1939	26	4	3	2	35
1940	20	1	5		26
1941	14	2	5	3	24
1942	7	2	5		14
1943	10	5	3		18
1944	13	5	3		21
1945	12	1	1		14
1946	2	6			8
Totals	110 (62.0%)	26 (12.4%)	43 (20.3%)	9 (4.3%)	208
Combined totals	222 (61.3%)	31 (8.5%)	86 (24.0%)	23 (6.3%)	362

under the heading "ill." Five or six of these, operated on at the end of 1946, are completing their cure and will soon be counted among the "well."

The most striking features of Table 7 are the almost equal proportions of patients well and working for the two ten-year periods: 59.7 per cent and 62 per cent, giving a combined rate of 61.3 per cent for the entire twenty years. If the "ill" are added

These deaths discounted, the proportion of survivals would reach about 65 per cent. These are very satisfying results.

EMPHYEMAS

The patients who received thoracoplasty for empyema fared almost as well as those with pulmonary tuberculosis. There were 16 mixed and 10 tuber-

Even the post-mortem findings are of little help since an unknown number of patients may presumably recover, leaving little or no trace, whereas other cases have undoubtedly been confused with tuberculosis. The disease may actually be commoner than has been suspected.

Although sarcoidosis manifests itself at any age, most of the cases occur in the period from fifteen to fifty, with a broad indefinite peak of incidence in the third and fourth decades. Kissmeyer<sup>5</sup> notes that more than half of 200 patients presented evidence of the disease before the age of thirty and two thirds before forty, and of Reisner's 35 cases more than two thirds were under thirty at onset.<sup>38</sup> Such figures are, of course, minimal since it is often impossible to be certain when the disease actually began. Of over 700 cases culled from the literature and his own experience, Gravesen<sup>5</sup> found only 19 under the age of ten and 30 over the age of sixty. Cases have been described in infants of three weeks,<sup>25</sup> three months<sup>39</sup> and twenty-five months,<sup>40</sup> and in persons of seventy<sup>26</sup> and eighty years.<sup>9</sup> Most authors record either no special sex incidence<sup>8, 41, 42</sup> or a predominance in the female of 2 to 1 or more.<sup>10, 24, 29, 35, 43, 44</sup>

The frequency of the disease in the white race, and especially in the Nordic groups, is clearly indicated by the numerous reports emanating from the Scandinavian countries. In this country, however, an unusually high incidence has been noted among Negroes.<sup>4, 35, 45-47</sup> A number of these reports come from the South, but Negroes also constitute 86.0 and 28.5 per cent, respectively, of two groups reported from New York City,<sup>38, 46</sup> 80 per cent of one from Philadelphia,<sup>41</sup> 42 per cent of another from San Francisco,<sup>4</sup> and over 50 per cent of an Army hospital group.<sup>47</sup> All these figures are considerably higher than the proportion of Negroes in the local populations. In Boston, at the Massachusetts General Hospital, Negroes have constituted only about 10 per cent of patients with sarcoidosis. Cases have been reported in an American Indian<sup>42</sup> and an Algerian Berber.<sup>45</sup>

The disease has been seen in siblings on a number of occasions.<sup>48-58</sup> Sella and Berger<sup>49</sup> describe a family of 7 siblings, 5 of whom had sarcoidosis proved by biopsy. Robinson and Hahn<sup>57</sup> note its occurrence in two unrelated Negro families, in one family at least 2 of 3 siblings were affected, whereas in the other, which included 10 siblings, a positive diagnosis was established in 3, and a probable or possible diagnosis in 3 others.

#### *Pathology and Pathogenesis*

The appearance of the typical sarcoid lesion varies little with the tissue in which it is found. It consists of a mass of noncaseating "tubercles" composed almost entirely of large, pale, epithelioid cells with little or no surrounding collar of lymphocytes. The granulomas tend to occur in large numbers, often cluster about small blood vessels or lymphatics and may diffusely replace an involved tissue, such as

lymph node or spleen, with a mass of closely packed lesions all more or less in the same stage of development. Even under such conditions the individual granulomas rarely tend to become confluent; reticulum or collagen stains may reveal discrete lesions in an apparently fused mass of fibrous tissue. Silver impregnation also discloses a fine network of reticulum penetrating the granulomas and tending to surround individual cells or groups of cells.

It is now known that the histologic appearance of the lesion, even in clinically typical cases, is subject to some variation. Moderate numbers of lymphocytes may be scattered among the epithelioid cells, but neutrophils and eosinophils are practically never present. Giant cells are frequently not prominent, but their rarity is not a dependable diagnostic point as was once thought. Such cells actually vary considerably in number from case to case and may be very large and numerous, many are of the typical Langhans variety, but large cells of the foreign-body type predominate in some cases. Both giant cells and epithelioid cells may contain vacuoles. Even the characteristic absence of necrosis is not constant, small necrotic foci in the central portions of the lesions have often been described and are no longer considered incompatible with the diagnosis.

Inclusion bodies of several varieties have been found usually within or in association with giant cells of the foreign-body type. All of them appear to be nonspecific and are without known significance, but it is of interest that they have not been observed in association with unequivocally tuberculous lesions in man.<sup>29, 59-61</sup> Radial or asteroid inclusions<sup>61-63</sup> have been described not only in sarcoidosis<sup>64, 65</sup> but also in association with the lesions of leprosy<sup>66</sup> and torulosis<sup>67</sup> and in many foreign-body granulomas.<sup>68</sup> Their nature is still uncertain, though Hirsch<sup>63</sup> concluded from animal experiments that they represented crystallized fat. Doubly contoured or laminated, often deep-staining bodies have been described by Schaumann<sup>63</sup> and others,<sup>59, 67-71</sup> and suggest concentric depositions of amorphous material impregnated with varying amounts of calcium and iron salts on some nucleus of foreign material, possibly remnants of elastic fibers. They seem to occur with greatest frequency, though not exclusively, in the lung. They have also been seen in association with beryllium lesions<sup>72, 73</sup> and were described by Metchnikoff<sup>74</sup> in lesions produced by tubercle bacilli in the African rat. Finally, irregular, often anisotropic particles have been seen. These stain very poorly and sometimes suggest minute fragments of glass or silica. They have, in fact, been described in local sarcoid granulomas developing after trauma by such substances<sup>75, 76</sup> and at times also suggest cotton or similar fibers.

In the material obtained by biopsy at the Massachusetts General Hospital, inclusions of all types have been noted in about 30 per cent of cases. Asteroid bodies have occurred with greatest fre-

## MEDICAL PROGRESS

### SARCOIDOSIS\*

DAVID G. FREIMAN, M.D.†

BOSTON

IN 1899 Boeck<sup>1, 2</sup> published almost simultaneously in Norway and in the United States a report on some apparently rare skin manifestations that have since come to be associated with his name. These dusky blue nodular or infiltrative lesions showed, on histologic examination, an epithelioid structure, which he at first interpreted as sarcoma-like ("sarkoid") and later assumed to be of tuberculous genesis.<sup>3</sup>

Since that time there has been a steadily mounting interest in a disease of which the skin lesions of Boeck are only one of many regional manifestations. An ever-increasing number of case reports have accumulated under a wide and confusing variety of names in turn descriptive, etiologic and eponymic, as a glance at the bibliography will indicate, at least 30 have been listed by Pinner,<sup>4</sup> Gravesen<sup>5</sup> and the numerous other reviewers. Fortunately, however, as the disease has been emerging from its status as a medical curiosity and has become more widely recognized as a fairly well defined entity, most of the earlier designations have been gradually discarded in favor of sarcoidosis (or Boeck's sarcoid) in this country and benign lymphogranulomatosis (or recognizable modifications of Besnier-Boeck-Schaumann's disease) in Europe. All these names leave something to be desired, but it seems best at present to let well enough alone until such time as the true nature of the condition becomes established beyond question.

The early history of the disease has been thoroughly reviewed by Hunter<sup>6</sup> and others<sup>7-10</sup> and will not be repeated here. It is worthy of note, however, that although Boeck appears to have been the first to describe the histologic characteristics of the skin lesions, Hutchinson<sup>11, 12</sup> had already published a clinical description of such a case in 1875, and 2 others in 1898. Besnier,<sup>13</sup> in 1889, and Tenneson,<sup>14</sup> in 1892, had also described lupus pernio, which was later shown to be another skin manifestation of the same disease.<sup>15</sup> The reports following Boeck's indicated that other organic systems could also be affected, so that by 1914 Schaumann<sup>16</sup> was able to postulate a generalized disease primarily affecting the lymphohematopoietic apparatus, and only incidentally the skin. It is only in recent years that such conditions as uveoparotid fever and at least some

cases of the Mikulicz syndrome have come to be recognized as special manifestations of the same disease.<sup>4, 9, 17-19</sup>

### CLINICAL AND PATHOLOGICAL ASPECTS

#### *Incidence*

Sarcoidosis was once considered a rare and unusual curiosity of primary interest to the dermatologist. Since its essentially disseminated character has been recognized, however, and particularly with the widespread use of the chest roentgenogram, the disease has been diagnosed with increasing frequency. A constantly enlarging literature includes reports of well over 1000 cases of this and such related syndromes as uveoparotid fever, and the mounting interest is reflected in numerous monographs and reviews from many countries.<sup>4, 5, 9-17</sup> Cases have been reported from practically every country in Europe, but especially the Scandinavian countries, from Australia, Japan, Latin-America and in increasing numbers from the United States and Canada. The distribution thus seems to be world wide, with at least an apparent predilection for the cooler countries.<sup>9, 10</sup> It is exceedingly difficult, however, to make even an approximation of the actual incidence. Routine fluoroscopy of more than half a million recruits for the Swiss Army revealed 115 provisional cases of sarcoidosis, of these, 67 were finally considered proved, an incidence of 0.13 per thousand.<sup>20</sup> Gravesen,<sup>5</sup> in Denmark, basing his figures on incidence in a tuberculosis sanatorium, arrived at about the same figure, but an unknown number of cases is certain to be overlooked by such methods. At the Massachusetts General Hospital, a diagnosis of sarcoidosis has been made by biopsy about 80 times during the past twenty years. In many of these cases, however, the lesion has been strictly localized, or the clinical data are incomplete or unavailable, so that a diagnosis is warranted in only about 45.<sup>29</sup> In at least 12 other patients lesions consistent with sarcoidosis, unsuspected during life, were accidentally discovered at autopsy. A few of these cases have already been reported.<sup>20-27</sup> All these findings are a very unreliable index of local incidence, however, a fair number of probable cases have never been confirmed by biopsy,<sup>20</sup> and still others have most certainly been overlooked since the course of the disease in many patients is so benign as to escape diagnosis except by accident.

\*From the Department of Pathology and Bacteriology, Massachusetts General Hospital.

†Instructor in pathology, Tufts College Medical School; assistant pathologist, Massachusetts General Hospital.

perfectly well, or diffuse pulmonary infiltration may be discovered quite by accident on a routine chest film. Often, however, minimal or moderate systemic symptoms are noted. Tiredness, weakness, loss of appetite, loss of weight, joint pains and low-grade fever may be present to a variable degree and may be of such low grade as to be scarcely recognized as symptoms. It is probable that such symptoms correspond with active dissemination of the disease, for they are often noted at times when new localizations are appearing, they usually subside as the disease enters the chronic phase, during which such localizations stabilize or regress, and may recur with the development of new clinical manifestations at a later date.<sup>35</sup>

**Lymph nodes** Involvement of lymph nodes as manifested by palpable or roentgenographic enlargement, is demonstrable in almost every case,<sup>9 35 42 47 95 96</sup> and lesions may be found on histologic section even in nodes not significantly enlarged.<sup>35 95</sup> The intrathoracic nodes appear to be the group most consistently affected, and in some series all<sup>47</sup> or almost all<sup>35 96</sup> cases have shown prominent hilar shadows so interpreted. The increase in size of the paratracheal group of lymph nodes parallels that of the peribronchial group, and although the bifurcation group of nodes is probably enlarged as well, this is difficult to demonstrate radiologically.<sup>47</sup> The enlargement is usually bilateral, as distinct from tuberculosis, which is frequently unilateral, the lymph nodes on the right may, however, be larger and more numerous than those on the left,<sup>43 47</sup> possibly because more are present on this side.<sup>97</sup> The nodes have little tendency to coalesce, a point in keeping with the histologic observation that the sarcoid lesions in lymph nodes show very little tendency to extend beyond the capsule. Even considerable enlargement of the hilar nodes is rarely associated with pressure or other obstructive phenomena, and studies in such cases have revealed complete absence of narrowing of the airway through massive nodes<sup>98</sup> or at most slight narrowing.<sup>47</sup> All these findings provide points of differentiation from the lymphomas or carcinomas, with which such lymph-node enlargement may be confused. Atelectasis has occasionally been reported and attributed to such enlargement.<sup>31 41 43</sup> In such cases, however, involvement of the bronchial mucous membrane with stenosis may be a contributory factor.<sup>29</sup> The esophagus may be displaced or compressed.<sup>47</sup> Vocal-cord paralysis has been described<sup>9 99</sup> but not phrenic-nerve involvement.

Although it is possible that other deep lymph-node groups are involved as frequently as those of the mediastinum, this is for obvious reasons difficult to estimate. Such involvement has been noted at a number of autopsies, however.<sup>69</sup> Palpable peripheral nodes are present in at least half to three fourths of the cases,<sup>35 47</sup> with cervical, axillary and inguinal groups affected about equally, and the epitrochlear

group only slightly less often. The nodes tend to be discrete, firm, freely movable and nontender.

The tonsils are involved in a large percentage of cases. Schaumann<sup>95</sup> found such involvement in all 21 active cases in which they were examined, and Gravesen<sup>5</sup> reports this in 45 of 70 cases in which the diagnosis was certain.

**Spleen** This organ is probably affected far more often than is evident from clinical reports. Considerable splenic enlargement is necessary before the organ becomes palpable, and extensive involvement has been demonstrable histologically in organs weighing 200 gm or less.<sup>64 80 100</sup> In a series of 29 autopsied cases from the literature,<sup>64</sup> splenic lesions were noted in 21 — the same frequency, incidentally, with which lymph-node involvement was reported in this group.

Marked splenomegaly may occur, some organs weighing well over a kilogram.<sup>101 102</sup> Such splenic enlargement has occasionally been the only detectable evidence of the disease, and in a number of cases removal of the organ for Banti's disease has revealed the sarcoid lesions. Such patients may complain of discomfort or a dragging sensation in the left upper quadrant due to the size and weight of the spleen, but surgical removal is likely to be of little value except as a symptomatic measure, even considerable splenomegaly appears capable of spontaneous regression.

Spontaneous rupture of the spleen has been reported on one occasion.<sup>103</sup> In this unusual case many lesions were noted in the intima of large sinuses and veins, some of which were thrombosed.

**Liver** The liver appears to be involved only slightly less often than the spleen.<sup>4 64 80</sup> A number of authors report a predilection for the portal areas,<sup>41 80 94 104 105</sup> but this is by no means invariable.<sup>26 100</sup> The organ may be considerably enlarged, but all such enlargements are not necessarily the result of specific involvement — particularly if failure of the right side of the heart is present. Diagnosis has been made by punch biopsy on a number of occasions.<sup>105-108</sup>

In spite of the frequency of involvement, liver function rarely seems to be significantly disturbed. Retention of bilirubin in a bilirubin tolerance test<sup>42</sup> and bromsulphalein retention up to about 30 per cent<sup>29</sup> have been noted. Jaundice has also been reported,<sup>9 109</sup> but a concomitant infectious hepatitis cannot be ruled out in these cases, punch biopsy should prove a useful method of clarifying this point.

**Lung** Involvement of the pulmonary parenchyma is often a prominent feature of the disease. The strong tendency of pulmonary infiltration to regress makes exact evaluation of incidence difficult, but it is likely that if cases are followed for a sufficient period, such involvement will be roentgenographically demonstrable in the large majority. In one series<sup>35</sup> development of such infiltrations was ob-

quency and represent about two thirds of the inclusions, in the spleen they have been seen in all 4 cases in which splenectomy was performed. On the other hand, the laminated inclusions have been seen only twice in cases of generalized sarcoidosis though they have been noted on several occasions in strictly localized sarcoid lesions.

Of the development of the sarcoid lesion relatively little is known with certainty. On several occasions early skin lesions have been examined with varied conclusions. According to Kissmeyer,<sup>8</sup> the initial process is a perivascular inflammatory reaction consisting at first of lymphocytes, later a few epithelioid cells and fibroblasts and, finally, the typical epithelioid cell granuloma. According to Pautrier,<sup>10</sup> the cellular elements are those of the adult lesion from the very start, the epithelioid cells arise by transformation of the local histiocytes and occasionally lymphocytes in the perivascular regions, extending from there into the surrounding tissues. It is possible that, as in many disagreements, there is an element of truth on both sides. Transformation of mononuclear phagocytes into epithelioid cells has been demonstrated both in vivo and in vitro under the influence of tubercle bacilli and their lipid fractions,<sup>77-78</sup> as well as such nonspecific phospholipids as lecithin.<sup>77</sup> Both the fixed reticuloendothelial elements and the wandering tissue macrophages are of this group and presumably capable of such transformation.<sup>79</sup> The various localizations might be expected to occur, therefore, wherever reticuloendothelial elements pre-exist, or wherever a group of wandering tissue macrophages happens to accumulate for any reason—including, possibly, even an unrelated chronic inflammatory process. This might account for the cases in which sarcoid lesions have no apparent relation to the blood vessels,<sup>80</sup> and even for occasional localizations of such lesions at the sites of old scars.<sup>2-81</sup> Apparent transformation of a diffuse and essentially nonspecific infiltration into characteristic lesions has been noted in 1 case.<sup>66</sup> A more certain knowledge of the early lesion would go far toward clarifying some of the many puzzling features of this disease.

The ultimate fate of the sarcoid lesion is not much more definitely known. The lesion may persist in its characteristic form and practically unchanged for indefinite periods, sometimes for years, or it may resorb in a few months. Lesions may be evolving in one area and resolving in others even within the same organ.<sup>85</sup> Although there is little definite evidence to prove it, it seems quite likely that such lesions may resolve completely in many cases, as the experimental tubercle does,<sup>79</sup> leaving little or no trace. On the other hand, a slow process of sclerosis may gradually transform the granuloma into a relatively acellular fibrous nodule or an apparently fused fibrous mass, as has often been noted in microscopical sections. Such extensive fibrosis may produce severe changes in the lung, or scars may follow skin

involvement. Collagen appears to condense about the periphery of the granuloma and extend inward along the reticulum fibers. The epithelioid cells elongate and come to resemble fibroblasts, at the same time diminishing in number. Focal masses of coarse collagen fibers, often seen in lymph nodes in association with these sclerosing nodules, seem to be one possible end-stage of the process, and in 1 autopsied case apparently represented the sole residual evidence of the disease.<sup>82</sup> Such foci are a common finding in routinely examined lymph nodes, however, and may represent a nonspecific termination of more than one pathologic process, or possibly an allergic phenomenon as suggested by Teilum.<sup>83</sup>

### *Clinical and Clinicopathological Features*

The lesions of sarcoidosis have been found in practically every organ in the body at one time or another, and the many regional manifestations so produced have resulted in an exceedingly polymorphic clinical picture. The usually benign character of the disease, as well as its prolonged, erratic and generally unpredictable course, has resulted in a relatively slow accumulation of the data, both anatomic and clinical, necessary to a clear understanding of the clinicopathological findings. It has also been difficult to make an accurate evaluation of the frequency with which the various localizations occur. Cases have been seen by dermatologists, ophthalmologists, roentgenologists and many other specialists, with the result that marked case selection is evident in the published reports, and there has also been a marked slanting in favor of the readily visible localizations. With the increasing number of autopsied cases, however, together with prolonged clinical follow-up study on others, it has become apparent that localizations such as those in the skin and eye actually occur in the minority of cases, whereas localizations in lymph nodes occur in almost all of them.

Pinner,<sup>4</sup> in 1938, and Rubin and Pinner,<sup>69</sup> in 1944, collected 44 autopsied cases from the literature, including their own. More than 70 such cases have now been reported,<sup>24-27, 38-40, 41, 43, 47, 53-90</sup> including those of the uveoparotid syndrome,<sup>91-94</sup> but many of these are incompletely described or are so complicated by caseating tuberculosis that they are difficult to interpret. In several others the diagnosis is open to considerable doubt, and in still others there has been inadequate clinical study before autopsy. From some of these cases, however, it has been possible to construct a composite picture that is in most respects consistent. The autopsy data have also been augmented by an increasing volume of biopsied material from skin, lymph nodes, spleen, liver, bone marrow and other areas.

One of the most characteristic features of the disease is the occurrence of rather extensive dissemination in the absence of significant symptoms. Patients with fairly extensive skin lesions may feel

thrombosis Emphysema, evidences of bronchiectasis and hypertrophy of the right ventricle were noted in a large proportion of the cases

**Heart** Involvement of the heart has been manifested by various clinically demonstrable irregularities such as rhythm disturbances, transient or permanent heart block, cardiac enlargement, congestive failure and electrocardiographic abnormalities, as well as being found at autopsy. Such involvement may be secondary to overburdening of the right side of the heart in cases of pulmonary fibrosis or to direct involvement of the heart by sarcoid lesions. Leitner<sup>110</sup> reports electrocardiographic evidence of myocardial lesions in 8 of 17 cases, intensified by physical work in 7 of 8 cases and abolished by oxygen inhalation in 2.

There is evidence that varying degrees of cor pulmonale probably occur in the majority of cases with extensive pulmonary fibrosis, either with or without demonstrable endarteritis. On the other hand, direct involvement of some part of the heart by sarcoid lesions has been demonstrated in only about 20 per cent of recorded autopsies, and there is little convincing evidence that disturbance of cardiac function can be specifically attributed to such localization in more than a few of them. In several cases such localizations occurred without clinical signs,<sup>92, 123</sup> or in association with marked cor pulmonale sufficient to explain the clinical findings.<sup>93, 123</sup> In another case<sup>87</sup> the history and lesions described strongly suggested a complicating periarthritis nodosa, and in still another, syphilis could not be entirely excluded as a cause of a large scar in the interventricular septum associated with a long history of auriculoventricular dissociation.<sup>123</sup> When the myocardium is massively infiltrated, however,<sup>91, 92, 104</sup> or when the coronary branches may have been involved,<sup>94</sup> cardiac alterations can be reasonably attributed to the specific lesions alone, and it may be of significance that most of the cases with the uveoparotid syndrome that have come to autopsy have shown such involvement. Occasionally, clinical evidence of failure has been difficult to explain except on the basis of such infiltrations, and even when failure is severe, marked improvement may take place.<sup>123</sup> Presumably, too, fortuitous localization in or near the bundle of His would produce derangements such as the transient block observed clinically in some cases.<sup>123, 124</sup> Unfortunately, the many more common causes of cardiac disturbance cannot often be satisfactorily eliminated.

**Kidney** Renal involvement has also been noted in about 20 per cent of the autopsied cases usually in the form of a few scattered lesions. However, in a significant proportion of cases the active phases of the disease have been associated with albuminuria, and in a few there has also been an azotemia, a low or fixed urinary specific gravity, reduced phenolsulfonphthalein excretion and casts.<sup>29, 96, 125-127</sup>

The blood pressure in these cases has usually, but not invariably, been within normal limits. Retinopathy has been described but this also occurs without renal involvement and probably represents an independent lesion.<sup>127</sup> Of particular interest is the fact that in several cases the renal findings and azotemia have cleared up concomitantly with the disappearance of other evidences of systemic sarcoidosis, and in some cases coincidentally with a fall in blood calcium.<sup>29, 127</sup>

Klinefelter and Salley<sup>127</sup> attributed these findings to the mechanical effect of invasion of the renal parenchyma by sarcoid lesions, but the anatomic evidence so far fails to bear this out satisfactorily. Massive invasion of the kidney is rare, but in at least 1 case there were no renal symptoms.<sup>93</sup> Several cases,<sup>127, 128</sup> including 2 seen at this hospital, have been associated with considerable hypercalcemia and hypercalciuria, and under such circumstances it is possible that calcium casts in the renal tubules cause renal shutdown as has been demonstrated in cases of hyperparathyroidism.<sup>129</sup> Such casts have been seen in at least 1 autopsied case<sup>125</sup> but no blood calcium level was recorded. Renal stones, either with or without renal insufficiency, have also been reported.<sup>29, 100, 130</sup>

(To be continued)

## REFERENCES

- 1 Boeck, C. Multipelt benignt hud sarkoid. *Norsk mag f lægevidensk* 60:1321-1334 1899.
- 2 Idem. Multiple benign sarkoid of skin. *J. Cutan. & Genito-Urin. Dis.* 17:543-550 1899.
- 3 Idem. Fortgesetzte Untersuchungen über das multiple benigne Sarkoid. *Arch. f. Dermat. u. Syph.* 73:71-86 and 301-332 1905.
- 4 Pinner, M. Noncaseating tuberculosis: analysis of literature. *Am. Rev. Tuberc.* 37:690-720 1938.
- 5 Gravesen, P. B. *Lymfomatosus benigna*. 235 pp. Odense, Denmark: I Kommission hos Andelsbogtrykkeriet, 1942.
- 6 Hunter, F. T. Hutchinson-Boeck's disease (generalized sarcoidosis): historical note and report of case with apparent cure. *New Eng. J. Med.* 214:346-352 1936.
- 7 Schaumann, J. Benign lymphogranuloma and its cutaneous manifestations. *Brit. J. Dermat.* 36:515-544 1924.
- 8 Kissmeyer, A. *La maladie de Boeck, sarcoïdes cutanées bénignes multiples*. 147 pp. Paris: Masson et Cie 1932.
- 9 Longcope, W. T., and Pierson, J. W. Boeck's sarcoid (sarcoidosis). *Bull. Johns Hopkins Hosp.* 60:223-296 1937.
- 10 Pautrier, L. M. *Une nouvelle grande reticulo-endothélieuse. La maladie de Besnier-Boeck-Schaumann*. 341 pp. Paris: Masson et Cie 1940.
- 11 Hutchinson, J. *Illustrations of Clinical Surgery*. 43 pp. London: J. & A. Churchill, 1875. P. 42.
- 12 Idem. Cases of Mortimer's malady (Lupus vulgaris multiplex non-ulcerosus et non serpinosus). *Arch. Surg. (London)* 9:307-314 1898.
- 13 Besnier, E. Lupus pernio de la face: synovites fongueuses (scrofulo-tuberculeuses) symétriques des extrémités supérieures. *Ann. de dermat. et syph.* 10:33-36 1889.
- 14 Tenneson, M. Lupus pernio. *Bull. Soc. franç. de dermat. et syph.* 3:417-419 1892.
- 15 Schaumann, J. Étude sur le lupus pernio et ses rapports avec les sarcoïdes et la tuberculose. *Ann. de dermat. et syph.* 6:357-373 1916-17.
- 16 Idem. *Sur le lupus pernio. Mémoire présenté en Novembre 1913 à la Société française de dermatologie et de syphilographie pour le Prix Zambaco*. Privately reprinted from a thesis. Stockholm 1914.
- 17 Bruins Slot, W. J. Ziekte van Besnier-Boeck en febris uveoparotidea (Heerfort). *Nederl. tijdschr. v. geneesk.* 83:285-286 1936.
- 18 Waldenström, J. Über gutartige universelle tuberkuloide Granulome mit besonderer Berücksichtigung der Uveoparotitis. *Zentralbl. f. d. ges. Tuberk.-Forsek.* 45:249-265 1936.
- 19 With, T. K. Om lymphogranulomatosis benigna (Boeck-Besnier-Schaumann-Jungling's syndrom) med særligt henblik paa dens relation til tuberkulose og febris uveo-parotidea. *Nord. med. tidsskr.* 12:1787-1795 1936.
- 20 Réunion dermatologique de Strasbourg. Séance spéciale du 13 mai 1934 consacrée à l'étude des sarcoïdes. *Bull. Soc. franç. de dermat. et syph.* 41:995-1392 1934.

served in 10 of 12 cases failing to show involvement on initial examination

The lack of correlation between the degree of demonstrable pulmonary infiltration and the respiratory symptoms exhibited by the patient has been repeatedly stressed. It is not uncommon to find extensive involvement in the complete absence of such symptoms, or at most mild cough or dyspnea. Physical signs also tend to be slight or absent unless frank pulmonary tuberculosis is present as well, but spirometric studies may reveal some impairment of pulmonary function.<sup>110</sup> Severe and progressive dyspnea is occasionally seen, usually in association with progressive fibrosing lesions or cardiac insufficiency.<sup>38</sup>

The roentgenographic pattern is by no means pathognomonic and may be mimicked by a wide variety of conditions. It has been described on many occasions<sup>5, 24, 30, 38, 44, 45, 47, 81, 82, 111-115</sup> and consists essentially of two main types, which may coexist: an appearance of disseminated miliary or more coarsely nodular foci, which must be distinguished from hematogenous tuberculosis, and a reticulated appearance associated with linear or strand-like areas extending outward from the hilus along the broncho-vascular ramifications, and resembling lymphangitic carcinomatosis or silicosis. More rarely, areas of coalescent density, suggesting fibrotic induration, or areas of confluent massive density, suggesting pneumonic infiltration, are seen.<sup>38, 43</sup> The infiltrations tend to be diffuse and bilateral, but may be localized in certain phases.<sup>38</sup> Associated hilar adenopathy is usually seen but may be absent.

The roentgenographic appearance of the chest is largely dependent upon the phase of evolution of the disease at any given time, and a number of authors have had the opportunity to follow the phases of development and regression of such lesions with serial roentgenograms.<sup>5, 38, 43, 81, 114</sup> In many cases hilar adenopathy has been the first manifestation, and pulmonary infiltration has appeared to extend fanwise into the parenchyma bilaterally.<sup>81</sup> Early lesions tend to be of the miliary or nodular disseminated type.<sup>5, 38, 43, 112</sup> they are in large measure reversible and may resorb, leaving little or no trace. The linear, strand-like type may also resorb partially or completely, but shows a greater tendency to fibrosis.<sup>38</sup> With the development of the parenchymal dissemination, the hilar lymph nodes may regress,<sup>111</sup> or different rates of development and regression may result in patchy distributions. Localized involvements show some predilection for the parahilar regions or midzones of the lung.<sup>38</sup> Occasionally the basal portions alone are involved,<sup>38, 115</sup> but such localization is not a characteristic feature as was once thought.<sup>47</sup> With regression of the pulmonary lesions, the hilar lymph nodes have sometimes been observed to re-enlarge.<sup>43, 111</sup>

It is probable that the pulmonary lesions resorb more or less completely in the majority of cases,

though regression may be slow. With the onset of interstitial fibrosis, however, complete resorption is no longer possible. This change may be heralded by a delicate striation of the lung fields associated with the areas of miliary density,<sup>5</sup> and eventually there is transformation with conglomerate involvement of varying extent usually associated with nodular or stringy fibrosis. This occurred in about a third of the cases under Reisner's observation,<sup>21</sup> though King<sup>30</sup> failed to observe it at all. Such transformation may be patchy or localized, so that areas of density persist while other lesions regress. The fibrosis may also be associated with areas of emphysema, bronchiectasis or extensive contraction of the lung field. Occasionally, cavitation has been described in the absence of pulmonary tuberculosis,<sup>30, 82, 88, 90, 116</sup> but in the cases that have come to autopsy, the findings seem consistent with a cystic bronchiectasis, others have been interpreted as bullous emphysema.<sup>117</sup> A few cases of spontaneous pneumothorax have also been reported,<sup>118, 119</sup> but whether there is any causal relation is difficult to say. The changes of active pulmonary tuberculosis supervene in about 10 per cent of all cases reported,<sup>41</sup> though the incidence is a little higher in some series.<sup>38</sup> The incidence of tuberculosis among the autopsied cases is, for obvious reasons, considerably greater.<sup>21, 120</sup>

Correlation of all these changes with the underlying pathological findings has been much limited by the relatively small number of detailed autopsy reports available. Sarcoid lesions are scattered throughout the interstitial tissue of the lung in a fashion suggesting a hematogenous seeding of the causative agent, but showing some predilection for regions about blood vessels and bronchi, the interlobular lymphatics and the subpleural areas. In view of the large amounts of lymphoid tissue in these areas,<sup>97</sup> such localization is not surprising and, when prominent, probably accounts for the strand-like linear roentgenographic pattern. It is possible, too, that varying degrees of lymphatic obstruction produced by such localizations account for the increased tendency of such linear infiltrations to fibrose.<sup>38</sup>

Mallory<sup>37</sup> describes 6 cases in which extensive pulmonary fibrosis was associated with miliary granulomatous lesions believed to be entirely consistent with sarcoidosis, and identical with many cases so described in the literature.<sup>86, 89, 116, 121, 122</sup> In these cases, the oldest lesions, consisting almost entirely of acellular whorled collagen, were present beneath the pleura, and about the blood vessels and bronchi near the hilus. More recent granulomas extended into the alveolar septums, which showed gross thickening and distortion. Contiguous lesions showed a marked tendency to fuse, with eventual loss of all traces of lung architecture in these foci. Bronchial walls and less frequently blood vessels were also invaded, the latter showing evidence of

99 Olsen A. M. Boeck's sarcoid: brief review and report of case in which diagnosis was made by bronchoscopic examination and biopsy. *Ann. Otol. Rhin. & Laryng.* 55: 629-637 1946

100 Spencer J. and Warren S. Boeck's sarcoid: report of case with clinical diagnosis confirmed at autopsy. *Arch. Int. Med.* 62: 285-296 1938

101 Luetner L. M. Splenomegalies et maladie de Besnier-Boeck-Schaumann. *Schweiz. med. Wchnschr.* 26: 507-911 1944

102 Little E. H. Splenic lesions in some cases of splenomegaly associated with secondary anaemia. *J. Path. & Bact.* 23: 415-425 1919-20

103 James L. and Wilson A. J. Spontaneous rupture of spleen in sarcoidosis. *Brit. J. Surg.* 33: 280-282 1946

104 Coffer E. F. Boeck's sarcoid: autopsy in case with visceral lesions. *Arch. Int. Med.* 64: 286-295 1939

105 van Beek, C. and Haax A. J. C. Aspiration biopsy of liver in mononucleosis infectiosa and in Besnier-Boeck-Schaumann's disease. *Acta med. Scandina.* 113: 125 1945

106 van Buchem F. S. P. On morbid conditions of liver and diagnosis of disease of Besnier-Boeck-Schaumann. *Acta med. Scandina.* 124: 168-184 1947

107 Scadding J. G. Disorders of chest sarcoidosis. *Lancet* 2: 445 1947

108 Volwiler W., and Jones C. M. Diagnostic and therapeutic value of liver biopsies with particular reference to trocar biopsy. *New Eng. J. Med.* 237: 651-656 1947

109 Gracikman W. H. Sarcoids and related lesions: report of 17 cases: review of recent literature. *Arch. Dermat. & Syph.* 18: 237-262 1926

110 Leit et St. J. Elektrokardiographische und spirometrische Untersuchungen bei der epitheloidzelligen Granulomatose (Morbus Besnier-Boeck-Schaumann). *Cardiologica* 10: 379-401 1946

111 Bernstein S. S., and Sussman M. L. Thoracic manifestations of sarcoidosis. *Radiology* 44: 37-43 1945

112 Bernstein S. S. Miliary form of pulmonary sarcoidosis. *J. Mt. Sinai Hosp.* 12: 1045-1049 1946

113 Ackerman A. J. Roentgenological aspect of sarcoidosis. *Am. J. Roentgenol.* 59: 318-326 1948

114 Meise E. Course of Besnier-Boeck's disease of lungs in serial roentgenograms. *Am. J. Roentgenol.* 44: 564-567 1940

115 Kirklin B. R. and Morton, S. A. Roentgenologic changes in sarcoid and related lesions. *Radiology* 16: 228-237 1931

116 Wahlgren F. Nagot om den patologiska anatomen vid lymphogranulomatosis benigna (Schaumann). *Nord. med. tidnkr.* 13: 965-972 1937

117 Pruvost, P. and Depierre. Forme pulmonaire d'une maladie de Besnier-Boeck-Schaumann avec bulles d'emphyseme. *Bull. et mem. Soc. med. & Hôp. de Paris* 61: 341-345 1946

118 Isbister J. Case of Besnier-Boeck-Schaumann syndrome or benign lymphogranulomatosis with pneumothoraces. *M. J. Australia* 1: 275-277 1945

119 Dressler M. Spontanpneumothorax bei der Besnier-Boeck-Schaumannschen Krankheit Schweiz. *Ztschr. f. Tuberk. u. Lung.* 4: 229 1947

120 Pinner M. Pulmonary Tuberculosis in the Adult. Its fundamental aspects. 379 pp. Springfield Ill. Charles C. Thomas 1945 Pp. 312-320

121 Tice F. and Sweany H. C. Fatal case of Besnier-Boeck-Schaumann's disease with autopsy findings. *Ann. Int. Med.* 15: 597-609 1941

122 Voldet, G. Étude anatomique et expérimentale de la maladie de Besnier-Boeck de poumon. *Schweiz. Ztschr. f. allg. Path. u. Bakt.* 3: 222-269 1941

123 Longcope W. T. and Fisher A. M. Involvement of heart in sarcoidosis or Besnier-Boeck-Schaumann's disease. *J. Mt. Sinai Hosp.* 8: 784-797 1942. Effect of Schaumann's disease upon heart and its mechanism. *Acta med. Scandina.* 108: 529-545 1941

124 Salvesen H. A. Sarcoid of Boeck: disease of importance to internal medicine. *Acta med. Scandina.* 86: 127-151 1935

125 Horton R. Lincoln S. and Pinner M. Non-cavitating tuberculois case reports. *Am. Rev. Tuberc.* 39: 186-203 1939

126 Rotenberg L., and Guggenheim, A. Boeck's sarcoid: report of case with renal involvement. *Dis. of Chest* 18: 392-395 1942

127 Khnefelter H. F. Jr. and Salley S. M. Sarcoidosis simulating glomerulonephritis. *Bull. Johns Hopkins Hosp.* 79: 555-561 1946

128 Schnpach A. and Wernly M. Hyperkalzaemie und Organver-kalkungen bei Boeck'scher Krankheit. *Acta med. Scandina.* 115: 401-422 1943

129 Albright, F. Parathyroids physiology and therapeutics. *J. A. M. A.* 117: 527-537 1941

130 van Creveld S. Disturbances of metabolism in Besnier-Boeck's disease. *Arr. Paediat.* 157: 1-16 1941

NEW HAMPSHIRE MEDICAL SOCIETY

PROCEEDINGS OF THE ONE-HUNDRED AND FIFTY-SEVENTH ANNIVERSARY

House of Delegates, June 1, 2 and 3, 1948

The report of the Committee on National Emergency Medical Service was then presented

At the spring meeting of the American Medical Association Council on National Emergency Medical Service, held at Chicago April 5 and 6, the New Hampshire Medical Society was represented by the chairman of the Committee. At that session various speakers from different branches of the government and various civilian organization officials were heard and outlined the kind of national emergency that might exist in case of another war. The meaning of atomic warfare was expounded and certain proposals were made for the purpose of arriving at a means of coping with the emergencies that might be created.

It was agreed by most speakers at this session that any future war would be aimed at ruining all the enemy's war-making potential. This would mean the total destruction of his means of communications and his civilian population engaged in operating these national assets. As a corollary it might be inferred that armies in the field and navies in the oceans might be by-passed by the enemy in his effort to strike at the civilian populations, which are the life blood and source of supplies of these armies and navies. This could be accomplished by waging war with atomic bombs and other weapons similarly horrible in their destructive effect and usually termed "special weapons". Under the classification of special weapons would be those having to do with chemical, biologic and bacteriologic warfare. The scope of the destruction caused by the atomic bomb at Nagasaki and Hiroshima is slowly being realized with the information that has accrued as a result of the study that was undertaken since the time of their explosions.

There is reason to believe, from the study of vegetable matter that the effect of the destructive action of atomic energy may be felt through the second and third generations. Whether or not this is applicable to human beings is

still open to question, and studies are being carried out in this direction. All females who were in the atomic area who have become pregnant are being registered, and their progeny will be studied.

It has been stated that we now have atomic bombs that are one hundred to one thousand times more powerful than those exploded at Nagasaki and Hiroshima. The implications of this are almost beyond imagination. It has been estimated by various persons that the Russians, who are now our main potential enemy, will have an atomic bomb by 1951-1955. Recent statements from an official in the air force also imply that the Russians now have or will shortly have an atomic bomb.

It is certainly reasonable to believe that the secret of atomic power cannot remain forever within the grasp of citizens of the United States. It therefore behooves us to devise ways and means of protection against an enemy who might employ atomic energy in his attack upon us. These ways and means may be very different from those conceived in our plans for civilian defense during World War II.

In Great Britain early in World War II and in this country the plan against incendiary bombs was to have fire-fighting units at strategic points in metropolitan and urban centers, and it was intended that these should go out and extinguish any fires that were started. Later in the war, in the face of overwhelming bombing, the method was changed. It then became apparent that the best means was to retire from the area of conflagration and try to protect the periphery. Now in the event of an atomic bomb attack, all our defensive resources would have to be concentrated on the periphery because nothing in the center of the bomb area would be of any use or value. In the central area there would be a great concentration of radioactive material.

This concentration of protection and protective material held on the periphery may have to be quite large in scope and in volume.

- 21 Lambie C G. Besnier Boeck's disease or benign lymphogranuloma-  
tosis of Schaumann (Besnier-Boeck Schaumann syndrome) *M J*  
*Australia* 1 815-826 1940
- 22 Celaya M. Enfermedad de Besnier-Boeck Schaumann su estado  
actual *Rev argent de tuberc* 6 118 133 1940
- 23 Haneson H. Besnier-Boeck's disease review *Brit J Tuberc* 35  
88 113 1941
- 24 Longcope W T. Sarcoidosis or Besnier Boeck Schaumann disease  
*J A M A* 117 1321 1327 1941
- 25 Leitner St. J. *Der Morbus Besnier Boeck Schaumann chronische*  
*epitheloidzellige Reticuloendotheliose sive Granulomatose* 138 pp  
Basel Schwabe & Co 1942
- 26 Cameron C and Dawson E K. Sarcoidosis review based on case  
of disease *Edinburgh M J* 49 737 756 1942
- 27 Palmer J H. Boeck's disease (sarcoid) its clinical groups and diag-  
nosis *Canad M A J* 43 11-18 1940
- 28 Schonholzer G. Morbus Besnier-Boeck Schaumann und Armeedureh-  
leuchtung *Schweiz. med Wchnschr* 77 585 588 1947
- 29 Freiman D G. Unpublished data
- 30 King D S. Sarcoid disease as revealed in chest roentgenogram *Am*  
*J Roentgenol* 45 505-512 1941
- 31 King M J. Ocular lesions of Boeck's sarcoid *Tr Am Ophth Soc*  
37 422-458 1939
- 32 Benedict E B. and Castleman B. Sarcoidosis with bronchial in-  
volvement report of case with bronchoscopic and pathological ob-  
servations *New Eng J Med* 224 186-189 1941
- 33 Case records of the Massachusetts General Hospital (Case 28161)  
*New Eng J Med* 226 657 659 1942
- 34 Case records of the Massachusetts General Hospital (Case 30312)  
*New Eng J Med* 231 208 211 1944
- 35 Case records of the Massachusetts General Hospital (Case 30331)  
*New Eng J Med* 231 268 271 1944
- 36 Case records of the Massachusetts General Hospital (Case 33412)  
*New Eng J Med* 237 555-557 1947
- 37 Mallory T B. Pathology of pulmonary fibrosis including chronic  
pulmonary sarcoidosis *Radiology* (in press)
- 38 Reissner D. Boeck's sarcoid and systemic sarcoidosis (Besnier Boeck-  
Schaumann disease) study of 35 cases *Am Rev Tuberc* 49 289-  
307 and 437-462 1944
- 39 Naumann O. Kasuistischer Beitrag zur Kenntnis der Schaumann-  
schen 'benignen Granulomatose' (Morbus Besnier-Boeck Schau-  
mann) *Ztschr J Kinderh* 60 1 8 1938
- 40 Posner I. Sarcoidosis case report *J Pediat* 20 486-495 1942
- 41 Snapper I and Pompen A W M. Pseudotuberculosis in Man  
I. Besnier-Boeck's disease. I. Local localization of the sarcoids of  
Boeck II. Regional ileitis 50 pp Haarlem de Erven F Bohn  
1938
- 42 Harrell G T. Generalized sarcoidosis of Boeck clinical review of 11  
cases with studies of blood and etiologic factors *Arch. Int Med*  
65 1003 1034 1940
- 43 Garland L H. Pulmonary sarcoidosis early roentgen findings  
*Radiology* 48 333-332 1947
- 44 Thomas C C. Sarcoidosis *Arch Dermat & Syph.* 47 58 73 1943
- 45 Oppenheim A. and Pollack R. S. Boeck's sarcoid (sarcoidosis)  
*Am J Roentgenol* 57 28 35, 1947
- 46 Katz, S. Calk C P and Reed H R. Sarcoidosis *New Eng J Med*  
229 498 508 1943
- 47 McCort, J J. Wood R. H. Hamilton J B and Ehrlich D E.  
Sarcoidosis clinical and roentgenologic study of twenty-eight  
proved cases *Arch Int Med* 80 293 321, 1947
- 48 Toulant and Morard. A propos d'un cas d'uveo-parotidite (syndrome  
d'Heerfordt) *Arch d'ophth* 53 321 345 1936
- 49 Selles, J and Berger M. Sarkoide Geschwulste in einer Familie  
(Sarkoide [Joseph] und uveoide allergische Reaktion) *Arch f*  
*Dermat u Syph.* 150 47 51 1926
- 50 Lindau A. So-called chronic military tuberculosis *Acta path et*  
*microbiol Scandinav* (Supp 26) 157 173 1936
- 51 Dressler M. Boeck'sche Krankheit der Lungen bei Geschwistern  
*Schweiz. med Wchnschr* 19 417-422 1938
- 52 Idem. Familiäres Vorkommen der Besnier Boeck'schen Krankheit  
*Schweiz. med Wchnschr* 20 269 272 1939
- 53 Bergmann A. Zur Klinik und Pathologie der Boeck'schen Lungen-  
krankheit ein Beitrag zum Konstitutionsproblem atypischer  
Tuberkulosen *Beitr. z. Klin d Tuberk* 92 581 601 1939
- 54 MacCormac H. Schaumann's disease in two sisters *Acta med*  
*Scandinav* 103 152 1940
- 55 Leitner St. J. Neue Untersuchungen beim Morbus Besnier Boeck-  
Schaumann (epitheloidzellige Granulomatose) *Schweiz. Ztschr*  
*Tuberk* 3 108-133 1946
- 56 Struyvenberg F M J. Ziekte van Besnier Boeck of Tuberculose  
*Nederl tijdschr v Geneesk* 91 2251 2258 1947
- 57 Robinson R C V and Hahn R. D. Sarcoidosis in siblings *Arch*  
*Int Med* 80 249 256 1947
- 58 Boggild D. Two cases of probable Boeck's sarcoid of fingers in sisters  
two and five years old *Nord med (Hosptalsid)* 21 416-418 1944
- 59 Rich A. R. *The Pathogenesis of Tuberculosis* 1008 pp Springfield  
Ill. Charles C Thomas 1944 P 722
- 60 Bergstrand. Discussion of Lindau \*\*
- 61 Wolbach S B. New type of cell inclusion not parasitic, associated  
with disseminated granulomatous lesions *J Med Research* 24  
243 257 1911
- 62 Vogel K. Über eigenartige Fremdkörperriesenzellen bei Bronchiolitis  
obliterans *Firchow's Arch J path Anat* 206 157-163 1911
- 63 Hirsch E F. Radial inclusions of giant cells *Arch Path* 20-665-671  
1935
- 64 Friedman M. Sarcoidosis of spleen report of case with autopsy and  
study of intracellular 'asteroid bodies' *Am J Path* 20-621-631  
1944
- 65 Lever W F and Freiman D G. Sarcoidosis report of atypical  
case with erythrodermic lesions subcutaneous nodes and asteroid  
inclusion bodies in giant cells *Arch Dermat & Syph.* 57-619  
654 1948
- 66 Mallory F B. *The Principles of Pathologic Histology* 671 pp.  
Philadelphia W B Saunders Co 1914 Pp 207 and 613
- 67 Stoddard J L and Cutler E. C. *Torula Infection in Man A Study*  
*of cases characterized by chronic lesions of the central nervous system*  
*with clinical symptoms suggestive of cerebral tumor produced by the*  
*organism belonging to the torula group* 98 pp (Monograph of the  
Rockefeller Institute for Medical Research No 6.) Baltimore  
Waverly Press 1916 P 55
- 68 Schaumann J. On nature of certain peculiar corpuscles present in  
tissue of lymphogranulomatosis benigna *Acta med Scandinav*  
106 239 253 1941
- 69 Rubin E H and Pinner M. Sarcoidosis one case report and litera-  
ture review of autopsied cases *Am Rev Tuberc* 49 146-169 1944
- 70 Tillgren J. Diabetes insipidus as symptom of Schaumann's disease  
*Brit J Dermat* 47 223 229, 1935
- 71 Kraus E J. Sarcoidosis (Besnier Boeck Schaumann's disease) as  
cause of pituitary syndrome *J Lab & Clin Med* 28 140-145,  
1942
- 72 Martland H S. Brodtkin H A, and Martland, H S., Jr. Occupa-  
tional beryllium poisoning in New Jersey (with special reference to  
its incidence diagnosis and compensation) *J M Soc New Jersey*  
45 5-14 1948
- 73 Grier R S. Nash P. and Freiman D G. Skin lesions occurring in  
persons exposed to beryllium compounds *J Indust Hyg &*  
*Toxicol* 30 228 237 1948
- 74 Metchnikoff E. *Lectures on the Comparative Pathology of Infections*  
*tion*. Translated by F A Starling and E. H. Starling 230 pp  
London Hegan Paul Trench Trubner & Co 1893 P 163
- 75 King, C. O. Posttraumatic sarcoid like lesions *South. M J* 39  
122-125 1946
- 76 German W M. Lupoid sarcoid induced by foreign-body (silica)  
*Am J Clin Path* 10 245 250 1940
- 77 Sabin F R. Cellular reactions to fractions isolated from tubercle  
bacilli *Physiol Rev* 12 141 165 1932
- 78 Smithburn K C and Sabin F R. Reactions of normal and tuber-  
culous animals to tuberculo-protein and tuberculo-phosphatide  
*J Exper Med* 68 641-658 1938
- 79 Rich A. R. and McCordock, H. A. Enquiry concerning role of al-  
lergy immunity and other factors of importance in pathogenesis of  
human tuberculosis *Bull Johns Hopkins Hosp* 44 273-423, 1979
- 80 Nickerson D A. Boeck's sarcoid report of 6 cases in which autopsies  
were made *Arch Path.* 24 19 29 1937
- 81 Bruce, T. and Wassen E. Clinical observations on course and prog-  
nosis of lymphogranulomatosis benigna Schaumann, particularly in  
regard to pulmonary lesions. *Acta med Scandinav* 104 63 104  
1940
- 82 Bernstein S S. and Oppenheimer B S. Boeck's sarcoid report of  
six cases with one necropsy *J Mt Sinai Hosp* 9 329 343 1947
- 83 Teilmann G. Allergic hyperglobulinosis and hyalinosis (paramyeloidosis)  
in reticulo-endothelial system in Boeck's sarcoid and other condi-  
tions morphologic immunity reaction *Am J Path.* 24 382-401  
1948
- 84 Danholt N. and Hval E. Le sarcoide (lupoid) de Boeck exam-  
ultérieur d'un des anciens clients du professeur Boeck, avec  
trouvailles autopsiques (mort de cancer après 29 ans) *Acta dermat.*  
*venereol* 17 477-493 1936
- 85 Ehrner, L. Lymphogranulomatosis benigna (Schaumann) compli-  
cated by military tuberculosis in B C G vaccinated patient. *Acta*  
*tuberc Scandinav* 20 138-157 1946
- 86 Hagn Meincke F. Boeck's sarcoid and its relation to tuberculosis  
*Acta tuberc Scandinav* 18 1 19 1944
- 87 Johnson J B and Jason R. S. Sarcoidosis of heart report of case  
with review of literature *Am Heart J* 27 246-258 1944
- 88 Hogan G F. Sarcoidosis report of five cases with one autopsy *Am*  
*Rev Tuberc* 54 166-178 1946
- 89 Erickson T C. Odum G L. and Stern K. Boeck's disease (sarcoid)  
of central nervous system report of case with complete clinical and  
pathologic study *Arch Neurol & Psychiat* 48 613-621 1942
- 90 Appelman A C. Overholtevorming bij de ziekte van Besnier Boeck.  
*Nederl tijdschr v Geneesk* 91 2985 2992 1947
- 91 Souter W C. Disease of choroid case of uveo-parotid fever with  
autopsy findings *Tr Ophth Soc U Kingdom* 49 113 127 1929
- 92 Garland H G. and Thompson J G. Uveoparotid tuberculosis  
(febris uveo-parotidea of Heerfordt) *Quart J Med* 2 151, 177  
1933
- 93 Bang S. Cited by Garland and Thompson \*\*
- 94 Granstrom K O. Gripwall E. Kristofferson C. E. and Lundgren  
A G H. Case of uveoparotid fever (Heerfordt) with autopsy  
findings *Acta med Scandinav* 126 307 318 1946
- 95 Schaumann J. Lymphogranulomatosis benigna in light of prolonged  
clinical observations and autopsy findings *Brit. J Dermat* 45  
399-446 1936.
- 96 Lstvedt, H J. Omkring det Boeck'ske sarkoids notografi og dia-  
gnose *Nord med* 2 1677-1685 1939
- 97 Miller W S. *The Lung* 209 pp London Balliere Tindall & Cox  
1937 Pp 112 130
- 98 Chamberlain W E. Discussion of Garland \*\*

the Manhattan project, and of the 40,000 employees on the Bikini Atoll project, not one was injured by radiation. This was due to the infinite care and the skill of the application of the safety factors that were devised and employed.

In this connection it may be pointed out that protection from the secondary radiation following atomic bombing is of tremendous scope. It involves the use by thousands of people of delicate machines and precision instruments. The number of Geiger counters that must be employed in an experiment like the Bikini Atoll experiment is tremendous. When one considers that such instruments must be made in large quantities not only for the urban centers but also for the suburban and rural areas, and when one considers that trained personnel must be ready to use them, it becomes obvious that in this minor division of defense the problem is immense.

It is consideration of these factors that leads one to the conclusion that planning must be on a national level. Cost might now transcend our imagination. Admiral Wilcutts pointed out that it cost Caesar and his Roman Legions 50 cents per enemy killed, that it cost Napoleon \$3000 per enemy killed. The Civil War cost the Union \$5000 for every Confederate killed, World War I cost this country \$20,000 for every enemy killed, and World War II cost this country \$200,000 for every German and Japanese killed. He estimated that World War III would cost this country \$1,000,000 for every enemy killed.

It must be evident from the brief foregoing comments that plans for such disaster and such national emergency must necessarily be on a national level. It must also be equally evident that planning, training and knowledge concerning this problem must be in everyone's mind. At the session of the Council on National Emergency Medical Service, specific recommendations were few because it was believed that if a great deal of work were done at a state level and much expense was involved in formulating and organizing and putting into effect a program on a state level, thereafter the program that would be formulated by the Office of Civilian Defense might be out of harmony with such state-level programs and that the whole thing would have to be done over. However, it was agreed that certain specific things might be done by the state medical societies while they were awaiting a policy and program from a higher level. Specifically, it was recommended that the societies appoint or elect a subsidiary national emergency medical committee, and that the various subdivisions of the state medical societies elect or appoint corresponding committees for national-emergency medical service. A resolution to this effect was adopted by the Council on National Emergency Medical Service. Our society has such a committee, but the county societies do not as yet.

It was especially recommended that all physicians inform themselves regarding atomic energy, the implications of its use in atomic warfare and measures that might be employed in defense against it.

It then follows that defense against the type of warfare outlined in the preceding paragraphs must have two components: military and civilian.

The perfection of the military component is not of detailed interest to us except as it affects us as physicians. The military must make known its needs and its probable methods of meeting these needs. The new Selective Service law, which is reported out of committee and which will probably be passed by Congress, gives the power to the President to call into service any physician, dentist or veterinarian up to the age of forty-five. The committee asks the House of Delegates to instruct its delegate to the American Medical Association to reaffirm and re-emphasize the principles endorsed in June, 1947, by the American Medical Association House of Delegates after its deliberations on the use of medical personnel by the military services during World War II.

Representatives of the Surgeon General of the Air Force and of the Surgeon General of the Army, present at the spring meeting of the Council on National Emergency Medical Service stated that their services were re-examining their physician needs and were attempting to draw plans that would more effectively utilize their medical personnel. They said that both services were in the process of making studies to see how the work load of the medical personnel might be lightened in administrative duties. They were also attempting to make plans for mobilization where-

by the physical facilities, plants and equipment for hospitals and other medical units might be activated by nonmedical personnel, thereby enabling them to leave the practicing physician where he is until these plants and equipment and facilities were actually ready for his services with patients to treat.

It is agreed that if the military establishment is enlarged by Selective Service or a universal-military-training program, a large number of physicians will have to be obtained for military service. The Council resolved to petition the Board of Trustees of the American Medical Association to seek regulation or legislation whereby selection of physicians for a new army or a universal-military-training program would operate as follows: graduates of V-12 or ASTP programs who had not repaid the Government for their education by serving a just length of time in the military service would be selected first. The next group for selection for service within the age groups mentioned should be physicians, otherwise qualified, who did not serve in World War II.

In the event of the passage of a selective service act or a universal-military-training program that would register the youths reaching ages eighteen or nineteen, it has been estimated that 1,200,000 men will reach the age of eighteen years every year until 1951, when that number drops off until 1958 by reason of a decline in the birth rate from 1933 to 1941. Of this number reaching the age of liability, so far as the Selective Service program goes, a large number would have to be examined. The Council on National Emergency Medical Service, recalling many mistakes of World War II, adopted a resolution asking that the examination machinery be set up so that these candidates would undergo one examination instead of several physical examinations as in World War II. This matter of examining a single candidate many times accounted for many physician man hours wasted in World War II.

Colonel Eanes, of the Office of Selective Service Records, stated that the Government would probably ask the physicians of this country to perform these examinations on a voluntary, free-of-charge basis. He stated that the reasons for asking for this were that the full value of physicians' services cannot be compensated, that any such payments would increase the public tax burden, and that the making of any payments would encourage cultist and other quasi-medical practitioners to seek inclusion as examiners.

This matter was discussed by the Council on National Emergency Medical Service, and it was believed that the reasons advanced for not paying physicians for their services were not reasonable, but that this matter should be decided by the medical profession through the delegates to the American Medical Association. The committee believes that physicians, as well as all others supplying services and material to the Government, should be paid in the amount that is just and proper for their services. It is certainly true that in World War II the division of work in the examination of candidates was often not equitable, with some ultra-conscientious physicians shouldering the greater part of the burden in many cases.

The Council also decided to recommend to the armed forces that they study plans whereby men might be rotated between foreign duty and duty within the continental United States. Also, they thought that some study might be given to the matter of rotating physicians between military and civilian duty in case of a prolonged conflict.

At the spring meeting of the Council on National Emergency Medical Service it was stated that the ratio of physicians to civilian population at the present time is 1:740. During World War II the ratio of doctors remaining in civilian practice to the population reached the low figure of 1:1450. This was a general cross-section figure. In some states, notably Tennessee and Missouri, the ratio dropped lower. In other states, notably New York, the ratio remained higher, and in metropolitan New York City district the ratio never dropped below 1:1000. A resolution was passed by the Council on National Emergency Medical Service that in the event of another national emergency the ratio of physicians to civilian population should be maintained at or above 1:1250.

In connection with the equitable distribution of physicians between the civilian population and the armed forces, it was pointed out that in the table of organization of the new national defense act, the Director of Civilian Defense

Immediately upon hearing of the disaster at Nagasaki, the Japanese medical officer of the district started toward Nagasaki with a whole trainload of medical supplies. He never got nearer than within 60 miles of Nagasaki before his whole trainload of medical supplies was used up by the outbound refugees streaming forth from the bomb area. The bomb victims remaining within the area never received medical treatment.

One must contemplate with some dismay a type of warfare that claims the lives of and maims not only civilians but also their doctors and nurses and their hospital personnel, to whom they constantly turn for relief in time of physical pain and disaster. At Nagasaki there was a medical school with 800 nurses and doctors. About 200 were on vacation at the time of the explosion. Of the remaining 600 there was not one survivor. At Hiroshima, out of 300 physicians, 260 were killed or injured, and 75 per cent of the nurses and technicians were killed or injured. All the hospitals were destroyed, and there was no light or power.

We must consider the problem of national defense against a type of warfare of this kind in terms of supplies and personnel, which heretofore we have never had to consider. It is estimated, for example, that if a bomb the size of the one that was dropped on Nagasaki were dropped on the City of Boston, we should need in the next thirty-six hours 200,000 units of blood or plasma. The need for this quantity of blood and plasma, as well as for the numbers of skilled personnel for the collection, processing and administration of all this blood, not to mention the numbers of donors required, almost staggers the imagination. If we can consider at the same time that such a disaster would have completely inactivated the Massachusetts General Hospital, the Peter Bent Brigham Hospital, the Boston City Hospital, the Children's Hospital and the Beth Israel Hospital, in addition to all their doctors and all their nurses, we can have a rough concept of the scope and magnitude of the problem of recovery and rehabilitation from such a blow. Let us again emphasize at this point that we now have atomic bombs one thousand times as powerful as those dropped on Nagasaki and Hiroshima.

The information gained by the explosions of the atomic bombs at Nagasaki, Hiroshima and the Bikini Atoll project teaches us that there are two effective ways to cause destruction: to explode the bomb in the water and to explode it just above roof-top level.

Almost all cities are weak at their roof tops, and the destruction caused by roof-top explosion is almost incalculable. In addition to the blast effect and the radiation effect, there is a tremendous effect from flying debris capable of inflicting severe damage.

In addition to the immediate local blast effect of exploding an atomic bomb in the water, it was pointed out not only that the water itself was seriously contaminated but also that the mist and spray that would shoot almost to the stratosphere loaded with radiation material was equal to several hundred tons of radium.

The gamma radiation from a bomb exploded at roof-top level equals that of several thousand tons of radium. In the water explosion it was estimated that there was radiation equal to from 1 to 100 tons of radium in the mist, which could be carried by prevailing winds over long distances and precipitate out at many points along its travels.

Dr. Stafford Warren drew an impressive analogy from an incident that occurred during his air travel from Los Angeles to Chicago. He stated that near Denver there was a sandstorm in progress. One hundred and fifty miles further east there was a bank of cumulus clouds. Their tops were yellow with the particles of sand that had been picked up in Denver. The bottoms of the clouds were pure white. This sand picked up in the storm in Denver was thus being carried a considerable distance. He then stated that it was a well known meteorologic fact that cumulus clouds 100 miles square in area could precipitate out in an area one mile square. He then pointed out that vegetable matter is capable of concentrating radio activity and mineral matter in the soil up to 100 or 1000 times during the process of growth. The inference is that if atomic radiant energy particles should be diluted in mist or cloud banks, they might, by precipitation, be concentrated in a small area. Even if they were precipitated out of clouds over a given area in dilute concentration, the vegetable matter in that

given area would or could concentrate them to a toxic or lethal degree.

The contamination of water that results from an explosion could create serious damage to a relatively large area. If a bomb exploded in Lake Michigan it might contaminate the whole St. Lawrence waterway, and the contamination might be carried down to the mouth of the St. Lawrence to ruin all the fishing banks off the coast, thus imperiling a large source of the nation's fish-food supply.

#### *Analysis of the Destructive Effect of the Atomic Bomb*

The difference between ordinary high explosives such as those used in World War II and atomic bombs is the almost inconceivable magnitude of the explosive force of the second over the first and, secondarily, the liberation of radiant energy by the atomic bomb covering the whole mass of wave lengths from heat waves to million-volt gamma waves.

The effects on people of atomic-bomb explosions may relatively be divided into three main groups: actual physical injury caused by destructive violence of flying debris and particles through the air (this results in contusions, lacerations and fractures with which every physician is familiar and which he is equipped to treat in both military and civilian life), the second effect is that due to blast (and here most physicians, especially veterans of World War II, are on familiar ground), including internal, concealed hemorrhage in vital organs, petechiae of the brain and small areas of bleeding in many parts of the vascular bed, often in solid organs and in the gastrointestinal tract, the third and important injuries are those due to radiant energy. Of the radiant energy resulting from an atomic-bomb explosion, the most important is the gamma radiation energy. This radiation is actually the same as x-radiation. In an atomic bomb area these are of 200,000,000-volts electromagnetic force. They are lethal to anyone within a mile and dangerous to anyone within a mile and a half, but their effective range is apparently limited to two miles. The injurious effect is produced immediately, since the rays move with the speed of light, and they are produced at the instant of explosion. There is little one can do about protection against these rays if he is within a two-mile area of the explosion.

It was estimated by Dr. Shields Warren that a person might be protected if he were a mile and a half away from the blast, and if he had already erected and stood behind a protected screen made up of a 12-foot-thick, steel, reinforced concrete wall, with a second layer composed of a wall of heavy oil 4 feet thick and a third layer composed of an 8-foot-thick wall of lead, but there was no positive assurance that he would be protected.

About a mile from the bomb explosion at Nagasaki there was an officers' club solidly constructed of bomb-proof material, which was not injured by the blast of the atomic bomb. There was no flying debris and no destruction to the building at the time the bomb went off. Inside were about 60 officers and men. None were apparently injured. But three months after the date of the bomb explosion there was not one survivor. All died from secondary effects of radiant energy.

The atomic bomb would immediately create many deaths. A single bomb on each of twenty key cities would result in millions of deaths. Large-scale work would be necessary to repair the immediate physical injury to human beings resulting from the flying debris and the blast. Secondary measures that would be tremendous in scope would be necessary for the treatment of victims of radiation. This would involve the co-operation of all. It would involve large scale checking of white-cell counts and differential blood counts on radiation victims, as well as accurate record-taking and record-keeping on such victims.

The streams of gamma rays penetrate immediately but the effects are noted later. This physical quality is already useful to us as physicians. We treat radiosensitive cancer cells with radiant energy to destroy them, but we are familiar with the later appearance of the destructive effect of the radiation on normal cells, as well as the toxic effect on the patient as a whole in case of overdosage.

The treatment of victims of radiation will involve large scale use of blood transfusions and penicillin to prevent secondary infection in victims until such time as their own hematopoietic systems can resume their normal function.

In all fairness, after putting forth this dire picture, it should be stated that of the 200,000 employees engaged on

formed the Grange, the Farm Bureau, the State Department of Health and other groups in the State that it exists and is anxious to co-operate in any matters falling within its sphere.

The chief conclusion to be drawn from the National Rural Health Conference is that there are many groups throughout the country actively pushing their favorite health programs, and that these people mean to get results through Government action if necessary or through voluntary plans of various kinds if these can be set in motion and made to work. The Farmers' Union, for instance, has been actively supporting the Wagner-Murray-Dingell Bill, whereas those in public-health work are seeking to extend the scope and function of public-health units and activities. Some of these things may be good and some bad, but the only way the medical profession can protect itself and the public from programs that are not good is to be conscious of what is going on and to be ready with something better.

Much Government-sponsored health activity is good and deserves our understanding and co-operation. Furthermore, there seems little doubt that the expense of much of the most important health activities especially in the realm of preventive medicine, is such that there is no practical hope of getting things done without financial aid from the federal Government. Hospital-construction and school-lunch programs are but illustrations that could be multiplied many times, quite apart from the many phases of public health that have long been taken for granted as Government responsibility. At the same time, it is very important to avoid duplication of services, and to avoid a situation in which lay personnel will have control of matters that can properly be handled only by physicians.

It is clear that there is an increasing demand for modern medical care, together with an increasingly clear understanding of what this involves, in the field of preventive as well as in curative medicine. If these demands are to be properly met, the medical profession must take an active part in meeting them.

WILLIAM F. PUTNAM, *Chairman*

Dr. Sycamore, for the Committee on Officers' Reports, recommended that the report be accepted, that the Committee be instructed to continue to study and report on the needs and the trends in rural medicine, and that it is desirable that the Committee be represented at the National Conference on Rural Health.

He moved the adoption of this portion of the report.

This motion was duly seconded and was carried.

The report of the Committee on Tuberculosis was then presented.

The year 1947 registered a new all-time low in tuberculosis mortality in New Hampshire. The Division of Vital Statistics of the State Department of Health reports that deaths from all forms of tuberculosis in 1947 dropped to 82, or 8 less than the previous low of 90 in 1945.

The Division of Vital Statistics further states that the 82 deaths include 74 of New Hampshire residents that occurred in the State, and 8 of New Hampshire residents that occurred outside the State—4 residents of Manchester (World War I veterans) who died at the Rutland State Sanatorium, Rutland, Massachusetts; 1 in Florida; 1 in Vermont; 1 at Saranac Lake, New York, and 1 in Massachusetts elsewhere than at Rutland.

The 1947 tuberculosis mortality, based upon deaths of residents occurring inside and outside the State, registers a new all-time low rate of 16 per 100,000 population as compared with the previous all-time low of 18.7 in 1945.

The large reduction in tuberculosis mortality in 1947 is particularly gratifying in view of the fact that the number of deaths increased in New Hampshire in 1946 to a toll of 115 and a rate of 22.5 as contrasted with the all-time low of 90 deaths and a rate of 18.7 in 1945.

Analysis of the statistics by three-year periods for the past thirty years indicates that there has been a persistent

and continuous decline in the tuberculosis mortality in the State. However, the degree of reduction in the mortality has lessened since 1942. It is a well recognized fact that it requires more intensive effort to lower a low death rate from an infectious disease than a high one.

The 1947 tuberculosis statistics for the states of the Union are not available as yet. However, it is confidently anticipated that New Hampshire will be in the sixth or seventh lowest place in the table of tuberculosis mortality.

It is perhaps advisable at this point to quote the old axiom—"Unceasing vigilance is the price of liberty." This is particularly true in the campaign for the eradication of human tuberculosis.

To maintain the gains already won, and to continue to advance toward winning the ultimate eradication of the disease, means ever-increasing extension and intensification of the well demonstrated program of early discovery, prompt treatment, supervision and rehabilitation of patients with tuberculosis.

The remarkable progress achieved in New Hampshire is due in a considerable degree to the wholehearted efforts of the members of the Society. The physicians of New Hampshire are the first line of defense and attack in the fight against the disease. This has been amply demonstrated during the past year in the increasing use of the tuberculin test and chest x-ray examination by the physicians in the examination of thousands of "suspects," "contacts" and even in their routine examinations.

We again urge increasing use of these effective methods for the early detection of tuberculous infection and disease. The New Hampshire Tuberculosis Association is ready to provide chest x-ray films for persons referred by physicians. Furthermore, the New Hampshire State Sanatorium and the New Hampshire Tuberculosis Association continue to offer their services for interpretation of chest x-ray films sent to them.

The records in the chest diagnostic clinics prove that the physicians of the State, if they are determined to do so, can perform a better service of suspecting and discovering active tuberculosis cases year in and year out, than any other agency. It is noteworthy that in the past year as in other years, more cases of active pulmonary tuberculosis were found among patients referred to the chest diagnostic clinics than in any other group of people examined, for the reason that significant symptoms cause patients to consult their physicians with resulting referral to the clinics.

Your committee hopes that some progress may be made in the near future in the routine chest x-ray examination of all patients admitted to hospitals. At present, health departments and hospital budgets do not permit such a procedure. However, a demonstration study may be developed in one of the smaller hospitals.

Bed rest and collapse therapy continue to be the most effective elements of treatment and cure for tuberculosis patients.

Despite considerable research activity, the full value of streptomycin in the treatment of tuberculosis is not yet known and the indiscriminate use of the drug is not advocated by medical opinion. It is quite possible that the vast increase in research brought about by streptomycin may result in the discovery of an antibiotic of more definite value.

During the past year interest has increased among public-health officials and the members of the medical profession, with reference to the possible use of BCG as a preventive in tuberculosis. In a recent statement of policy adopted by the Executive Committee of the American Trudeau Society, the following conclusions are announced:

Vaccination with BCG does not provide complete protection against tuberculosis and until further controlled studies are conducted, cannot be recommended for the general population. However, since BCG appears to provide some degree of protection, it is recommended for members of groups constantly exposed to tuberculosis, if they have a negative reaction to the tuberculin test.

BCG is recommended for the following groups if they are subjected to more than ordinary exposure to tuberculosis: doctors, medical students and nurses, hospital and laboratory personnel whose work brings them constantly in contact with the tubercle bacillus, persons who are unavoidably exposed to tuberculosis in the home and patients and em-

is under the aegis of the Secretary of the Army, the Secretary of the Navy and the Secretary of the Air Force. He would probably make recommendations regarding the allocation of civilian physicians after consulting with his superiors. It was pointed out that the physicians of the United States as a whole were represented at a relatively low echelon. It was strongly urged by the Council on National Emergency Medical Service that the physicians of the United States have representation on the National Security Resources Board, which is directly responsible to the President.

As stated above, plans and enabling legislation for civilian defense must necessarily be on a national level. It was pointed out at the meeting of the Council on National Emergency Medical Service that two things might be done now while we are awaiting directives or a plan from the Office of the Director of Civilian Defense: physicians should be trained and educated in the knowledge and implications of atomic warfare—they should then ready themselves to take an active part in imparting this knowledge to the civilian population, and a complete inventory should be made of the medical resources within the state. This might well entail an integration of the Governor's plan for coping with civil disaster.

The committee has the following recommendations to make to the House of Delegates: that the machinery for procurement and assignment of physicians within the medical society be reviewed (it is recommended that a procurement and assignment board be set up rather than have the responsibility for procurement fall upon one person), that the physicians of this Society be informed regarding atomic energy, its destructive effects and the measures that might be employed to protect people against these destructive effects, and that they be kept currently cognizant of new developments in protective devices and methods as these become known, that component county-medical-society groups within the New Hampshire Medical Society be asked to appoint or elect county committees on National Emergency Medical Service to work with the State committee of the same name, that the House of Delegates instruct its delegate to the American Medical Association to move that in the event of the passage of a selective service act or a universal-military-training program, a single physical examination for candidates, which is acceptable to the armed forces, be made operative, that the House of Delegates instruct the delegate to the American Medical Association to move that physicians engaged in these examinations should be paid for their work, and that the House of Delegates instruct the delegate to the American Medical Association to vote affirmatively in a proposal in the American Medical Association House of Delegates to attempt to obtain American Medical Association representation on the National Security Resources Board.

DANIEL J. SULLIVAN, *Chairman*  
JOSEPH M. MCCARTHY  
CLARENCE E. DUNBAR  
BERNARD J. MANNING  
JOHN C. ECKELS

Dr. Sycamore, for the Committee on Officers' Reports, moved that the House of Delegates express its commendation of the Committee for its comprehensive and illuminating report.

This motion was duly seconded and was carried.

He then recommended that the resolutions of the Committee on National Emergency Medical Service be adopted.

This motion was duly seconded and was carried.

The Committee on Officers' Reports then recommended that the Committee on Emergency Medical Service be instructed to consider and make recommendations to the officers of the Society regarding appropriate means of educating the physicians of New Hampshire concerning the medical implications of atomic energy.

This motion was duly seconded and was carried.

The report of the Committee on Rural Health was then read, as follows:

This consists of a report on the activities of this committee, and a report on the National Conference on Rural Health held in Chicago, February 6 and 7, 1948.

The reasons for the existence of this new committee may not be altogether apparent, depending largely on whether one considers that rural health problems exist in this state. Fortunately they do not exist to the extent that is true in some parts of the country, where there are large groups of people seriously underprivileged because of belonging to a racial minority group, or for other reasons. In general it is true that in New Hampshire most of the people can get at least fairly satisfactory medical care; on the other hand, many of our people are existing at a level of health below that which is commensurate with present medical knowledge, and many will believe that a real problem exists so long as that is true.

The question what the Society is called upon to do about it depends largely on how important we consider it for the medical profession to have something to do with health plans and programs that may be put into effect. For as was made abundantly clear at the national conference, many groups fostering schemes and programs of various kinds may in the future have an influence not only on the health of the country but also on the conditions of medical practice.

Your committee has had one formal meeting, some informal conversations and a considerable amount of correspondence. The chairman attended the National Conference on Rural Health representing the Society. Not to go too far afield, the Committee confined its attention largely to the following matters: the supply of physicians (and other medical personnel) in rural areas, the number and adequacy of hospitals, the question of so-called state medicine as it might affect rural medicine in New Hampshire, and organizations and groups interested in these matters and their programs.

In the absence of a formal survey such as has been carried out by the rural health committees of some of the other states, we have no statistical data to present, so far as the Committee has learned, there are no areas of desperate medical need in the State at the present time, though there are many areas where additional medical personnel and facilities could be used. The Committee is convinced, however, that two types of areas constitute potential danger spots for the future—namely, areas that are remote from good hospitals, and areas that are served exclusively by so-called closed staff hospitals. Well trained young physicians are increasingly unwilling to enter rural general practice in such locations. The rapidly growing extent to which the modern practice of medicine is dependent on hospital facilities, need not be dwelt upon, and although it is still possible to practice scientific medicine in the office and home with relatively little dependence on hospitals, the labor, time and other difficulties involved make it seem almost wholly out of the question to those with present-day medical training.

The Committee endorses the purposes of the Hill Burton Hospital Construction Act, and hopes that the New Hampshire communities in need of new or improved hospital facilities will take full advantage of its provisions.

The Committee also believes that it is in line with the present-day trend to include a section on general practice on hospital staffs, and to admit general practitioners to the hospital staffs as officially recommended by the American Medical Association, to re-evaluate the policies governing the so-called closed-staff hospitals, with a view to eliminating from this State areas in which well trained general practitioners will believe that the practice of medicine is unattractive or impossible. It seems to the Committee that if this situation continues, in the foreseeable future there may be a serious lack of competent general practitioners not only in some of our more remote areas but also in the very shadow of some of our best institutions.

In addition to the points just mentioned, the Committee recommends that its existence be continued, that organized medicine may keep its finger on the pulse of movements and trends in the field of rural health that may be of vital concern to all of us, and that for the same reason, the Society continue to be represented, preferably not by the same individual, at national conferences. The Committee also

formed the Grange, the Farm Bureau, the State Department of Health and other groups in the State that it exists and is anxious to co-operate in any matters falling within its sphere

The chief conclusion to be drawn from the National Rural Health Conference is that there are many groups throughout the country actively pushing their favorite health programs, and that these people mean to get results, through Government action if necessary, or through voluntary plans of various kinds if these can be set in motion and made to work. The Farmers' Union, for instance, has been actively supporting the Wagner-Murray-Dingell Bill, whereas those in public-health work are seeking to extend the scope and function of public-health units and activities. Some of these things may be good and some bad, but the only way the medical profession can protect itself and the public from programs that are not good is to be conscious of what is going on and to be ready with something better.

Much Government-sponsored health activity is good and deserves our understanding and co-operation. Furthermore, there seems little doubt that the expense of much of the most important health activities, especially in the realm of preventive medicine, is such that there is no practical hope of getting things done without financial aid from the federal Government. Hospital-construction and school-lunch programs are but illustrations that could be multiplied many times, quite apart from the many phases of public health that have long been taken for granted as Government responsibility. At the same time, it is very important to avoid duplication of services, and to avoid a situation in which lay personnel will have control of matters that can properly be handled only by physicians.

It is clear that there is an increasing demand for modern medical care, together with an increasingly clear understanding of what this involves, in the field of preventive as well as in curative medicine. If these demands are to be properly met, the medical profession must take an active part in meeting them.

WILLIAM F. PUTNAM, *Chairman*

Dr. Sycamore, for the Committee on Officers' Reports, recommended that the report be accepted, that the Committee be instructed to continue to study and report on the needs and the trends in rural medicine, and that it is desirable that the Committee be represented at the National Conference on Rural Health.

He moved the adoption of this portion of the report.

This motion was duly seconded and was carried.

The report of the Committee on Tuberculosis was then presented.

The year 1947 registered a new all-time low in tuberculosis mortality in New Hampshire. The Division of Vital Statistics of the State Department of Health reports that deaths from all forms of tuberculosis in 1947 dropped to 82, or 8 less than the previous low of 90 in 1945.

The Division of Vital Statistics further states that the 82 deaths include 74 of New Hampshire residents that occurred in the State, and 8 of New Hampshire residents that occurred outside the State—4 residents of Manchester (World War I veterans) who died at the Rutland State Sanatorium, Rutland, Massachusetts, 1 in Florida, 1 in Vermont, 1 at Saranac Lake, New York, and 1 in Massachusetts elsewhere than at Rutland.

The 1947 tuberculosis mortality, based upon deaths of residents occurring inside and outside the State, registers a new all-time low rate of 16 per 100,000 population as compared with the previous all-time low of 18.7 in 1945.

The large reduction in tuberculosis mortality in 1947 is particularly gratifying in view of the fact that the number of deaths increased in New Hampshire in 1946 to a toll of 115 and a rate of 22.5 as contrasted with the all-time low of 90 deaths and a rate of 18.7 in 1945.

Analysis of the statistics by three-year periods for the past thirty years indicates that there has been a persistent

and continuous decline in the tuberculosis mortality in the State. However, the degree of reduction in the mortality has lessened since 1942. It is a well recognized fact that it requires more intensive effort to lower a low death rate from an infectious disease than a high one.

The 1947 tuberculosis statistics for the states of the Union are not available as yet. However it is confidently anticipated that New Hampshire will be in the sixth or seventh lowest place in the table of tuberculosis mortality.

It is perhaps advisable at this point to quote the old axiom—"Unceasing vigilance is the price of liberty." This is particularly true in the campaign for the eradication of human tuberculosis.

To maintain the gains already won and to continue to advance toward winning the ultimate eradication of the disease, means ever-increasing extension and intensification of the well demonstrated program of early discovery, prompt treatment, supervision and rehabilitation of patients with tuberculosis.

The remarkable progress achieved in New Hampshire is due in a considerable degree to the wholehearted efforts of the members of the Society. The physicians of New Hampshire are the first line of defense and attack in the fight against the disease. This has been amply demonstrated during the past year in the increasing use of the tuberculin test and chest x-ray examination by the physicians in the examination of thousands of "suspects," "contacts" and even in their routine examinations.

We again urge increasing use of these effective methods for the early detection of tuberculous infection and disease. The New Hampshire Tuberculosis Association is ready to provide chest x-ray films for persons referred by physicians. Furthermore, the New Hampshire State Sanatorium and the New Hampshire Tuberculosis Association continue to offer their services for interpretation of chest x-ray films sent to them.

The records in the chest diagnostic clinics prove that the physicians of the State, if they are determined to do so, can perform a better service of suspecting and discovering active tuberculosis cases year in and year out, than any other agency. It is noteworthy that in the past year, as in other years, more cases of active pulmonary tuberculosis were found among patients referred to the chest diagnostic clinics than in any other group of people examined, for the reason that significant symptoms cause patients to consult their physicians with resulting referral to the clinics.

Your committee hopes that some progress may be made in the near future in the routine chest x-ray examination of all patients admitted to hospitals. At present, health departments and hospital budgets do not permit such a procedure. However, a demonstration study may be developed in one of the smaller hospitals.

Bed rest and collapse therapy continue to be the most effective elements of treatment and cure for tuberculosis patients.

Despite considerable research activity the full value of streptomycin in the treatment of tuberculosis is not yet known, and the indiscriminate use of the drug is not advocated by medical opinion. It is quite possible that the vast increase in research brought about by streptomycin may result in the discovery of an antibiotic of more definite value.

During the past year interest has increased among public-health officials, and the members of the medical profession, with reference to the possible use of BCG as a preventive in tuberculosis. In a recent statement of policy adopted by the Executive Committee of the American Trudeau Society, the following conclusions are announced:

Vaccination with BCG does not provide complete protection against tuberculosis and until further controlled studies are conducted, cannot be recommended for the general population. However, since BCG appears to provide some degree of protection, it is recommended for members of groups constantly exposed to tuberculosis, if they have a negative reaction to the tuberculin test.

BCG is recommended for the following groups if they are subjected to more than ordinary exposure to tuberculosis: doctors, medical students and nurses, hospital and laboratory personnel whose work brings them constantly in contact with the tubercle bacillus, persons who are unavoidably exposed to tuberculosis in the home and patients and em-

is under the aegis of the Secretary of the Army, the Secretary of the Navy and the Secretary of the Air Force. He would probably make recommendations regarding the allocation of civilian physicians after consulting with his superiors. It was pointed out that the physicians of the United States as a whole were represented at a relatively low echelon. It was strongly urged by the Council on National Emergency Medical Service that the physicians of the United States have representation on the National Security Resources Board, which is directly responsible to the President.

As stated above, plans and enabling legislation for civilian defense must necessarily be on a national level. It was pointed out at the meeting of the Council on National Emergency Medical Service that two things might be done now while we are awaiting directives or a plan from the Office of the Director of Civilian Defense: physicians should be trained and educated in the knowledge and implications of atomic warfare—they should then ready themselves to take an active part in imparting this knowledge to the civilian population, and a complete inventory should be made of the medical resources within the state. This might well entail an integration of the Governor's plan for coping with civil disaster.

The committee has the following recommendations to make to the House of Delegates: that the machinery for procurement and assignment of physicians within the medical society be reviewed (it is recommended that a procurement and assignment board be set up rather than have the responsibility for procurement fall upon one person); that the physicians of this Society be informed regarding atomic energy, its destructive effects and the measures that might be employed to protect people against these destructive effects, and that they be kept currently cognizant of new developments in protective devices and methods as these become known; that component county-medical-society groups within the New Hampshire Medical Society be asked to appoint or elect county committees on National Emergency Medical Service to work with the State committee of the same name; that the House of Delegates instruct its delegate to the American Medical Association to move that in the event of the passage of a selective service act or a universal-military-training program, a single physical examination for candidates, which is acceptable to the armed forces, be made operative; that the House of Delegates instruct the delegate to the American Medical Association to move that physicians engaged in these examinations should be paid for their work; and that the House of Delegates instruct the delegate to the American Medical Association to vote affirmatively in a proposal in the American Medical Association House of Delegates to attempt to obtain American Medical Association representation on the National Security Resources Board.

DANIEL J. SULLIVAN, *Chairman*  
JOSEPH M. MCCARTHY  
CLARENCE E. DUNBAR  
BERNARD J. MANNING  
JOHN C. ECKELS

Dr. Sycamore, for the Committee on Officers' Reports, moved that the House of Delegates express its commendation of the Committee for its comprehensive and illuminating report.

This motion was duly seconded and was carried.

He then recommended that the resolutions of the Committee on National Emergency Medical Service be adopted.

This motion was duly seconded and was carried.

The Committee on Officers' Reports then recommended that the Committee on Emergency Medical Service be instructed to consider and make recommendations to the officers of the Society regarding appropriate means of educating the physicians of New Hampshire concerning the medical implications of atomic energy.

This motion was duly seconded and was carried.

The report of the Committee on Rural Health was then read, as follows:

This consists of a report on the activities of this committee, and a report on the National Conference on Rural Health held in Chicago, February 6 and 7, 1948.

The reasons for the existence of this new committee may not be altogether apparent, depending largely on whether one considers that rural health problems exist in this state. Fortunately they do not exist to the extent that is true in some parts of the country, where there are large groups of people seriously underprivileged because of belonging to a racial minority group, or for other reasons. In general it is true that in New Hampshire most of the people can get at least fairly satisfactory medical care; on the other hand, many of our people are existing at a level of health below that which is commensurate with present medical knowledge, and many will believe that a real problem exists so long as that is true.

The question what the Society is called upon to do about it depends largely on how important we consider it for the medical profession to have something to do with health plans and programs that may be put into effect. For as was made abundantly clear at the national conference, many groups fostering schemes and programs of various kinds may in the future have an influence not only on the health of the country but also on the conditions of medical practice.

Your committee has had one formal meeting, some informal conversations and a considerable amount of correspondence. The chairman attended the National Conference on Rural Health representing the Society. Not to go too far afield, the Committee confined its attention largely to the following matters: the supply of physicians (and other medical personnel) in rural areas, the number and adequacy of hospitals, the question of so-called state medicine as it might affect rural medicine in New Hampshire, and organizations and groups interested in these matters and their programs.

In the absence of a formal survey such as has been carried out by the rural health committees of some of the other states, we have no statistical data to present, so far as the Committee has learned, there are no areas of desperate medical need in the State at the present time, though there are many areas where additional medical personnel and facilities could be used. The Committee is convinced however, that two types of areas constitute potential danger spots for the future—namely, areas that are remote from good hospitals, and areas that are served exclusively by so-called closed staff hospitals. Well trained young physicians are increasingly unwilling to enter rural general practice in such locations. The rapidly growing extent to which the modern practice of medicine is dependent on hospital facilities, need not be dwelt upon, and although it is still possible to practice scientific medicine in the office and home with relatively little dependence on hospitals, the labor, time and other difficulties involved make it seem almost wholly out of the question to those with present-day medical training.

The Committee endorses the purposes of the Hill Burton Hospital Construction Act, and hopes that the New Hampshire communities in need of new or improved hospital facilities will take full advantage of its provisions.

The Committee also believes that it is in line with the present-day trend to include a section on general practice on hospital staffs, and to admit general practitioners to hospital staffs as officially recommended by the American Medical Association, to re-evaluate the policies governing the so-called closed-staff hospitals, with a view to eliminating from this State areas in which well trained general practitioners will believe that the practice of medicine is unattractive or impossible. It seems to the Committee that if this situation continues, in the foreseeable future there may be a serious lack of competent general practitioners not only in some of our more remote areas but also in the very shadow of some of our best institutions.

In addition to the points just mentioned, the Committee recommends that its existence be continued, that organized medicine may keep its finger on the pulse of movements and trends in the field of rural health that may be of vital concern to all of us, and that for the same reason, the Society continue to be represented, preferably not by the same individual, at national conferences. The Committee has

more patients died of accidents of pregnancy than of anything else, with hemorrhage of childbirth coming into second place. It is the hope of the Committee that the maternal death rate will soon reach what might be considered an irreducible minimum.

The Committee further classifies the cases, for purposes of this study, into four groups, as follows:

- Group I Cases in which the patient was at fault because of refusal of prenatal care, neglect, self-induced abortion and so forth (5 cases)
- Group II Those in which the obstetric treatment was inadequate (2 cases)
- Group III Those which were apparently unavoidable (7 cases)
- Group IV Cases in which data were insufficient and, therefore, undetermined (1 case)

After the Committee has made a decision in each case, including suggestions for conduct in the individual case,

TABLE 1 Maternal Deaths by Cause

CAUSE	NO OF DEATHS	
	ASSIGNED BY INTERNATIONAL LIST OF CAUSES OF DEATH	ASSIGNED BY COMMITTEE
Abortion (spontaneous therapeutic, or of unspecified origin) with mention of other infection	1	1
Abortion (induced for nontherapeutic reasons by persons other than mother herself) with mention of infection	1	1
Ectopic gestation without mention of infection	1	1
Hemorrhage of childbirth and puerperium other and unspecified hemorrhages	2	2
Puerperal thrombophlebitis	1	1
Acute yellow atrophy of liver (puerperal)	1	1
Other puerperal toxemias	2	2
Other specified conditions of childbirth	3	1
Other and unspecified conditions of childbirth and puerperium	3	1
Deaths due to anesthesia	—	3
Surgical death (following cesarean section)	—	1
	15	15

a letter is written to the reporting physician containing this information for his use.

Tables 1-3 show the maternal death rates by years since 1935, maternal death rates by counties and the number of maternal deaths by cause for the year 1947.

The Committee cannot do an exhaustive study of infant deaths or stillbirths in this report, but Table 4 demonstrates

TABLE 2 Maternal Death Rates per 1000 Live Births \*

YEAR	RATE
1935	6.5
1936	5.4
1937	6.1
1938	4.8
1939	4.2
1940	5.8
1941	3.1
1942	1.9
1943	1.7
1944	2.9
1945	1.8
1946	1.4
1947	1.1

\*The number of births in 1947 was 13,638.

causes of death of infants under one year of age, and Table 5 the chief causes of death in stillbirths.

This year, as a new phase of the study of maternal deaths the Committee asked all hospitals in the State to report the number of cesarean sections performed during the calendar year 1947. Of 31 hospitals contacted, all but two responded

The total number of cesarean sections performed in New Hampshire in 1947 was 383 (Table 6). This means that of 13,638 live births, the method of delivery in 383 was by cesarean section. In this year's report 5 of the 15 mothers

TABLE 3 Number of Maternal Deaths By County

COUNTY	URBAN	RURAL	TOTAL
Belknap	1	0	1
Carroll	0	0	0
Cheshire	1	0	1
Coot	1	1	2
Grafton	3	0	3
Hillsborough	2	0	2
Merrimack	2	0	2
Rockingham	0	2	2
Stratford	1	0	1
Sullivan	1	0	1
Totals	12	3	15

who died had had cesarean sections for various indications.

In terms of percentage, this means that of the 15 mothers who died 33.3 per cent had cesarean sections. However, it should be noted that in terms of deaths of all mothers on whom sections were performed, slightly more than 1 mother out of 100, or 1.3 per cent, died. The Committee believes

TABLE 4 Infant Deaths Under One Year of Age, According to Sex \*

CAUSE	SEX		TOTAL
	MALE	FEMALE	
Whooping cough	0	3	3
Septicemia	1	0	1
Influenza with respiratory complications specified	1	1	2
Influenza without respiratory complications specified	1	2	3
Simple gonorrhea	0	1	1
Diseases of thymus glands	1	0	1
Scurvy	1	0	1
Simple meningitis	1	2	3
Acute cerebrospinal meningitis (not due to meningococcus)	1	0	1
Otitis and other diseases of ear	0	1	1
Diseases of larynx	0	1	1
Acute bronchitis	1	0	1
Bronchopneumonia (including capillary bronchitis)	10	8	18
Lobar pneumonia	7	1	8
Pneumonia (unspecified)	2	3	5
Other and unspecified diseases of respiratory system	2	0	2
Diseases of pharynx and tonsils	0	1	1
Diarrhea and enteritis	15	9	24
Intestinal obstruction	0	1	1
Diseases of pancreas	1	0	1
Other diseases of kidneys and ureters	1	0	1
Other diseases of skin and cellular tissue	0	1	1
Congenital hydrocephalus	1	3	4
Spina bifida and meningocele	3	2	5
Anencephalus	3	2	5
Congenital malformations of heart	18	20	38
Congenital malformations of digestive system	2	2	4
Other and unspecified congenital malformations	3	4	7
Congenital debility (cause not stated)	3	3	6
Premature birth (cause not stated)	81	64	145
Intracranial or spinal hemorrhage	17	5	22
Other injuries at birth	10	6	16
Asphyxia (cause not specified) atelectasis	13	8	21
Other specified diseases peculiar to first year of life	6	5	11
Homicide by other means	0	1	1
Accidental mechanical suffocation	4	2	6
Accidental injury by fall	0	1	1
Obstruction suffocation or puncture by ingested objects	3	1	4
Other and unspecified accidents	0	1	1
Totals	215	168	383

\*Infant death rate per 1000 live births in 1947 28.1

that the figures speak for themselves and is attaching to the report a tabulation of cesarean sections by counties.

In studying maternal mortality rates by years (Table 2), it is interesting to note that the highest rate recorded oc-

ployees of mental hospitals, prisons and other custodial institutions among whom the incidence of tuberculosis is known to be high

It appears that in New Hampshire, which has a low tuberculosis death rate, experimental methods are out of place while the well demonstrated fundamental procedures in the discovery, diagnosis, prevention and treatment of tuberculosis continue to win results. We must continue and extend these well developed resources, ever hopeful that a specific cure or preventive may be found, and thus hasten the victorious conclusion of humanity's struggle against the tubercle bacillus

ROBERT B. KERR  
FRANK G. SELDON  
JOHN D. SPRING

Dr Sycamore moved that this report be accepted

This motion was duly seconded and was carried

The report of the Committee on Child Health was then read, as follows

In the year 1947 the Committee sent out a letter to the doctors in the State, encouraging them to advocate breast feeding of babies. In co-operation with the New Hampshire State Department of Health, it has revised the baby's feeding card. This card is widely used in the State as a schedule for infant feeding, and is distributed by the Division of Maternal and Child Health.

The New Hampshire Pediatric Society visited the Laconia State School on February 18, 1948. The following motion was passed by this Society:

That the Chairman of the Child Health Committee of the New Hampshire Medical Society report to the House of Delegates at the next annual meeting, expressing appreciation of the work done at the Laconia State School by Dr Depner. Realizing that there are many needs to be met at the State School, particularly with regard to increased personnel, it is requested that the New Hampshire Medical Society express the need for increased appropriations for the Laconia State School.

It is the opinion of the Committee that the main need for improvement in the medical care of our children is for more health supervision and routine checkups. The American Academy of Pediatrics survey will be completed this year, and our future plan of attack will probably coincide with theirs.

THOMAS B. WALKER, *Chairman*

Dr Sycamore for the Committee on Officers' Reports recommended that the following resolution be considered, with reference to the report of the Committee on Child Health:

WHEREAS, the work of the Laconia State School is of great importance, both in the care of the individuals committed to it, and in the protection of the Communities from which such individuals come, and

WHEREAS, the facilities and personnel of the Laconia State School are inadequate to the need,

NOW, THEREFORE, BE IT RESOLVED That the New Hampshire Medical Society urges that the appropriation for the Laconia State School be increased sufficiently to provide adequate personnel and facilities, including a special pavilion for feeble-minded children under the age of five years,

AND BE IT FURTHER RESOLVED That a copy of this resolution be sent to the appropriate officers and committees of the General Court.

He moved the adoption of this resolution

This motion was duly seconded and was carried

The report of the Committee on Maternity and Infancy was then presented

The Committee has conducted an annual study of maternal deaths, infant deaths and stillbirths for fourteen years. The deaths studied in this report are those occurring during the calendar year 1947. This study, as all others in

the past, was conducted with the co-operation of the Department of Health, which gives the services of personnel in the divisions of Maternal and Child Health and Vital Statistics. That the Committee may review and study all facts concerning each case and render an unbiased decision, the Division of Maternal and Child Health, acting for the Committee, gathers all data, compiles pertinent facts, and presents the material to the Committee. In this way all information is kept confidential and the members of the Committee do not know the identity of the patient, physician reporting, hospital or community where the infant was delivered. It should be pointed out that a study of this kind is made possible only through the co-operation of the reporting physicians, who must furnish all the facts concerning the care of the patient and the events which lead up to the patient's death. The Committee realizes its responsibility in deciding how each case should be classified. As in the past, the Committee has endeavored to appraise the data as fairly as possible, making its decisions on the facts presented and knowing that it is much easier to decide the proper method of approach to a case after it is finished than it may have been for the physician who was attempting to perform the best possible conduct at the time when the patient needed it. It is the hope of the Committee that this report, as others in the past, may be helpful in pointing out in retrospect certain suggestions that future conduct in the handling of cases, presenting similar problems, may prove helpful.

It is with this thought in mind that the Committee wishes physicians to read the recommendations and suggestions made, with the hope that the comments may prove of future value.

In the event that copies of past maternal-death studies are not available, it seems desirable to include in this report a brief description of the method used by the Committee in conducting this study. After the data are gathered, either through personal contact by a member of the Department of Health or by letter, including a questionnaire, it is presented to the Committee without identifying information. Each member of the Committee has a copy of the information to study. The Committee then discusses the details of each case, weighs the facts and finally reaches a decision concerning the cause of death and the conduct of the case. The Committee in classifying the causes of death, in accordance with the facts, may differ from the classification as coded according to the International List of Causes of Death by the Division of Vital Statistics. The discrepancies in classification are due to the fact that the Committee has obtained as full information as possible concerning each case, whereas the Division of Vital Statistics must depend upon the recorded diagnosis of the physician as included on the death certificate. This year, for instance, one death, which was not coded by Vital Statistics as a maternal death, was so classified by the Committee. Although the death certificate mentioned that the patient at the time of death was pregnant, the cause was listed as paralytic ileus with intestinal obstruction, which, according to the code, takes precedence over the pregnancy. The Committee found that the intestinal obstruction followed a cesarean section, and it was therefore classified as a maternal death. However, the death was deemed due to surgical causes. On the other hand, the Committee assigned 4 cases to other causes, which were listed as maternal deaths by the Division of Vital Statistics in accordance with the International Code—namely, deaths due to anesthesia, diabetes and accidents.

In looking back over the years during which these studies have been performed, two important facts seemed to stand out. In the first place, there has been a very real and significant decrease in the maternal death rate over a period of fifteen years. This is true even in years in which the birth rate has been high. The lowest maternal death rate in New Hampshire is for the year 1947, and the number of births in the State has reached an all-time high. The second interesting fact is that, over the years, the causes of maternal deaths have been strikingly narrowed down to conditions that may be considered accidental and unavoidable. There was a time, not too long ago, when the causes of maternal deaths were due to glaring mistakes, poor obstetrics, infections or gross hemorrhages. Only a few years ago, the three chief causes of maternal deaths were puerperal sepsis, post-partum hemorrhage and toxemia of pregnancy, in that order. In 1947,

tributed to toxemia of pregnancy. This was one of 2 cases of toxemias reported. It is interesting that fewer toxemias of pregnancy were listed than in any previous year during which this study has been conducted. The Committee would like to believe that its efforts in outlining repeatedly its recommendations concerning the treatment of toxemia may in part be responsible for the decrease in the number of deaths due to toxemia. In 1946, or the year of the last report, the leading cause of death, in the cases studied was toxemia of pregnancy. In the past the Committee considered the treatment for toxemia as reported by physicians to be entirely inadequate. In a case reported in 1947 the patient was a twenty-two-year-old woman who, during her first pregnancy, received excellent prenatal care. During the last trimester, the patient's blood pressure started to rise. There was some albumin in the urine, and the patient was hospitalized on two separate admissions during which she received intensive treatment for toxemia. This consisted of the administration of adequate doses of intravenous magnesium sulfate and sedation. On the last admission when she went into labor, she received continuous therapy for the toxemia and after a trial labor was delivered by cesarean section. During the post-partum period, she was digitalized, given oxygen, kept under sedation and finally given a blood transfusion. About six and a half hours after the operation, however, the patient died. Autopsy revealed extensive damage to the liver indicating that the toxemia had been overwhelming. The Committee believed that, in all probability, the treatment had been adequate.

Two of the cases that the Committee classified in Group III were attributed to anesthesia. One of these occurred in an eighteen-year-old primipara who aspirated a large quantity of recently ingested material during a light nitrous oxide and oxygen anesthesia. The Committee considers it a wise precaution to choose carefully the type of anesthesia that is safest to administer under such circumstances. The other death in this group occurred approximately three quarters of an hour after the normal delivery of a child under spinal anesthesia. The physician was engaged in repairing an episiotomy when the patient, who had been gaily conversing, stopped talking, became cyanotic, lost consciousness, and suddenly died. There can be little doubt that this death was caused by the paralysis of the respiratory centers due to the anesthetic. It was not clear whether the patient was being attended by an anesthetist or not, but from what could be gathered the physician who performed the delivery also administered the anesthetic. The Committee believes that a spinal anesthetic, when it is chosen, should be administered by a physician trained in such techniques and by one who can be in constant attendance to the patient for purposes of checking blood pressure, pulse and respiration and can be at all times thoroughly observant of the patient's general condition. The physician who is delivering the patient cannot be in two places at the same time. It may be well at this point to comment about the third anesthetic death reported in 1947. This death was one of 2 deaths classified by the Committee in Group II. This case occurred during a normal spontaneous delivery in the course of which the patient suddenly ceased breathing and died despite the supposed efforts of resuscitation through administration of oxygen. After the death occurred, it was found that the nitrous oxide tank was attached to the auxiliary oxygen. This case thoroughly illustrates the importance and necessity of careful checking by the anesthetist of apparatus, tanks, patient and everything concerned before the anesthesia is induced as well as during the anesthesia. Because 3 of the 15 maternal deaths were considered due to anesthesia, the Committee believes that it should include in this report the opinion of the New England Society of Anesthesiology that was included in last year's report since repetition may sharpen the consciousness of physicians in the consideration of the importance of anesthesia.

There are so many dangers inherent in all types of anesthesia that the success and safety of all the various methods is directly proportional to the experience and training of the person responsible. These dangers are so numerous and serious accidents are so imminent that it is imperative for a physician to be in constant attendance throughout the entire administration.

Serious or potentially fatal complications are especially prone to occur during the course of intravenous anesthesia, spinal anesthesia and caudal analgesia. These accidents are usually preventable. It is our opinion that a physician conversant with these dangers should be in constant attendance.

Group I numbers 5 cases. This represents 33.3 per cent of the maternal deaths in 1947. Of these, 2 were due to abortions. One of these involved the criminal participation of two laymen, who were charged and found guilty and are serving prison sentences. The other was a self-induced abortion ending in the only case of puerperal sepsis reported. Causes of death of the other cases in this category were myocarditis in a patient with long-standing heart disease, who did not seek medical attention and a toxemia of pregnancy in a case in which no prenatal care was sought. One patient presented herself for the first time to the physician when in labor, and was found to have a marked and severe anemia. She died after delivery, followed by an excessive post-partum hemorrhage from a flaccid and atonic uterus. The Committee believes that the medical profession must continue an increased determination to educate the public concerning the importance and necessity of prenatal care.

### COMMENTS AND RECOMMENDATIONS

In the analysis of the 15 cases studied, it was shown that almost half, or 7 cases, were probably unavoidable. Five cases or one third, were due to the neglect of the patient herself. Since this is true, and since one third of the cases occurred in mothers who had had cesarean sections, admitting that most had reasonable indications and with 3 anesthetic deaths this year the Committee believes that the following recommendations should be made.

The Committee wishes to stress the importance and necessity for good prenatal care to ensure safe and logical planning for the conduct and method of delivery. It cannot stress too much the role of the physician, the nurse, public-health agencies and hospitals in making available to the public accurate information on facilities for prenatal care on a local and state level. Although efforts have always been made to educate the adult population concerning prenatal care, the Committee recommends that the private practitioner increase his efforts toward this end, and to assist in every way the efforts of both public and private agencies in the adequate and more intensive dissemination of information. The Committee wishes to enumerate the essential components of initial prenatal care. This should consist of a complete history, that a thorough appraisal of the patient's past, present and future status can be determined, a complete physical examination including a blood test, urine test and any other indicated laboratory tests and monthly return visits for the first six or seven months, after which more frequent visits should be made if indicated. The use of special diagnostic aids such as pelvic x-ray study should be employed if necessary.

The Committee wishes to stress the importance of anesthesia in obstetrics and recommends that the obstetrician obtain the services of trained anesthetists in assisting him with his deliveries. The Committee believes that physicians should be encouraged to acquire training in the skill of anesthesia.

The Committee believes that cesarean sections are performed too frequently without clear-cut or accepted indications. To say that the pelvis is contracted does not prove disproportion. It is true that physicians today may have adequate indication to do a cesarean section, since one may have been performed for a previous delivery. The Committee believes that sections should not be performed because the patient requests the surgical procedure, unless there is a definite indication for the operation. There is too much risk in choosing a surgical delivery for the purpose of sterilization. It is recognized that sterilization may be done at the time of the section when the latter is indicated.

The Committee wishes to comment on the encouraging increase in the number of autopsies performed in this

curred in 1933, about the time the maternal-death studies began. There was a slowly receding rate through 1942, but in 1943 there was a rise in the rate, which remained through 1944 and started to drop again in 1945. In the next two years, the drop in the rate seems to be tending toward a more rapid fall. In 1946 the number of births increased from 8551 in the previous year to 11,489. There were 16 maternal deaths reported in 1946, giving a maternal death rate of 1.4. In 1947 the year of this study, there were 15

tion and should be considered responsible for her own death. There was only 1 case in the undetermined group, for the Committee, in this case, could not determine from the facts what had caused the death of the patient. It may be interesting to review some of the facts in certain of the maternal deaths studied this year.

In Group IV, 1 patient was reported as having died of acute dilatation of the heart. The patient was a 38-year-old primipara who had a contracted pelvis. A planned cesarean

TABLE 5 *Stillbirths, according to Sex, 1947\**

CAUSE	MALE	FEMALE	UNKNOWN	TOTALS
Determined in fetus, placenta and cord				
Malformations of central nervous system	13	17		30
Malformations of cardiovascular system	1			1
Malformations of other specified systems or parts	4	4		8
Unspecified congenital malformations		3		3
Cord condition without mention of placental state	14	13	1	27
Placental states without mention of cord condition	25	13		38
Placental states with mention of cord condition	1			1
Birth injury (fetal death during labor)	1	1		2
Birth injury with mention of abnormality of bones of pelvis	1			1
Birth injury with mention of malposition of fetus	3	1		4
Birth injury with mention of abnormality of forces of labor		1		1
Birth injury with mention of difficult labor but no mention of underlying condition	1	1		2
Birth injury with no mention of difficult labor	1			1
Erythroblastosis	1			1
Other causes determined in fetus	5	4		9
Conditions in mother associated with fetal death		2		2
Diabetes mellitus	1	1		2
Chronic diseases of genitourinary system	1			1
Other acute diseases and conditions	1			1
Toxemia with convulsions during pregnancy or labor (eclampsia)	2	1		3
Other toxemias of pregnancy	1	5		6
Difficult labor with mention of abnormality of bones of pelvis		1		1
Difficult labor with mention of disproportion but no mention of abnormality of pelvis	2			2
Difficult labor with mention of malposition of fetus	2			2
Difficult labor with no mention of underlying condition	1	3		4
Falls	1			1
Ill defined and unknown				
Ill defined	66	54		120
Unknown	11	8		19
Totals	159	133	1	293

\*Stillbirth rate per 1000 live births in 1947: 21.5

maternal deaths reported, and the number of births jumped to 12,912, which is an all-time high. The maternal death rate for 1947 is 1.1 per 1000 live births, an all-time low.

### MATERNAL DEATHS

There were 15 maternal deaths in 1947. The number of births was 12,912, giving a maternal death rate of 1.1 per

section was done at term, under spinal anesthesia and was completed with no incidents. Twenty-four hours after the operation, an intravenous injection of 5 per cent glucose in saline solution was administered. Almost immediately the patient had a chill, her temperature became elevated, and she died a little more than twenty-four hours after the section. Autopsy revealed nothing unusual, except what might have been expected after sudden death. The Com-

TABLE 6 *Maternal Deaths and Death Rates and Reported Cesarean Sections\* Performed, according to County Involved*

DATUM	BELKAP	CARROLL	CHESHIRE	COOS	GRAFTON	HILLS-BOROUGH	MERRIMACK	ROCKINGHAM	STRAFFORD	SULLY	TOTALS
Maternal deaths	1	0	1	2	3	2	2	2	1	1	15
Total live births (estimate)	642	430	730	776	1580	4128	1314	1484	1316	512	12,912
Maternal death rate (maternal deaths per 1000 live births)	1.56	0	1.37	2.58	1.26	0.48	1.52	1.35	1.52	1.95	1.07
Cesarean sections performed as reported by hospitals	28	20†	34	24	42	121	41	43	21*	9	183
Percentage of living infants delivered by cesarean section	4.36	†	4.66	3.07	2.66	2.93	3.12	2.89	*	1.76	2.80

\*Of the 15 maternal deaths 5 (33.3 per cent) had cesarean sections. Of all reported cesarean sections performed 1.3 per cent of the mothers having the sections died.

†Not all hospitals reported.

1000 live births. In conducting the study of maternal deaths, the Committee attempts to place each death in a specific classification or group according to where the responsibility seems to fall. To determine this classification the Committee carefully appraises all the facts and without bias places each case in one of the four groups listed above. The Committee is gratified that in 1947 the largest number of deaths were classed as unavoidable. The next largest group was assigned to the patient, who either did not seek prenatal care, refused treatment, or performed a self-inflicted abor-

mittee could not assign the death to acute dilatation of the heart, but from the facts presented, could not determine the cause of death.

The largest group, including 7 deaths, the Committee classified as unavoidable. This group of cases presents some interesting facts. These cases fell roughly into 3 groups, namely, deaths due to anesthesia, deaths due to surgical causes, one of which was uncontrollable bleeding and accidents of pregnancy, such as pulmonary embolism, and ruptured ectopic pregnancy. One of these deaths was at

The number of conjunctival petechiae increased. The temperature ranged from 102 to 103°F, and the pulse from 90 to 100, rising in the last twenty-four hours to 120. There was no other change in physical signs. On the sixth hospital day the patient died without regaining consciousness.

#### DIFFERENTIAL DIAGNOSIS

DR F DENNETTE ADAMS This case will be discussed from the standpoints, first of the underlying disease and second of the terminal illness. The history is not very helpful except that it seems to bring out clearly that the patient had a failing heart. The most likely cause of the sudden attack of weakness is concealed hemorrhage, since no mention is made of blood in the vomitus, hemorrhage, if it occurred, was below the duodenum or not in the intestinal tract at all. Pulmonary embolism is another possible cause of the episode of weakness. From the description of the murmur it seems reasonable to assume that cardiac enlargement and failure were due to aortic valvular disease. The character of the murmur—systolic in time, most marked at the second right interspace, widely distributed, transmitted to the neck and accompanied by palpable thrill—points definitely toward aortic stenosis. The murmur was louder than one ordinarily hears with atheroma of the aorta—with or without hypertension. Without knowing the previous blood-pressure level, we have no grounds for assuming that the patient ever had hypertension even though we recognize the fact that the current reading, 120 systolic, 80 diastolic, may not have represented the patient's true blood pressure, it may have been low for her because of failing myocardium or peripheral vascular failure secondary to the process causing the episode of weakness discussed above. There are three other possibilities to be considered in connection with the murmur—syphilis, rheumatic disease and calcareous aortic-valve disease. Syphilis is excluded. In syphilitic aortic disease sufficient to give so loud and extensive a systolic murmur, one would also hear a loud diastolic murmur. No mention is made of this. The negative blood Hinton test is another item of evidence against syphilitic aortic disease, it is almost always positive in cardiovascular syphilis. Without a definite history of previous rheumatic infection one cannot, with any degree of assurance, differentiate rheumatic aortic disease and calcareous disease, but on the law of probability I would vote for the latter. The patient was in the right age group, there was no history of rheumatic infection. Some authorities believe that calcareous aortic-valve disease is actually the end result of rheumatic disease. In this hospital I believe that it is regarded not as rheumatic but as an unusual arteriosclerotic manifestation. Is that correct, Dr Castleman?

DR BENJAMIN CASTLEMAN Not quite. It may well be a nonspecific infectious process, not necessarily rheumatic.

DR ADAMS In any event, I believe that the patient had calcareous aortic-valve disease. We may get help from the x-ray film, which sometimes shows calcium deposits in the leaflets, but failure to demonstrate them would not alter my opinion. The aortic second sound was not heard because the valve leaflets were fixed and did not snap shut as in the normal heart. It is harder to explain absence of the pulmonic second sound unless it was concealed by the very loud murmur. Theoretically, with left-sided failure and pulmonary congestion, back pressure on the pulmonic valve should make the pulmonic second sound louder than normal. The ankle edema could have been due to any one of several conditions: right-sided heart failure, thrombophlebitis or phlebothrombosis. If it was due to right-sided failure, one would expect a palpable, perhaps tender liver and distended neck veins. Varicosities are not mentioned, it seems probable that if the edema had been due to this disturbance it should not have been so pronounced after some days in bed. Thrombotic disease of the leg veins is favored by congestive failure and inactivity of the patient. One cannot with certainty explain the signs in the lungs but only mention the probabilities: congestive failure, pneumonia, pulmonary infarction or any combination of these. The x-ray film may help us decide, but often the roentgenologist cannot be sure either.

The urinary examination is consistent with congestion or perhaps, as we will see later, with infection or both. The findings do not necessarily indicate a primary nephritis. The blood picture indicates acute infection. Perhaps Dr Wyman can help us out with the lungs.

DR STANLEY M WYMAN The mottling in the right lung is more pronounced in the lower portion. There is some in the upper lobe as well. The left-lung field is relatively spared, but there is some mottling in the left base. This film was taken with the patient lying on her back, and the heart shadow cannot be measured in terms of cardiothoracic ratio, the heart appears to be prominent in the region of the left ventricle, dipping down below the diaphragm, and is prominent to the right as well. The aorta is tortuous, arising at this point and extending far to the right, explaining why the murmur was heard so far to the right. Calcification is visible in the arch. The lateral view shows the heart to extend rather far posteriorly in the chest. It is definitely increased in the anteroposterior diameter, suggesting that the patient has been a victim of emphysema and fibrosis for some time. This shadow suggests enlargement of the left auricle. The hilar vascular shadows seen on the left do not appear unusually prominent.

year's series of deaths. It wishes to encourage this practice that actual causes of death may be verified and properly classified.

The Committee is confident that the drop in post-partum infections as a cause of death has come to stay. The only infections reported in cases in this series were due to neglect on the part of the patient or to criminal interference. It may be anticipated that infection as a cause of death in maternity will disappear.

The Committee would like to comment concerning the stillbirth rate and infant death rate for 1947 by pointing out that these rates have reached an all-time low. The stillbirth rate for 1947 was 21.5 per 1000 live births. The infant death rate for 1947 was 28.1 per 1000 live births, or slightly lower than the rate for 1946, which was 28.7 per 1000 live births. However, it should be noted that up to 1944, the infant mortality rate was as high as 37 per 1000 live births.

Since there were 9 stillbirths reported as due to erythroblastosis and since there may have been many more, the Committee would like to include in its recommendations a statement concerning the importance of the Rh factor in obstetrics. In cases in which the mother is Rh— and the father is Rh+, danger may exist for the fetus, in that fatality may occur two or three weeks before term or shortly after birth from erythroblastosis and hemolytic jaundice.

The Committee stresses that it is important that laboratory facilities throughout the State provide the means of determining the presence of this factor in the mothers' blood prenatally, that the possibility of such danger may be foreseen. Occasionally a stillbirth will occur that is perhaps preventable.

The Committee recommends that mothers be tested for Rh factor and that when such fetuses are born they be carefully watched for the development of severe hemolytic jaundice and a marked drop in the red cells, and that treatment be available in the form of transfusion from an Rh— donor, accurately typed and cross-matched.

The Committee wishes to thank all physicians and hospitals responding to the requests for information that was necessary to conduct this study and to make a report. As in the past the Committee wishes to state that any recommendations or suggestions from the physicians throughout the State will be welcome.

The Committee wishes to acknowledge with appreciation and co-operation of the Department of Health through its Divisions of Maternal and Child Health and Vital Statistics in furnishing data and personnel in the preparation of this report.

ROBERT O. BLOOD, M.D., *Chairman*  
BENJAMIN P. BURPEE, M.D.  
JAMES SANDERS, M.D.

Dr. Sycamore moved that the recommendations of the Committee be approved.

This motion was duly seconded and was carried.

(To be concluded)

## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

EDITH E. PARRIS, *Assistant Editor*

#### CASE 34441

##### PRESENTATION OF CASE

An eighty-year-old widow was admitted to the hospital complaining of weakness.

The patient had been in slight congestive failure about six weeks previously and had taken digitalis since that time. One month prior to admission she had a severe respiratory infection, from which she apparently recovered except for a persistent cough. Four hours prior to admission, while preparing supper, she experienced a sudden attack of weakness, was nauseated and vomited. She was seen by a physician, who referred her to the hospital.

Physical examination revealed the heart to be enlarged, the border of cardiac dullness extending 11 cm. to the left of the midsternal line in the fifth interspace. A rough, Grade IV systolic murmur with an associated thrill was present, most marked in the second interspace, 7 cm. to the right of the midsternal line. The murmur was widely transmitted,

both to the neck and over the whole chest anteriorly. Neither the aortic nor the pulmonic second sound could be heard. Rales were present at both bases posteriorly, particularly on the right, where there was a small area of bronchovesicular breathing. The liver was not palpated. Marked edema of the ankles was present. The left knee jerk was more active than the right.

The temperature was 104°F, the pulse 100, and the respirations 30. The blood pressure was 120 systolic, 80 diastolic.

Examination of the blood disclosed a white-cell count of 26,300, with 85 per cent neutrophils, 3 per cent lymphocytes, 10 per cent monocytes and 2 per cent late myelocytes. Frequent band forms were observed. Urinalysis showed a specific gravity of 1.024 and a ++ test for albumin, with occasional casts, 40 red cells and 25 white cells per high-power field in the sediment. The blood Hinton test was negative. X-ray examination revealed the heart to be enlarged in the region of the left ventricle. The aorta was tortuous and calcified. The right leaf of the diaphragm was slightly elevated and poorly defined, owing to poor aeration of the right lower lobe. The right lower lobe showed some diffuse and mottled increased density with one larger patch. The left lung appeared normal.

On the third hospital day the patient was "drowsy but responsive," and petechiae were observed on the conjunctivas. The temperature continued elevated, and a blood culture showed a growth of *Staphylococcus aureus* on two occasions. She gradually became unresponsive and then comatose. On the fifth hospital day it was possible to demonstrate a flaccid paralysis of the left arm and leg.

DR ADAMS I cannot rule out either one with certainty. On the law of probability a murmur of this type in an eighty-year-old woman is more likely due to aortic calcareous disease than to rheumatic disease. As I said at the outset, some observers believe that calcareous aortic disease is the end result of rheumatic disease. Conceivably, such a murmur could be due to a congenital bicuspid aortic valve, with superimposed calcareous disease.

#### CLINICAL DIAGNOSES

Calcific aortic stenosis  
Acute bacterial endocarditis  
Cerebral emboli

#### DR ADAMS'S DIAGNOSES

Calcareous aortic stenosis, with hypertrophy and dilatation of heart  
Acute bacterial endocarditis of aortic valve  
Generalized septicemia (*Staph aureus*)  
Multiple septic infarcts of brain, lungs, kidneys, spleen and perhaps other viscera  
Thrombophlebitis of leg veins?

#### ANATOMICAL DIAGNOSES

*Endocarditis acute, bacterial, aortic calc* (*Staph aureus*)  
*Calcific aortic stenosis*  
*Mycotic aneurysm, left circumflex coronary artery, with rupture*  
Hemopericardium  
Infarcts, septic, of spleen, kidney and brain  
Bronchitis, acute, purulent  
Pulmonary edema  
Pulmonary fibrosis, right

#### PATHOLOGICAL DISCUSSION

DR CASTLEMAN This patient did have calcific aortic stenosis. The cusps were thickened with the calcareous deposits in the sinuses of Valsalva, which is in contrast to what is seen in the rheumatic heart. In the true rheumatic heart stenosis is produced by interadherence between the cusps, whereas in this type of case stenosis is more apt to be produced by calcareous masses within the sinuses of Valsalva. There was a vegetation on the aortic valve and also one on the mitral valve.

DR ADAMS But not a large one?

DR CASTLEMAN No.

A PHYSICIAN Would you not have expected a murmur in the mitral region?

DR ADAMS That could have been obscured by the aortic murmur.

DR CASTLEMAN The pericardial cavity contained about 200 cc of blood, and on the epicardium were shreds of blood clot. Along the course of the circumflex branch of the left coronary artery was a huge, very red, bulbous mass. Careful dissection of this area revealed a tear in this mass, which proved to be a mycotic aneurysm. I am certain

that this tear was the cause of the sudden attack of weakness. It is not the same as ruptured heart that produces death suddenly because of cardiac tamponade. Here the opening from the coronary artery was enough to fill the pericardial sac partially but not to balloon it out to produce sudden tamponade. As might have been expected, there were septic infarcts of the kidney, of the spleen and also of the liver, which is not too common. The bronchi were filled with polymorphonuclears but there was no acute pneumonia anywhere. There was some edema, but most of the process seen in the lungs was due to fibrosis. The patient had long-standing fibrosis with slight bronchiectasis as a result of scarring, especially marked in the right lower lobe, but also present in the right middle and upper lobes. The infections four years previously were probably just exacerbations of an old chronic, fibrotic process.

DR WYMAN How about the aorta?

DR CASTLEMAN It was tremendously dilated and arteriosclerotic, and showed calcification in the descending portion, not in the ascending portion. This absence of arteriosclerosis in the ascending aorta is almost the rule with calcareous aortic stenosis, and is one of the arguments that is used against believing that the valvular process is arteriosclerotic. When arteriosclerosis affects the ascending aorta one has to think of syphilis.

DR ADAMS The head was not examined?

DR CASTLEMAN Yes, it was, we found an infarct of the right parietal lobe that caused the terminal symptoms, and, in addition, numerous small septic infarcts were noted throughout the brain.

A PHYSICIAN Did an electrocardiogram show any coronary-artery involvement?

DR CASTLEMAN The patient was too sick. No electrocardiogram was taken. Until the blood cultures became positive on the fourth day she really had not been given all the penicillin possible — only 30,000 units every three hours; the dose was doubled on the fourth day.

#### REFERENCES

1. Buchbinder, W. C. and Saphir, O. Heart failure in subacute bacterial endocarditis. *Arch. Int. Med.* 64: 36-347, 1939.
2. de Navasquez, S. Incidence and pathogenesis of myocardial lesions in subacute bacterial endocarditis. *J. Path. & Bact.* 49: 33-38, 1939.

#### CASE 3442

#### PRESENTATION OF CASE

*First admission* A forty-five-year-old woman, a telephone operator, was seen in the Emergency Ward because of painful swollen legs.

The patient had experienced bouts of ankle and lower-leg swelling for the past ten years, each attack lasting one to six weeks. This swelling disappeared after she stopped working. Three months before entry she had an initial attack of palpitation and

DR ADAMS Can you see calcification in the aortic-valve leaflets?

DR WYMAN This film is not good enough to make such an observation. If a heavy film had been taken, with the patient rotated so that the aortic-valve area, which lies here, were away from the spine, we might have seen it better. There is a suggestion of an area of density at this point where the aortic valve might lie, but it is not sufficient for me to say that it is calcification. The heart is shifted to the right, the right lung is definitely underaerated. This shadow shows tortuosity of the aorta.

DR ADAMS Just a large aorta?

DR WYMAN Yes. The ascending portion is wide.

DR ADAMS With this degree of widening of the aorta, one must think of aneurysm, but aortic arteriosclerosis and calcareous aortic disease are much more likely.

Having committed myself to a diagnosis of the primary disease, I must now explain the terminal events. The fever and leukocytosis indicate serious acute infection. With a history of recent respiratory infection, followed by persistent cough and signs of trouble in the lungs, one would first postulate lobar or bronchopneumonia. The conjunctival petechiae strongly suggest septicemia, and the report of two blood cultures positive for *Staph aureus* confirm this diagnosis. Septicemia occurring in a patient with valvular heart disease usually means endocarditis, *Staph aureus* infection is an acute fulminating disease, and endocarditis, if present, is acute. In the absence of any other portal of entry, such as a furuncle or other local abscess, it seems reasonable to assume that the staphylococcus entered through the respiratory tract, implanted itself on the chronically damaged heart valve and established an acute bacterial endocarditis, which, in turn, gave rise to multiple septic emboli. One could postulate that the loud murmur was due to the presence of a large vegetation on the valve, but only if it were known that the murmur had not been there previously or that a previously existing murmur had changed appreciably within the past few days. Lacking this information, it seems wiser to suppose that the murmur was due to calcareous disease. If we assume the presence of a septic vegetation on the heart valve, it is easy to explain the other terminal findings. Multiple septic emboli would account for the neurologic signs, — inequality of knee jerks on initial physical examination and the subsequent left-sided paralysis, — the urinary findings, especially the red cells and white cells, and the pulmonary signs.

To summarize, I believe this patient had calcareous disease of the aortic valve, with superimposed acute vegetative endocarditis on the valve, and multiple septic emboli involving the brain, kidneys, lungs and perhaps other organs, notably the spleen, and that she died of the septicemic

process. Thrombophlebitis of the legs cannot be excluded, but there is no definite evidence that it existed.

DR CASTLEMAN One does not usually see septic infarcts in the lung with a bacterial endocarditis unless they are coming from the right side of the heart.

DR ADAMS I am not certain, but it seems to me that I have seen cases of acute septic endocarditis in which septic infarcts have been found on both sides of the circulatory system and that one does not necessarily have to presuppose damage on the right side of the heart to get trouble in the lungs. One could also postulate emboli arising in the legs as the cause of the pulmonary signs.

DR CASTLEMAN That would be all right.

DR ADAMS In generalized pyemia cannot one find embolic abscess on both sides?

DR CASTLEMAN One can get abscesses in the lung with generalized septicemia.

DR ADAMS That is just what I am talking about.

DR CASTLEMAN What caused the sudden attack of weakness four hours before admission?

DR ADAMS I cannot answer that question. A certain number of old people who get severe infection do get sick terribly suddenly, and this may be the answer. Earlier in the discussion I stated that a sudden attack of weakness is most likely due to hemorrhage, but here we have no evidence on which to base a diagnosis of hemorrhage. A third possibility would be a pulmonary embolus.

A PHYSICIAN How about involvement of the coronary vessels?

DR ADAMS Yes. An embolus breaking off the aortic valve and landing in a coronary vessel might have caused the episode.

DR CASTLEMAN One almost always finds tiny emboli in the small coronary vessels, and Buchbinder and Saphir<sup>1</sup> believe that the miliary infarcts that develop are sufficiently numerous to produce real heart failure. In a series of 40 autopsied cases of subacute bacterial endocarditis, they found evidence of heart failure in 45 per cent. On the other hand, de Navasquez,<sup>2</sup> admitting the finding of miliary myocardial infarcts in subacute bacterial endocarditis in 95 per cent of the cases, was unable to demonstrate any relation with heart failure. Now that so many of these cases are being treated successfully, the healed miliary infarcts may become an important factor in the development of heart failure.

DR ADAMS This patient certainly presented the picture of infection rather than heart failure from the standpoint of the terminal illness. I believe that the infection was generalized septicemia.

A PHYSICIAN I still cannot see how a rheumatic heart can be ruled out completely. It is true that this was not a classic picture of rheumatic heart disease. I wonder also how you rule out congenital heart disease.

DR ADAMS I cannot rule out either one with certainty. On the law of probability a murmur of this type in an eighty-year-old woman is more likely due to aortic calcareous disease than to rheumatic disease. As I said at the outset, some observers believe that calcareous aortic disease is the end result of rheumatic disease. Conceivably, such a murmur could be due to a congenital bicuspid aortic valve, with superimposed calcareous disease.

#### CLINICAL DIAGNOSES

Calcific aortic stenosis  
Acute bacterial endocarditis  
Cerebral emboli

#### DR ADAMS'S DIAGNOSES

Calcareous aortic stenosis, with hypertrophy and dilatation of heart  
Acute bacterial endocarditis of aortic valve  
Generalized septicemia (*Staph aureus*)  
Multiple septic infarcts of brain, lungs, kidneys, spleen and perhaps other viscera  
Thrombophlebitis of leg veins?

#### ANATOMICAL DIAGNOSES

Endocarditis, acute, bacterial, aortic valve (*Staph aureus*)  
Calcific aortic stenosis  
Mycotic aneurysm, left circumflex coronary artery, with rupture  
Hemopericardium  
Infarcts septic, of spleen, kidney and brain  
Bronchitis, acute, purulent  
Pulmonary edema  
Pulmonary fibrosis, right

#### PATHOLOGICAL DISCUSSION

DR CASTLEMAN This patient did have calcific aortic stenosis. The cusps were thickened with the calcareous deposits in the sinuses of Valsalva, which is in contrast to what is seen in the rheumatic heart. In the true rheumatic heart stenosis is produced by interadherence between the cusps, whereas in this type of case stenosis is more apt to be produced by calcareous masses within the sinuses of Valsalva. There was a vegetation on the aortic valve and also one on the mitral valve.

DR ADAMS But not a large one?

DR CASTLEMAN No.

A PHYSICIAN Would you not have expected a murmur in the mitral region?

DR ADAMS That could have been obscured by the aortic murmur.

DR CASTLEMAN The pericardial cavity contained about 200 cc of blood, and on the epicardium were shreds of blood clot. Along the course of the circumflex branch of the left coronary artery was a huge, very red, bulbous mass. Careful dissection of this area revealed a tear in this mass, which proved to be a mycotic aneurysm. I am certain

that this tear was the cause of the sudden attack of weakness. It is not the same as ruptured heart that produces death suddenly because of cardiac tamponade. Here the opening from the coronary artery was enough to fill the pericardial sac partially, but not to balloon it out to produce sudden tamponade. As might have been expected, there were septic infarcts of the kidney, of the spleen and also of the liver, which is not too common. The bronchi were filled with polymorphonuclears but there was no acute pneumonia anywhere. There was some edema, but most of the process seen in the lungs was due to fibrosis. The patient had long-standing fibrosis with slight bronchiectasis as a result of scarring, especially marked in the right lower lobe, but also present in the right middle and upper lobes. The infections four years previously were probably just exacerbations of an old, chronic, fibrotic process.

DR WYMAN How about the aorta?

DR CASTLEMAN It was tremendously dilated and arteriosclerotic, and showed calcification in the descending portion, not in the ascending portion. This absence of arteriosclerosis in the ascending aorta is almost the rule with calcareous aortic stenosis, and is one of the arguments that is used against believing that the valvular process is arteriosclerotic. When arteriosclerosis affects the ascending aorta one has to think of syphilis.

DR ADAMS The head was not examined?

DR CASTLEMAN Yes, it was, we found an infarct of the right parietal lobe that caused the terminal symptoms, and, in addition, numerous small septic infarcts were noted throughout the brain.

A PHYSICIAN Did an electrocardiogram show any coronary-artery involvement?

DR CASTLEMAN The patient was too sick. No electrocardiogram was taken. Until the blood cultures became positive on the fourth day she really had not been given all the penicillin possible — only 30,000 units every three hours, the dose was doubled on the fourth day.

#### REFERENCES

1. Buchbinder W. C. and Saphir O. Heart failure in subacute bacterial endocarditis. *Arch Int Med* 64 336-347 1959
2. de Navasquez S. Incidence and pathogenesis of myocardial lesions in subacute bacterial endocarditis. *J Path & Bact* 49 35-38 1959

#### CASE 3442

#### PRESENTATION OF CASE

*First admission* A forty-five-year-old woman, a telephone operator, was seen in the Emergency Ward because of painful swollen legs.

The patient had experienced bouts of ankle and lower-leg swelling for the past ten years, each attack lasting one to six weeks. This swelling disappeared after she stopped working. Three months before entry she had an initial attack of palpitation and

DR ADAMS Can you see calcification in the aortic-valve leaflets?

DR WYMAN This film is not good enough to make such an observation. If a heavy film had been taken, with the patient rotated so that the aortic-valve area, which lies here, were away from the spine, we might have seen it better. There is a suggestion of an area of density at this point where the aortic valve might lie, but it is not sufficient for me to say that it is calcification. The heart is shifted to the right, the right lung is definitely underaerated. This shadow shows tortuosity of the aorta.

DR ADAMS Just a large aorta?

DR WYMAN Yes. The ascending portion is wide.

DR ADAMS With this degree of widening of the aorta, one must think of aneurysm, but aortic arteriosclerosis and calcareous aortic disease are much more likely.

Having committed myself to a diagnosis of the primary disease, I must now explain the terminal events. The fever and leukocytosis indicate serious acute infection. With a history of recent respiratory infection, followed by persistent cough and signs of trouble in the lungs, one would first postulate lobar or bronchopneumonia. The conjunctival petechiae strongly suggest septicemia, and the report of two blood cultures positive for *Staph aureus* confirm this diagnosis. Septicemia occurring in a patient with valvular heart disease usually means endocarditis, *Staph aureus* infection is an acute fulminating disease, and endocarditis, if present, is acute. In the absence of any other portal of entry, such as a furuncle or other local abscess, it seems reasonable to assume that the staphylococcus entered through the respiratory tract, implanted itself on the chronically damaged heart valve and established an acute bacterial endocarditis, which, in turn, gave rise to multiple septic emboli. One could postulate that the loud murmur was due to the presence of a large vegetation on the valve, but only if it were known that the murmur had not been there previously or that a previously existing murmur had changed appreciably within the past few days. Lacking this information, it seems wiser to suppose that the murmur was due to calcareous disease. If we assume the presence of a septic vegetation on the heart valve, it is easy to explain the other terminal findings. Multiple septic emboli would account for the neurologic signs, — inequality of knee jerks on initial physical examination and the subsequent left-sided paralysis, — the urinary findings, especially the red cells and white cells, and the pulmonary signs.

To summarize, I believe this patient had calcareous disease of the aortic valve, with superimposed acute vegetative endocarditis on the valve, and multiple septic emboli involving the brain, kidneys, lungs and perhaps other organs, notably the spleen, and that she died of the septicemic

process. Thrombophlebitis of the legs cannot be excluded, but there is no definite evidence that it existed.

DR CASTLEMAN One does not usually see septic infarcts in the lung with a bacterial endocarditis unless they are coming from the right side of the heart.

DR ADAMS I am not certain, but it seems to me that I have seen cases of acute septic endocarditis in which septic infarcts have been found on both sides of the circulatory system and that one does not necessarily have to presuppose damage on the right side of the heart to get trouble in the lungs. One could also postulate emboli arising in the legs as the cause of the pulmonary signs.

DR CASTLEMAN That would be all right.

DR ADAMS In generalized pyemia cannot one find embolic abscess on both sides?

DR CASTLEMAN One can get abscesses in the lung with generalized septicemia.

DR ADAMS That is just what I am talking about.

DR CASTLEMAN What caused the sudden attack of weakness four hours before admission?

DR ADAMS I cannot answer that question. A certain number of old people who get severe infection do get sick terribly suddenly, and this may be the answer. Earlier in the discussion I stated that a sudden attack of weakness is most likely due to hemorrhage, but here we have no evidence on which to base a diagnosis of hemorrhage. A third possibility would be a pulmonary embolus.

A PHYSICIAN How about involvement of the coronary vessels?

DR ADAMS Yes. An embolus breaking off the aortic valve and landing in a coronary vessel might have caused the episode.

DR CASTLEMAN One almost always finds tiny emboli in the small coronary vessels, and Buchbinder and Saphir<sup>1</sup> believe that the miliary infarcts that develop are sufficiently numerous to produce real heart failure. In a series of 40 autopsied cases of subacute bacterial endocarditis, they found evidence of heart failure in 45 per cent. On the other hand, de Navasquez,<sup>2</sup> admitting the finding of miliary myocardial infarcts in subacute bacterial endocarditis in 95 per cent of the cases, was unable to demonstrate any relation with heart failure. Now that so many of these cases are being treated successfully, the healed miliary infarcts may become an important factor in the development of heart failure.

DR ADAMS This patient certainly presented the picture of infection rather than heart failure from the standpoint of the terminal illness. I believe that the infection was generalized septicemia.

A PHYSICIAN I still cannot see how a rheumatic heart can be ruled out completely. It is true that this was not a classic picture of rheumatic heart disease. I wonder also how you rule out congenital heart disease.

lar 270 There were multiple ventricular ectopic beats

Four days after admission the patient was started on puriodigin and ammonium chloride. This was followed by nausea and vomiting, which became progressively worse. This therapy was stopped two days later. The nausea and vomiting persisted for five days after the digitalis had been withheld. At this time the patient showed a questionable slight sacral edema and a slight nonpitting edema of the stumps. The lungs were dry. There was great and frequent variation in the degree of pulse deficit. The apical pulse rate was 120 and grossly irregular and the radial pulse 45. On the thirteenth hospital day the patient was given cedilanid intravenously after which the nausea stopped. This was continued for four days, and then puriodigin again begun. One day later, the pulse had slowed and was regular, with rare extrasystoles. She no longer had a pulse deficit. An electrocardiogram taken on the following day disclosed a normal rhythm with a rate of 95.

With the exception of a short period of bigeminal rhythm, the patient remained improved symptomatically for the next eight days. On the twenty-seventh hospital day, however, she suddenly developed a severe, sharp pain in the lower anterior portion of the right side of the chest. Physical examination of the chest was negative, the pain was relieved by 75 mg of demerol subcutaneously, and the patient did not look acutely ill. Half an hour later, however, the blood pressure and pulse were unobtainable. The skin was cold and sweaty but not cyanotic. There were scattered coarse rales in both lungs.

The patient remained in collapse for two or more hours. She gradually showed improvement, however, and six hours later the blood pressure was 105 systolic, 80 diastolic. The pulse was good and regular. An electrocardiogram revealed the presence of an infrequent fusion beat.

The patient suffered a similar episode of shock on the following day, from which she again recovered. On the afternoon of the next day she asked for the oxygen mask, having no definite complaints but saying that she "felt scared." Half an hour later she was found breathing very rapidly and gasping for breath. She became cyanotic and died a few minutes later.

#### DIFFERENTIAL DIAGNOSIS

DR HOWARD B. SPRAGUE This is a rather peculiar story, as usual in these exercises. At the age of thirty-five the patient began to have attacks of edema of the ankles and lower legs, relieved by rest. These attacks lasted from one to six weeks. There does not seem to have been any history of dyspnea at that time, and one wonders whether the sedentary occupation of telephone operator, rather than a cardiac condition, led to the development

of edema of the legs. Of course, swelling of the legs, as studied in patients in the Out-Patient Department, is more commonly not due to heart disease than due to heart disease, but we do have evidence as we go along that there was something wrong with this patient's heart. She apparently had some venous difficulty with the legs, and it was not particularly related to the final disease. However, ten years later, she began to have palpitation, swelling of the ankles and what was probably ectopic rhythm, auricular fibrillation. These attacks recurred and were relieved by cardiac therapy, at least so far as the edema is concerned. Previously, this had been alleviated by stopping work, but now digitalis and mercurials were necessary. The sudden onset six days before admission consisted of an attack of interference with circulation of the legs. By the time of admission there were cyanosis, pain and tenderness and some swelling and gangrene of the feet and absence of arterial pulsation. From the fact that cyanosis was present and from what I interpreted as some pulsation of the femoral arteries, I judge that this was a partial occlusion of the circulation, presumably at the bifurcation of the iliac vessels or above. The electrocardiogram suggested some left, or at least the absence of right, ventricular strain pattern. The blood pressure was somewhat elevated, the diastolic pressure was 110, and the heart was enlarged to the left.

What about this red herring of the one attack of crushing pain in the chest? When did she have that? Can anyone answer that? Was it in relation to this episode in which the circulation of the legs was obstructed, or was that something that occurred some time in the past? We do not know.

The second admission, three and a half months later, seems to have been that of a person with cardiac difficulty, and therapy was hard to manage. There was some evidence of digitalis intoxication, such as bigeminy, and the cardiac findings were those, presumably, of some pulmonary hypertension. The pulmonic second sound was accentuated, and there was a definitely enlarged heart to the left.

Are the x-ray films available?

DR JAMES J. MCCORT Yes. This film of the chest was made at the time of the first admission. The heart is definitely enlarged to the left and most likely represents enlargement of the left ventricle. The pulmonary vascular markings are within normal limits. The aorta is not tortuous or sclerotic. Both lungs are clear, there is no fluid in the costophrenic sinuses. This next chest examination, three and a half years later at the time of the third admission, shows a large heart, again with enlargement to the left. The lungs are clear and no fluid can be demonstrated in the costophrenic sinuses. On the third examination made three weeks after the third admission, the heart is unchanged in size, but there is some accentuation of the vascular markings as compared with the previous examination.

nervousness associated with swelling of the ankles. Such attacks recurred with almost any form of exercise. At about this same time she was told that she had heart disease and was given digitalis and mercupurin, after which the edema disappeared. Six days before admission the legs suddenly became blue, cold and painful. She never had orthopnea or cough but did have one attack of pain in the upper chest, crushing in character. She denied having any history of heart disease when young.

On physical examination the heart seemed to be enlarged to the left, the rhythm was regular. An inconstant gallop with frequent extrasystoles and a very soft systolic murmur were heard at the apex. The legs were swollen, bluish and tender, the feet were gangrenous. There was no arterial pulsation below the femoral arteries.

The blood pressure was 154 systolic, 110 diastolic.

An electrocardiogram showed a normal rhythm at a rate of 90, a PR interval of 0.19 second, low upright T waves in Leads 1 and 2 and a flat T wave in Lead 3, there was slight slurring of the QRS complexes and a tendency to left-axis deviation. The T waves were upright in Lead CF<sub>2</sub>, low upright in Lead CF<sub>4</sub>, and flat in Lead CF<sub>3</sub>, the R wave was low in Lead 4.

Bilateral low-thigh amputations were done, followed two days later by bilateral ligations of the common femoral veins. The patient was placed on a cardiac regime and discharged twenty-one days after admission feeling well.

*Second admission* (approximately three and a half months later). In the interval the patient was followed in the Out-Patient Clinic, where she complained of intermittent nausea, vomiting, palpitation and swelling of the stumps. An electrocardiogram showed bigeminy and other findings interpreted as digitalis effect.

Physical examination revealed the heart to be enlarged, the point of maximal intensity being 13 cm to the left of the midsternal line in the sixth interspace, it was diffuse and forceful. There was a Grade I apical systolic murmur, which was not transmitted. The pulmonic second sound was split and markedly accentuated. There was no gallop rhythm. The liver edge was not palpable. There was slight pitting edema of the stumps.

The blood pressure was 150 systolic, 100 diastolic.

The blood and urine were not remarkable. The nonprotein nitrogen was 30 mg, and the total protein 7.3 gm per 100 cc, with 4.92 gm of albumin and 2.38 gm of globulin. A blood Hinton test was negative. The circulation time with calcium gluconate was twenty seconds (arm to tongue) and with ether, ten seconds (arm to lung). The venous pressure in the antecubital vein 10 cm above the posterior axillary line was equivalent to 11.75 cm of water. The vital capacity was 2.8 liters, or 82 per cent. An electrocardiogram showed

bigeminy in Leads 1 and 4, with ventricular premature beats occurring after each normal beat. The axis was normal. The T waves were flat in Leads 1 and 4 and inverted in Leads 2 and 3. The ST segments were sagging in Leads 2 and 3. Digitalis was withheld for two weeks, transient bouts of bigeminy persisted, however. Edema of the stump was absent at the end of this time. Digitalis was reconstituted in small doses, and the patient was discharged.

*Final admission* (approximately three and a half years later). Following the second hospitalization, the patient showed marked progressive improvement on very limited activity. The pulse was regular, the murmur previously heard disappeared, and she suffered no shortness of breath or edema. One month before entry she developed nausea and slowly progressive swelling of the stumps and abdominal wall. She had only rare vomiting. The nausea was not associated with pain or diarrhea and diminished somewhat during the following two weeks. At that time, however, two weeks before admission, she noted dyspnea and orthopnea. Four days later she experienced a severe episode of sharp substernal pain, which "took her breath away." She was given an injection by a physician, which brought about relief ten minutes after the onset of pain. The nausea persisted, and there was progressive edema, dyspnea, orthopnea and weakness. She had no digitalis during the two weeks before admission.

Physical examination revealed a well developed, well nourished woman, who was comfortable on two pillows. The abdominal wall, sacrum and stumps appeared full but showed very little pitting. The skin was moist, and there was no evidence of cyanosis. The apex of the heart was 13 cm to the left of the midsternal line in the sixth interspace. The sounds were distant. There was a Grade II systolic murmur, heard best just to the left of the sternum. The pulmonic second sound was greater than the aortic second sound. There were numerous extrasystoles. The liver edge was slightly tender and was felt two fingerbreadths below the costal margin.

The temperature was normal, the pulse 110, and the respirations 24. The blood pressure was 120 systolic, 82 diastolic.

Laboratory study disclosed a prothrombin time of 20 seconds (control, 16 seconds). The nonprotein nitrogen was 44 mg, the total protein 5.6 gm, and the cholesterol 208 mg per 100 cc, and the sodium 136.7 milliequiv per liter.

A roentgenogram showed the heart grossly enlarged, the cardiothoracic ratio being 175.24/0. The left-lower-lung field was almost entirely obliterated by the overlying heart shadow.

An electrocardiogram done on the day following admission was interpreted as showing auricular flutter, the ventricular rate was 120, and the auricu-

aortic second sound was less than the pulmonic I think that she had had an embolus at the bifurcation of the aorta, presumably an embolus arising from the heart. But other sources can be the aorta itself, and extremely rarely the pulmonary veins. Just for the dubious credit of having mentioned dissecting aneurysm of the aorta, I think I should put it in but with several question marks.

DR EDWARD F. BLAND: Let us ask Dr Gephart if he would comment on why the common femoral iliac veins were tied following low amputation. Was that to ensure circulation locally or was it a preventive measure?

DR F. THOMAS GEPHART: It was a preventive measure. At amputation a few years back, although we still do it occasionally, we more frequently tied the common femoral veins to prevent pulmonary embolism from the stump. It was purely a protective measure.

DR MALLORY: Have you any comment on the cardiac disease, Dr Bland?

DR BLAND: No, but I am not sure what Dr Sprague's final diagnosis is.

DR SPRAGUE: I would have to call it hypertensive heart disease for want of a better diagnosis.

DR BLAND: This case was a puzzle, as you see — it may still be after Dr Mallory presents his findings.

DR RICHARD J. CLARK: Where does Dr Sprague think the terminal emboli came from? If there were terminal pulmonary emboli, what was the source?

DR SPRAGUE: Presumably in the venous system above where they ligated.

DR BLAND: For the sake of the record I think it is correct that Dr Paul D. White saw the patient some time before the final admission, and he, like the rest of us, was puzzled but decided that she had heart disease of undetermined cause, or perhaps she belonged to the small group of cases that Dr Mallory may have trouble in deciding about too.

#### CLINICAL DIAGNOSES

Myocarditis of unknown etiology?

Pulmonary embolism

#### DR SPRAGUE'S DIAGNOSES

Cardiac disease of unknown etiology (hypertensive?)

Embolism to bifurcation of aorta

Terminal pulmonary embolism

#### ANATOMICAL DIAGNOSES

Hypertrophy and dilatation of heart, generalized

Coronary arteriosclerosis with occlusion, descending branch of right coronary artery

Infarct of right ventricle

Mural thrombi of right auricle and right ventricle

Pulmonary emboli, multiple, with infarction

Amputation of legs

#### PATHOLOGICAL DISCUSSION

DR MALLORY: There is a comment in the record by Dr White three years ago, suggesting the probability of idiopathic myocarditis of the type described by Levy.\* I think, as in so many of these clinically difficult cases, the problem remains difficult after autopsy. I can only tell you what we found. The heart was very diffusely enlarged, in both right and left ventricles. We were particularly impressed by the enlargement in the right ventricle. There were thrombi present in the right auricle and numerous thrombi overlying the endocardium in the right ventricle. There were some gross foci of scarring in the right ventricle. The large coronary branches were relatively free from atheroma, but looking over the heart a second time we demonstrated an occlusion of one of the terminal branches of the right coronary artery. Microscopical sections from the right ventricle showed an area of infarction, underlying the thrombus. Sections of the left ventricle revealed only a spotty fibrosis, with nothing to suggest infarction. The aorta showed a rather minimal degree of arteriosclerosis. We found absolutely nothing in the left side of the heart to provide a focus for systemic embolism. Of course, that embolism occurred four years previously. The endocardium of the left ventricle was a little thick. It is possible that there was thrombosis at one time, most of which broke off, and the fibrous healing of the remainder showed only as a thickened endocardium. The patient had numerous pulmonary infarcts for which there were two sources — the right auricle and the right ventricle — so I do not believe we have to assume that she had further trouble in the remainder of the iliac veins. The amputated legs showed complete thrombotic occlusion of the popliteal vessels. About a month before death she had a rather definite episode of gnawing, substernal pain, and the infarct in the right ventricle was histologically compatible with that duration. I think those two episodes can be put together — first cardiac infarction and then pulmonary embolism secondary to the intracardiac thrombosis. We have no etiologic explanation for the diffuse hypertrophy of the heart. As Dr Sprague suggests, it may have been hypertensive heart disease, although the hypertension was not very convincing in the later period of life, or as Dr White suggested, it was at some earlier period an idiopathic enlargement of the heart, which we can no longer prove.

DR SPRAGUE: Was there a separate embolus in each popliteal artery, or was it a thrombotic process?

DR MALLORY: The emboli were apparently separate, we do not know.

\*Levy, R. L., and von Glahn, W. C. Cardiac hypertrophy of unknown cause: study of clinical and pathologic features in 10 adults. *Am Heart J* 28:714-741, 1944.

These last two films, on the day before death and on the day of death, are taken with the patient lying down and are not too satisfactory. However, there is a suggestion of an area of slightly increased density in the right perihilar region and a smaller one in the right-lower-lung field. They may represent infarcts, but that is difficult to determine because of slight motion.

**DR. SPRAGUE:** The patient had improved for three and a half years. She had no legs, so she could not be very active presumably, and there was not too much test of her cardiac function. Auricular flutter was present on the third admission. I neglected one note about the second admission that the renal findings do not suggest an underlying kidney disease or an ischemic condition in the renal circulation. To return to the third admission, the patient had auricular flutter, a month of progressive edema of the leg stumps and the abdominal wall and, for the first time, dyspnea and orthopnea. She had the attacks of sharp pain in the chest, which suggest pulmonary embolism, the systolic murmur reappeared, the pulmonic second sound remained accentuated, the blood pressure was normal, and she had a very large heart. The auricular flutter was restored to normal rhythm, perhaps through temporary auricular fibrillation, which is the classic course in these cases. The lungs on physical examination were noted as being dry, but that probably was not true in the terminal films. I think that she presumably did have a terminal pulmonary embolism.

We should now consider the question of the underlying situation. If we start at the periphery of this patient, with the gangrenous feet, and go toward the heart, we have three possibilities to consider. The first is peripheral vascular disease, but it would be extraordinary for two thrombi to develop simultaneously in the two legs. It would be less extraordinary, but still unusual, to have simultaneous emboli to both legs. Therefore, it seems more reasonable to assume that the obstruction was higher up, presumably at the bifurcation of the iliac veins or higher. A rider embolus at the iliac bifurcation one often diagnoses by listening to the heart and finding mitral stenosis. There did not seem to be mitral stenosis in this patient, however. In no way can we bring in mitral stenosis unless we pick it out of the dark and say that there are some patients who have no murmurs with mitral stenosis. There is no evidence that this patient had had a coronary occlusion to give a basis for an intracardiac thrombosis. Is there anything further about the history of chest pain?

**DR. TRACY B. MALLORY:** On the final admission just before the shock-like episode, she had two sharp attacks of pain on the right side of the chest along the costal margin. Before the amputation she had complained of attacks of pounding of the heart but not of pain.

**DR. SPRAGUE:** We do not know about any attack of pain before amputation. The patient did not have

the shock or the abdominal pain that is usually associated with a large embolus to the iliac bifurcation, but she had a large heart, as well as auricular fibrillation, premature beats and auricular flutter, and she could have had an intracardiac thrombosis on that basis. How about primary thrombosis of the aorta, acute or slowly progressive? This history is pretty much against the picture of slowly progressive aortic thrombosis because there was no history of previous intermittent claudication. This was a sudden episode, whereas in the slowly occluding cases, according to the literature, there is in general either extensive ulcerative arteriosclerosis of the aorta or embolism to the bifurcation. It has been reported following irradiation of the pelvis. However, gangrene is very rare in slowly occlusive aortic thrombosis. Another part of that picture is the late appearance of hypertension due to involvement of renal circulation following occlusion of the aorta and later infarction of the kidneys. Acute thrombosis of the aorta, I suppose, might be a possibility, but this woman became extraordinarily well for three and a half years after amputation of both legs, which seems to me to be against a process that would by itself probably continue occluding vessels higher up.

One has to mention dissecting aneurysm because there was a history of a crushing pain in the chest and because dissecting aortic aneurysm, which has ruptured back into the lumen and caused a double-barreled aorta, turns up at autopsy every so often. But I think we must assume some degree of thrombosis of the aorta in addition. By the time of admission, apparently, the Surgical Service did not believe that the patient was a candidate for embolectomy or anything except amputation. Dissecting aneurysm of the aorta has often been confused, even here, with a rider embolism, and embolectomy has been attempted. But in this case there was no history of pains in the back or in the arms, or suggestion of obstruction to other branches of the aorta. One ought to mention, I suppose, ball or mass thrombus of the left auricle, because peripheral gangrene occurs in that condition. There are no cases, however, due to tumor of the auricle, and, so far as I know, only 1 case in the absence of mitral stenosis. But with mitral stenosis the patient would have had cyanosis, obvious rheumatic heart disease, auricular fibrillation and ischemic involvement of the arms and perhaps of the ears and tip of the nose due to obstruction of the mitral orifice, and she would not have become so well for three and a half years. So I do not know what type of heart disease this was, unless it was hypertensive heart disease, and I cannot make out any type of congenital anomaly or any valvular disease.

I would not like to be caught with one of these cases of aortic stenosis that keep turning up at these conferences. This patient was a young woman instead of an old man as is usually the case in that condition, and there is not much to go on. The

aortic second sound was less than the pulmonic I think that she had had an embolus at the bifurcation of the aorta, presumably an embolus arising from the heart. But other sources can be the aorta itself, and extremely rarely the pulmonary veins. Just for the dubious credit of having mentioned dissecting aneurysm of the aorta, I think I should put it in but with several question marks.

DR EDWARD F. BLAND: Let us ask Dr Gephart if he would comment on why the common femoral iliac veins were tied following low amputation. Was that to ensure circulation locally or was it a preventive measure?

DR F. THOMAS GEPHART: It was a preventive measure. At amputation a few years back, although we still do it occasionally, we more frequently tied the common femoral veins to prevent pulmonary embolism from the stump. It was purely a protective measure.

DR MALLORY: Have you any comment on the cardiac disease, Dr Bland?

DR BLAND: No, but I am not sure what Dr Sprague's final diagnosis is.

DR SPRAGUE: I would have to call it hypertensive heart disease for want of a better diagnosis.

DR BLAND: This case was a puzzle, as you see — it may still be after Dr Mallory presents his findings.

DR RICHARD J. CLARK: Where does Dr Sprague think the terminal emboli came from? If there were terminal pulmonary emboli, what was the source?

DR SPRAGUE: Presumably in the venous system above where they ligated.

DR BLAND: For the sake of the record I think it is correct that Dr Paul D. White saw the patient some time before the final admission, and he, like the rest of us, was puzzled but decided that she had heart disease of undetermined cause, or perhaps she belonged to the small group of cases that Dr Mallory may have trouble in deciding about too.

#### CLINICAL DIAGNOSES

Myocarditis of unknown etiology?  
Pulmonary embolism

#### DR SPRAGUE'S DIAGNOSES

Cardiac disease of unknown etiology (hypertensive?)  
Embolism to bifurcation of aorta  
Terminal pulmonary embolism

#### ANATOMICAL DIAGNOSES

Hypertrophy and dilatation of heart, generalized  
Coronary arteriosclerosis with occlusion, descending branch of right coronary artery  
Infarct of right ventricle  
Mural thrombi of right auricle and right ventricle  
Pulmonary emboli, multiple, with infarction  
Amputation of legs

#### PATHOLOGICAL DISCUSSION

DR MALLORY: There is a comment in the record by Dr White three years ago suggesting the probability of idiopathic myocarditis of the type described by Levy\*. I think, as in so many of these clinically difficult cases, the problem remains difficult after autopsy. I can only tell you what we found. The heart was very diffusely enlarged, in both right and left ventricles. We were particularly impressed by the enlargement in the right ventricle. There were thrombi present in the right auricle and numerous thrombi overlying the endocardium in the right ventricle. There were some gross foci of scarring in the right ventricle. The large coronary branches were relatively free from atheroma, but looking over the heart a second time we demonstrated an occlusion of one of the terminal branches of the right coronary artery. Microscopical sections from the right ventricle showed an area of infarction, underlying the thrombus. Sections of the left ventricle revealed only a spotty fibrosis, with nothing to suggest infarction. The aorta showed a rather minimal degree of arteriosclerosis. We found absolutely nothing in the left side of the heart to provide a focus for systemic embolism. Of course, that embolism occurred four years previously. The endocardium of the left ventricle was a little thick. It is possible that there was thrombosis at one time, most of which broke off, and the fibrous healing of the remainder showed only as a thickened endocardium. The patient had numerous pulmonary infarcts for which there were two sources — the right auricle and the right ventricle — so I do not believe we have to assume that she had further trouble in the remainder of the iliac veins. The amputated legs showed complete thrombotic occlusion of the popliteal vessels. About a month before death she had a rather definite episode of gnawing, substernal pain, and the infarct in the right ventricle was histologically compatible with that duration. I think those two episodes can be put together — first cardiac infarction and then pulmonary embolism secondary to the intracardiac thrombosis. We have no etiologic explanation for the diffuse hypertrophy of the heart. As Dr Sprague suggests, it may have been hypertensive heart disease, although the hypertension was not very convincing in the later period of life, or as Dr White suggested, it was at some earlier period an idiopathic enlargement of the heart, which we can no longer prove.

DR SPRAGUE: Was there a separate embolus in each popliteal artery, or was it a thrombotic process?

DR MALLORY: The emboli were apparently separate, we do not know.

\*Levy R. L., and von Glahn W. C. Cardiac hypertrophy of unknown cause: study of clinical and pathologic features in 10 adults. *Am. Heart J.* 28:714-731, 1944.

# The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established 1828

Official Organ of

THE MASSACHUSETTS MEDICAL SOCIETY

and

THE NEW HAMPSHIRE MEDICAL SOCIETY

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND

PUBLISHED WEEKLY UNDER THE JURISDICTION OF THE  
COMMITTEE ON PUBLICATIONS

James P. O'Hare, M.D. Richard M. Smith, M.D., Chairman  
Oliver Cope, M.D. Conrad Wesselhoeft, M.D.  
John Fallon, M.D.

Joseph Garland, M.D., Editor

ASSOCIATE EDITORS

Thomas H. Lanman, M.D. Donald Munro, M.D.

Henry Jackson, Jr., M.D.

Clara D. Davies, Executive Editor

Robert O. Leary, Assistant Editor

EDITORIAL BOARD

C. Guy Lane, M.D. Maxwell Finland, M.D.  
Henry R. Viles, M.D. James M. Faulkner, M.D.  
Robert M. Green, M.D. Carroll B. Larson, M.D.  
Dwight O'Hara, M.D. Francis D. Moore, M.D.  
Fletcher H. Colby, M.D. C. Stuart Welch, M.D.  
Robert L. Goodale, M.D. Vernon P. Williams, M.D.  
Chester M. Jones, M.D. Benjamin Castleman, M.D.  
Harvey R. Morrison, M.D. Hugh R. Leavell, M.D.

SUBSCRIPTION TERMS: \$7.00 per year in advance, postage paid for the United States (medical students, \$4.00 per year); Canada, \$8.00 per year (Boston funds); \$9.50 per year for all foreign countries belonging to the Postal Union.

MATERIAL should be received not later than noon on Thursday three weeks before date of publication.

THE JOURNAL does not hold itself responsible for statements made by any contributor.

COMMUNICATIONS, including those concerning classified advertising but not those regarding other advertising, should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts. Telephone KE 6-2094.

NEW ENGLAND ADVERTISING REPRESENTATIVE (except for classified advertising): Edwin B. Tyler, 89 State Street, Boston, Massachusetts. Telephone LA 3-5516.

## FALL MEETING OF THE COUNCIL

THE Council of the Massachusetts Medical Society met on October 6. The meeting was conspicuous by the absence of the usual reports of councilors' deaths since the previous meeting, and by the presentation of a new gavel to the President. The acceptance was in verse, graceful, gracious and witty.

President James C. McCann of Massachusetts Medical Service reported on the organization and current activities of Blue Shield, after which the main business of the Council was taken up—the consideration of reports of committees. The meeting was in many spots wholesomely controversial, as befits a democratic procedure, but was kept on a level course by skillful handling and wise decisions from the chair.

The report of the Committee on Cancer was referred back to the Committee for the development of a method of voluntary registration of cancer cases that might be acceptable to the Council.

The Committee on Tax-Supported Medical Care had recommended the approval of certain policies and procedures for a medical care program of the Office of Veterans' Services, subject to renegotiation. It was pointed out by a councilor that this program called for day rates to be paid to physicians from 7 a.m. to 11 p.m. and night rates not until after 11 p.m. The apparent endorsement of a sixteen-hour day for physicians by an agency of a Government that otherwise recognizes a forty-hour week seemed to verge on inconsistency. The report was ordered tabled until after the program had been published in the *Journal*.

The Committee on Veterans' Affairs offered a resolution protesting against the policy of the Veterans Administration—previously condemned in a letter and editorial in the *Journal* on July 22, 1948—in advising veterans that they may attend any medical school in Europe at the expense of the Government. This report was approved, and the resolution adopted by the Council.

The Council in considering the usual long report of the Committee on Public Relations approved a public-health exhibit, disapproved a student loan fund, approved a state-wide health meeting and tabled the endorsement of an ascending scale of membership dues. It approved and referred to the Committee on Education the matter of granting an annual award to a fourth-year student in each of the three medical schools of the state.

The report of the Committee on Public Health concerned the prevention of sexual psychopathology and the inclusion of this subject in the postgraduate medical education program, the Heart Demonstration in Newton and Framingham, active immunization against tetanus, the endorsement of Diabetes Week and the problem of geriatrics. The report was accepted, and its recommendations approved by the Council.

All other committee reports were approved. These included the reports of the Committee on Membership, the Advisory Committee to the Red Cross Blood Bank, the Committee on Arrange-

ments, the Subcommittee on Mental Health and the Committee on Benevolence. The last-named committee recommended that the by-laws be amended to provide for a standing committee on benevolence that would co-operate with the Massachusetts Medical Benevolent Society, with an annual budget.

Certain matters that had been referred to the Executive Committee by the Council at the annual meeting in May were considered. The Committee on Postgraduate Assembly was made a subcommittee of the Committee on Postgraduate Medical Education. The Council voted that the Society sponsor the art exhibit of the Massachusetts Physicians Art Association. A Section on Pathology and Physiology was recommended. A committee was approved that would confer with the directors of the newly formed Bay State Medical Rehabilitation Clinic, to consider in what manner the Society might best assist in the establishment of the clinic.

Under suspension of rules the Council endorsed in principle, on motion of Dr W A R Chapin, of Hampden, certain resolutions on specialty boards that have been presented to the House of Delegates of the American Medical Association by the delegates of the Medical Society of the State of New York.

### RUTLAND'S GOLDEN JUBILEE

THE Great and General Court of the Commonwealth of Massachusetts on June 5, 1895, approved a bill for the establishment of a "Massachusetts Hospital for Consumptives and Tubercular Patients." On September 24, 1898, a proclamation by Governor Roger Wolcott announced that the same "Massachusetts Hospital for Tuberculous Patients," the title somewhat modified, would open on or after October 1 of that year, on October 3 the first patient was admitted.

Thus there came into existence the first state sanatorium for tuberculous patients to be built in this country. The Trudeau Sanatorium at Saranac was already in operation, and Dr Vincent Y Bowditch had established his hospital in Sharon, Massachusetts in 1891, but these were both private institutions. With the opening of the sanatorium at Rutland a new marker was set in place beside

the road of progress in public health. As Dr Paul Dufault, its present superintendent has written, "What is considered obvious today was in the realm of bold thinking fifty years ago."

The sanatorium at Rutland, however, came near to missing its mark at the very beginning of its career, the original bill called for the establishment of a hospital for the terminal care of advanced cases of tuberculosis. It was owing to Dr Alfred Worcester, general practitioner extraordinary and a member of the original commission and board of trustees, that the idea was changed and the purpose of the establishment directed toward the treatment of patients in whom the prognosis might be considered as favorable.

The first superintendent of The Massachusetts Hospital for Tuberculous Patients, now the Rutland State Sanatorium, was Dr Walter J Marcle. The first visiting physicians were Dr Vincent Y Bowditch and Dr Herbert C Clapp. Treatment of the patients was conservative, for, as Dr Clapp wrote at the end of the first year

— in addition to constant and copious potations of the beautiful Rutland fresh air, *day and night*, and the other modern hygienic measures now recognized necessities for consumptives, medicines have been given in almost all cases, but use has been made only of those which are well known to our physicians generally.\*

Dr Clapp also disagreed with most authorities of the time, who believed that whisky, up to a pint a day, was beneficial to tuberculous patients.

The experiment at Rutland was followed with considerable interest outside Massachusetts. In 1905 an Ohio State Commission visited the institution, and delegations are recorded from Maryland, Indiana, Virginia, Alabama, Minnesota, New York, Nevada, New Mexico, Louisiana, Missouri, Iowa, California, New Hampshire, Maine and Vermont, as well as from Canada, England and Korea. Assistance from Rutland was sought in the organization of other state sanatoriums. In 1907 Dr Marcle went to the State Sanatorium of Minnesota, and in the same year Dr Bayard T Crane left to become the head of the Maryland State Sanatorium, and Dr Henry B Dunham to become an assistant at New Jersey's first institution of the kind.

\*Dufault, P. Fiftieth anniversary of Rutland State Sanatorium. *Massachusetts Health J.* 29:6, 1948.

As Kronick indicates in his paper published elsewhere in this issue of the *Journal*, at first only incipient cases of tuberculosis were accepted at Rutland, because they were considered to be reasonably curable. During the first twenty-five years of the institution's existence over 45 per cent of the applicants were rejected as having disease that was too advanced for treatment. The second twenty-five years have shown a great increase in advanced cases, and consequently in the average age of patients, to the point where, in 1947, far advanced cases made up 60.5 per cent of the sanatorium population.

The records at Rutland represent also, as Kronick shows, a catalogue of the progress that half a century has brought in the treatment of tuberculosis. Although whisky was frowned on from the beginning, overfeeding was at first the rule and the overstuffed patients were encouraged to take more exercise than is now permitted. As the bed rest was increased the calories were reduced, from a maximum of 5000 to an average of 2300 daily.

Pneumothorax was introduced in 1911, first with nitrogen, later with air, bronchoscopy and thoracoplasty came together in 1927, the first increasing and the second decreasing in use since that time, the first lobectomy was performed in 1940.

So the Rutland State Sanatorium, its golden jubilee over, continues to serve the people of the Commonwealth. Venerable so far as institutions of its kind are concerned, it has seen great changes in the vital statistics of the disease that it was built to treat. Its patients, like itself, have grown older, it is in the realm of possibility that coming generations will no longer need its services and that its destiny may some day be considered as fulfilled.

## THE CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ON October 25, 1923, the Case Records of the Massachusetts General Hospital became a special feature of the *Journal*. When these reports, previously published independently by the Hospital, were about to be discontinued for lack of financial support,<sup>1</sup> the *Boston Medical and Surgical Journal* undertook to incorporate them into its pages. In

announcing this fact the *Journal* emphasized the value of the exercises in presenting "correct and modern methods of treatment."<sup>2</sup> Throughout the years in which they have been a regular part of the *Journal*, the Case Records have not only fulfilled the high standard promised but also proved one of its most interesting and popular features. Moreover, clinicopathological conferences, of which the "Cabot Case Records" were the prototype, have become "one of the most characteristic features of American medical teaching."<sup>3</sup>

The history of the Case Records actually goes back to 1895, when Dr. Richard C. Cabot first began using "in private quiz exercises at my own office, some of the printed case histories which had been used by Dr. Frederick C. Shattuck on the examinations in clinical medicine."<sup>4</sup> The first published cases appeared in 1911, and the exercises were continued in the *Journal* under the editorial supervision of Dr. Cabot until July 4, 1935, when Case 21271 was published with Dr. Tracy B. Mallory as editor.<sup>4</sup> The reports have since then been published under Dr. Mallory's expert guidance, with the assistance of Dr. Benjamin Castleman and Miss Edith E. Parris.

Among the many anniversaries celebrated this fall, none is more deserving of hearty congratulations than the twenty-fifth in their present form of the Case Records of the Massachusetts General Hospital. The high standard of these exercises has never been relaxed, and their editors have merited the praise and thanks of all who find the reports a source of inspiration. Having established the form of the clinicopathological conference, the Case Records have remained foremost in interest and value and have continued to justify the high regard in which such conferences are universally held. "the clinicopathological conference is the wonder of many of our foreign visitors, who see in it a candor and fearlessness altogether to the credit of American medicine."<sup>5</sup>

## REFERENCES

- 1 Editorial. Case records of Massachusetts General Hospital. *Boston M & S J* 189:79 1923
- 2 Editorial. Case histories of Massachusetts General Hospital. *Boston M & S J* 189:70 1923
- 3 Mallory T B. Richard Clarke Cabot and clinicopathologic conference. *New Eng J Med* 220:880 1939
- 4 Case Records of the Massachusetts General Hospital (Case 21271). *New Eng J Med* 213:26-31 1935
- 5 Gregg A. Border view of post mortem examination. *Ann Int Med* 12:249-252 1938

## RED CROSS CONFERENCE

CERTAIN principles of warfare as it should be waged when war becomes inevitable were reaffirmed at the seventeenth International Red Cross conference held in Sweden in August of this year. One new treaty that would afford wartime protection to civilians and revisions of others were proposed and approved, and many new resolutions were passed. The proposed new treaty and revisions will be presented for adoption to a diplomatic conference of nations to be held in Switzerland at a later date.

One of the resolutions that was passed called upon nations to outlaw the atomic bomb, a righteous exhortation and one that will fall upon receptive ears if it seems to the best interest of those nations concerned to heed it. That this situation is not altogether impossible of attainment may be adduced from the absence of gas warfare in the open hostilities so recently suspended. People who live in glass houses do not throw stones, and the enlightened nations of the world may still be considered as genuinely opposed to indiscriminate slaughter.

The main change proposed in the Geneva treaty for the relief of the wounded and sick on the battlefield had to do with the status of captured military medical personnel. Instead of being returned home at once when captured as is supposed to be their disposition under the present convention, medical officers may be detained by the captor in sufficient numbers to care for the captured sick and wounded of their own army.

In view of the unparalleled ferocity and barbarity with which certain belligerents waged the recent war, the present efforts of the Red Cross may seem like a totally unrealistic excursion into the realms of wishful thinking. Such is not the case. Only by frequent reaffirmation of the basic principles of acceptable human conduct can the distinction between right and wrong remain clearcut. Any country that disregards the generally accepted standards of civilized behavior must be made aware that its actions are intolerable to the majority of nations.

## MASSACHUSETTS MEDICAL SOCIETY

## DEATHS

ALLEN — William H. Allen, M.D. of Mansfield died on September 19. He was in his eighty-first year. Dr. Allen received his degree from Harvard Medical School in 1894.

His widow survives.

DUNPHY — Henry A. Dunphy, M.D. of Palmer, died on June 11. He was in his sixty-seventh year.

Dr. Dunphy received his degree from Baltimore Medical College in 1908. He was a member of the staff of Mercy Hospital in Springfield and was associate medical examiner for the Palmer District of Hampden County. He was a fellow of the American Medical Association.

His widow, four sons, two daughters and four brothers survive.

FAUNCE — Calvin B. Faunce, M.D. of Boston, died on September 22. He was in his sixty-seventh year.

Dr. Faunce received his degree from University of Maryland School of Medicine in 1904. He was formerly assistant professor of otology at Harvard Medical School and was chief of staff of the Eye, Ear, Nose and Throat Division, Faulkner Hospital and a member of the staffs of the Massachusetts Eye and Ear Infirmary, Massachusetts General Hospital, Children's Hospital and Brookline Contagious Hospital. He was a member of the American Laryngological, Rhinological and Otolological Society, American Otolological Society, Incorporated and New England Otolological and Laryngological Society and a fellow of the American College of Surgeons and American Medical Association.

His widow, a son and two daughters survive.

KLEIN — George Klein, M.D. of Norwood, died on June 18. He was in his fifty-eighth year.

Dr. Klein received his degree from Tufts College Medical School in 1914. He was a member of the staffs of Norwood and Faulkner hospitals and was a member of the American Society of Anesthetists, Inc., and a fellow of the American Medical Association.

His widow, a son, three brothers and two sisters survive.

LUBINSKY — Henry Lubinsky, M.D. of Fall River, died on May 25. He was in his forty-sixth year.

Dr. Lubinsky received his degree from Tufts College Medical School in 1927. He was chief of pediatrics at Fall River General and St. Anne's hospitals and a member of the staff of Union Hospital. He was a fellow of the American Medical Association.

His widow, a daughter, two brothers and six sisters survive.

## BLUE CROSS—BLUE SHIELD

## PREMATURE INFANTS

Effective immediately Blue Shield will interpret care rendered to a premature infant weighing  $4\frac{1}{2}$  pounds or less as being other than routine. This means that payment for such care will be made to any participating physicians beginning on the day of delivery.

## MISCELLANY

## DR. HOWARD M. CLUTE MEMORIAL

A movement has been put on foot and a committee formed to erect a memorial that will pay tribute to Dr. Howard M. Clute's long and unselfish services to the New England Baptist Hospital and the community. It has been proposed that this memorial take the form of an auditorium in connection with the Hospital to meet the educational needs of nurses, of doctors and of the community.

## "IN TIME OF PEACE —"

Demands on the nation's health resources in the event of war would far exceed the supply, according to the medical advisory committee of the National Security Resources Board. The committee has therefore recommended that the Board include administration of an over-all national health policy in planning for wartime organization of the Government.

## NOTICES

### ANNOUNCEMENT

Dr Benjamin F. Sieve announces the removal of his office to 314 Commonwealth Avenue, Boston.

### NEW ENGLAND HOSPITAL FOR WOMEN AND CHILDREN

The monthly clinical conference and meeting of the staff will be held in the Classroom of the Nurses' Residence, on Thursday, November 4, at 7:15 p.m., with Dr Augusta Hayck as chairman. Dr William L. Fleming will speak on the subject, "Modern Concept of Syphilology".

### MASSACHUSETTS PUBLIC HEALTH ASSOCIATION

The fall meeting of the Massachusetts Public Health Association will be held on the opening day (November 8) of the convention of the American Public Health Association, in the Salle Moderne of the Hotel Statler at 2:30 p.m. A program entitled "A Progress Report of Activities of the Special Legislative Commission on Public Health for the Commonwealth of Massachusetts" will be presided over by Dr Vlado A. Getting, with introductory remarks by Senator Richard H. Lee. The reports of the technical committees will be presented by the chairmen, as follows: Local Health Administration, Dr Hugh R. Leavell; Preventable and Chronic Diseases, Dr Conrad Wesselhoef; Sanitation, Dr John H. Cauley; and Maternal and Child Health, Dr Warren R. Sisson. The discussion will be led by Dr Henry D. Chadwick, Professor Curtis M. Hilliard and Dr L. Jackson Smith.

The meeting will be open to all interested persons.

### NEW ENGLAND HEART ASSOCIATION

A meeting of the New England Heart Association will be held at the Peter Bent Brigham Hospital, Boston, on Monday, November 8, at 8:15 p.m., Dr Samuel A. Levine, presiding.

#### PROGRAM

Dicumarol in the Prevention of Thromboembolic Phenomena in Congestive Failure. Drs Clement A. Finch and W. Proctor Harvey.

Uncomplicated Pulmonic Stenosis. Drs Harper Hellemis, Milton Elkin and Lewis Dexter.

The Enlarged Pulmonary Artery. Drs James E. Dow, Raymond Healey, James Whittenberger and Eugene C. Eppinger.

Diodrast Studies in Congenital Heart Disease. Drs Martin Wittenborg and Edward B. D. Neuhauser.

Grafting of Blood Vessels. Dr Robert E. Gross.

Further Notes on Auscultation of the Heart. Drs Samuel A. Levine and W. Proctor Harvey.

Interested physicians and medical students are cordially invited to attend.

Future meetings are planned as follows (all meetings on Mondays at 8:15 p.m.): December 6, 1948, at the Massachusetts General Hospital, Boston, Dr Paul D. White, chairman; January 10, 1949, at the Boston City Hospital, Dr Laurence B. Ellis, chairman; February 7, 1949, at the Massachusetts Memorial Hospitals, Boston, Dr Robert W. Wilkins, chairman; and March 28, 1949, at the Beth Israel

Hospital, Boston, Dr Herrman Blumgart, chairman. At its annual meeting, on a date to be specified, the Jackson Lecture will be delivered.

Members who wish to present papers and are staff members of hospitals in which no meeting has been scheduled can probably be fitted into the program of one of the other hospitals and should get in touch with the secretary of the New England Heart Association as soon as possible.

### FREE MONOGRAPHS ON CANCER

The American Cancer Society has prepared a brochure series of illustrated monographs aimed at providing physicians with up-to-date information for the early recognition of cancer. Available free to all physicians, these articles are written by cancer specialists highly competent in their fields, and will appear at two-month intervals.

Physicians who have received notice of this series from the American Cancer Society (Massachusetts Division) are asked to return their cards at their earliest convenience. Any Massachusetts physician who wishes to be placed on the mailing list and who has not received a notice, may write to the American Cancer Society, 462 Boylston Street, Boston 16, or call Copley 7-2650.

### SOCIETY MEETINGS AND CONFERENCES

#### CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, NOVEMBER 4

##### THURSDAY NOVEMBER 4

\*7:15 p.m. Monthly Clinical Conference and Staff Meeting. Nurses' Residence. New England Hospital for Women and Children.

##### FRIDAY NOVEMBER 5

\*9:00 a.m. 12:00 p.m. Combined Medical and Surgical Staff Rounds. Peter Bent Brigham Hospital.  
\*12:00 p.m. X-Ray Conference. Margaret Jewett Hall. Mt. Auburn Hospital. Cambridge.

##### MONDAY NOVEMBER 8

\*12:15-1:15 p.m. Clinicopathological Conference. Main Amphitheater. Peter Bent Brigham Hospital.  
\*2:30 p.m. Massachusetts Public Health Association. Salle Moderne. Hotel Statler.  
\*8:15 p.m. New England Heart Association. Peter Bent Brigham Hospital.

##### TUESDAY NOVEMBER 9

\*12:15-1:15 p.m. Clinicoröntgenological Conference. Peter Bent Brigham Hospital.  
\*1:30-2:30 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children. Massachusetts General Hospital.

##### WEDNESDAY NOVEMBER 10

\*11:00 a.m. 12:00 p.m. Medical Rounds. Amphitheater. Children's Hospital.  
\*12:00 p.m. 1:00 p.m. Clinicopathological Conference (Children's Hospital). Amphitheater. Peter Bent Brigham Hospital.  
\*2:00-3:00 p.m. Combined Clinic by the Medical, Surgical and Orthopedic Services. Amphitheater. Children's Hospital.

\*Open to the medical profession.

OCTOBER 1 MAY 20. Metropolitan State Hospital. Page 418 issue of September 9.

OCTOBER 31 and NOVEMBER 1. American Society for the Study of Arteriosclerosis. Page 530 issue of September 30.

NOVEMBER 1-3. American Clinical and Climatological Association. Page 582 issue of April 15.

NOVEMBER 3 and 4. Annual Meeting of National Committee for Mental Hygiene. Inc. Page 282 issue of August 12.

NOVEMBER 3-5. Seventh New England Postgraduate Assembly. Copley Plaza Hotel, Boston.

NOVEMBER 4. New England Hospital for Women and Children. Notice above.

NOVEMBER 4-6. American Society of Anesthesiologists. Page 418 issue of September 9.

NOVEMBER 6 and 7. American Cancer Society. Incorporated. Page 644 issue of October 21.

NOVEMBER 8. Massachusetts Public Health Association. Notice above.

NOVEMBER 8. New England Heart Association. Page 470 issue of March 18.

NOVEMBER 8-12. American Public Health Association. Page 470 issue of March 18.

NOVEMBER 9-12. Interstate Postgraduate Medical Association of North America. Page 644 issue of October 21.

NOVEMBER 10-13. Association of Military Surgeons of the United States. Page 722 issue of May 13.

NOVEMBER 12. The Use of Hormones in Breast Cancer. Dr. Ira T. Nabstenson. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

(Notices concluded on page xv)

## NOTICES (Concluded from page 692)

- NOVEMBER 17 Middlesex East District Medical Society Page 644  
 of October 21
- NOVEMBER 20-23 American Academy of Pediatrics Annual Meeting  
 Balfonte-Haddon Hall Hotel Atlantic City New Jersey
- NOVEMBER 30 Hampden District Medical Society Page 492 issue  
 of September 25
- DECEMBER 2 Suffolk Censors Meeting Page 492 issue of September 25
- DECEMBER 4 American Federation for Clinical Research Page 644  
 issue of October 21
- DECEMBER 7-9 Southern Surgical Association Annual Meeting  
 Page 543 issue of April 8
- DECEMBER 9 and 10 New York State Society of Anesthesiologists  
 Page 54 issue of July 1
- FEBRUARY 4 1949 American Board of Obstetrics and Gynecology  
 Inc. Page 244, issue of August 5
- MARCH 2-APRIL 1 1949 American College of Physicians Page 1  
 issue of July 22
- MAY 16-19 1949 American Urological Association Baltimore Hotel  
 Los Angeles California
- MAY 26-28 1949 American Gynecological Association Hotel Loraine Madison  
 Wisconsin
- NOVEMBER 11-17 1949 Third Inter-American Congress of Radiology  
 Page 158 issue of July 22

## DISTRICT MEDICAL SOCIETIES

## HAMPDEN

- NOVEMBER 9 8:30 p.m. Academy of Medicine Springfield Car  
 agenda of the Breast Dr. Grantley W. Taylor

## MIDDLESEX EAST

- NOVEMBER 17  
 JANUARY 19  
 MARCH 25  
 MAY 11

## SUFFOLK

- DECEMBER 2 Suffolk Censors Meeting

## WORCESTER NORTH

- NOVEMBER 10 Henry Heywood Memorial Hospital Gardner  
 DECEMBER 15 Leominster Hospital Leominster  
 FEBRUARY 25 Borbank Hospital Fitchburg  
 APRIL 27 Annual Meeting

## Washingtonian Hospital

41-43 WALTHAM STREET, BOSTON, MASS

Incorporated 1859

Conditioned Reflex, Psychotherapy, Semi-Hospitalization  
 For Rehabilitation of Male Alcoholics  
 Treatment of Acute Intoxication and Alcoholic Psychoses  
 Included  
 Outpatient Clinic and Social-Service Department for  
 Male and Female Patients

JOSEPH THIMANN, M.D., Medical Director

Visiting Psychiatric and Neurologic Staff  
 Consultants in Medicine, Surgery and the Other Specialties  
 Telephone HA 6-1750

## Valleyhead Hospital

CONCORD, MASSACHUSETTS

For the treatment of psychoneuroses alcoholism, mild  
 mental disorders and chronic diseases Pleasant pastoral  
 setting near historic Concord Accepted modern therapies  
 used Complete occupational and recreational facilities  
 available including outdoor swimming pool and tennis  
 court

S GAGNON, M.D.  
SuperintendentJ BUTLER TOMPEINS, M.D.  
Director of Clinical PsychiatryJ P THORNTON, M.D.  
Consultant in Neuro-  
psychiatryIRVING KAUFMAN, M.D.  
Psychiatrist

Post Office, Box 151 Concord, Mass Tel Concord 1600

## Tablets Ferglate-B with C

High in vitamin B complex content to quicken hemo-  
 globin response to iron therapy

## EACH TABLET CONTAINS

Ferrous Gluconate (5 grains)	0.375 gm	Pyridoxine HCl	0.15 mg
Thiamin HCl	3 mg	Calcium Pantothenate	0.5 mg
Riboflavin	2 mg	Ascorbic Acid	30 mc
Nicotinamide	20 mg	Yeast Liver Base	q.s.

## INDICATIONS

Iron deficiency and nutritional anemias as a source of iron and  
 B complex factors

Write Department N12 for Professional  
 Sample and Literature

## KENMORE PHARMACAL CO.

500 COMMONWEALTH AVENUE  
 BOSTON 15 MASS



To a patient with troubles internal  
 That seemed to be centered sub-  
 sternal,

Said our friend, Dr. Wise,

'I must digitalize

After checking the ads in the  
 Journal"

## Firm, Natural Support Need Never Be Sacrificed for ANY Fashion

A functional garment, properly fitted, will mold  
 a figure to the fashion's new requirements with-  
 out causing displacement of organs

## EVELYN L. WEIGEL

25 HUNTINGTON AVE. MASSACHUSETTS AVE., ROUTE 111  
 BOSTON 16, MASS WEST ACTON, MASS.  
 KENMORE 6-2718 ACTON 504-3

## SHOE SHINES Are Easy with the New HOME VALET




Made of strong aluminum,  
 complete with two toe plates  
 for narrow or wide shoes. Fits  
 them all! Demonstrate wall  
 bracket. Thousands of satis-  
 fied users everywhere

**\$2.50**

Belongs in every home and  
 office. An excellent gift  
 idea. Guaranteed. Order  
 now. Dealers invited

Postpaid with your check or  
 money order. Postage extra  
 for C O D

J. M. CRIMMINS, Norristown 7, Pa.



This baby's mother learned about Mead's Oleum Percomorphum from her physician, not from public advertising or displays

*"Servamus Fidem"*

## HOW much sun does the infant really get?

*Not very much* (1) When the baby is bundled to protect against weather or (2) when shaded to protect against glare or (3) when the sun does not shine for days at a time Mead's Oleum Percomorphum is a prophylactic against rickets available 365½ days in the year, in measurable potency and in controllable dosage *Use the sun, too*

Mead Johnson & Co., Evansville, Ind., U.S.A

# The New England Journal of Medicine

Copyright, 1948 by the Massachusetts Medical Society

Volume 239

NOVEMBER 4, 1948

Number 19

## ACUTE RENAL INSUFFICIENCY DUE TO LOWER-NEPHRON NEPHROSIS\*

MAURICE B. STRAUSS, M.D.†

FRAMINGHAM, MASSACHUSETTS

### PATHOLOGY

ACUTE renal insufficiency due to the disorder now known as lower-nephron nephrosis<sup>1</sup> or hemoglobinuric nephrosis<sup>2</sup> occurs in association with a large variety of conditions, including intravascular hemolysis associated with transfusion reactions,<sup>3-7</sup> blackwater fever,<sup>8</sup> quinine sensitivity<sup>9</sup> and transurethral prostatectomy,<sup>10, 11</sup> as well as in the crush syndrome,<sup>12-23</sup> nontraumatic muscle ischemia,<sup>24</sup> electrical injury to muscle,<sup>25</sup> heat stroke,<sup>26</sup> uretero-placental damage,<sup>27, 28</sup> after abortion,<sup>29</sup> alkalosis from excessive vomiting,<sup>30</sup> thermal burns,<sup>31, 32</sup> sulfonamide sensitivity<sup>33-36</sup> and from various poisons of diverse origin,<sup>1</sup> including the most common offender, carbon tetrachloride.<sup>37-45</sup>

The purpose of this communication is to present certain data pertinent to this syndrome and to suggest that treatment based on the pathological physiology of this type of renal failure offers considerable promise.

### CLINICAL ASPECTS

Irrespective of the antecedent condition associated with this syndrome the clinical features and the histologic pathology appear similar if not identical. With or without an initial period of shock, dependent on the precipitating cause, patients often develop nausea, vomiting, weakness, malaise, sometimes pain in the abdomen or back and, abruptly or insidiously, oliguria or anuria. The magnitude and severity of the general manifestations frequently so divert attention from what at the moment seems a minor matter that it is often difficult to determine just when the urine volume declined or became nil. After renal shutdown, edema generally develops (the magnitude depending on the nature of the treatment), the blood pressure rises, the nonprotein nitrogen steadily mounts, acidosis becomes chemically apparent, and death generally ensues from pulmonary edema or, in certain cases, from potassium intoxication.

The histologic pathology as noted by Lucké<sup>1</sup> and Mallory<sup>2</sup> and others is essentially as follows: eighteen to twenty-four hours after onset there is lipid vacuolization of the ascending limbs of Henle's loop. Precipitation of pigment casts in the distal convoluted and collecting tubules is generally noted thirty-six to seventy-two hours after onset. This pigment usually gives a positive reaction to benzidine, but does not contain stainable iron. Moderate dilatation of the proximal and sometimes of the distal convoluted tubules follows the pigment precipitation. Sometimes on the third day, and regularly by the fourth and fifth days, necrosis and regeneration of the epithelium in the ascending portions of Henle's loop and in the distal convoluted tubules become evident, and simultaneously lymphocytes appear between the tubules and about the vessels. From the fifth day on rupture of the tubules becomes frequent. There is no significant change in the glomerular capillaries. The capsular space and the lumen of the proximal convoluted tubules may contain a variable amount of amorphous and granular debris. Edema of the interstitial spaces of the kidney is frequently seen. This may well be related to the generalized edema induced by the administration of large quantities of parenteral fluids. The basement membrane of the tubules is usually intact. Available evidence suggests that the re-epithelization of the tubules, albeit imperfect, is completed generally within two weeks of onset.

Although emphasis in the literature has been placed on the anuria and renal pathology it is to be noted that liver damage also occurs.<sup>2, 3, 8, 9, 12, 20, 21, 26, 27, 33, 36</sup> Bywaters,<sup>49</sup> one of the original describers of the crush syndrome, has recently reported central or midzonal liver-cell necrosis following crush or other skeletal injury in 42 patients, the majority of whom died in uremia. In carbon tetrachloride poisoning liver damage is so constant that many physicians are surprised that renal failure often overshadows the hepatic injury.<sup>45</sup>

\*From the Medical Service, Cushing Veterans Administration Hospital, Framingham, Massachusetts, and the Department of Medicine, Harvard Medical School.

†Associate in medicine, Harvard Medical School, chief, Medical Service, Cushing Veterans Administration Hospital, Framingham, Massachusetts.

### SURVIVAL TIME AND CAUSE OF DEATH IN FATAL CASES

Lucké<sup>1</sup> has determined the survival time in 100 fatal cases of lower-nephron nephrosis. Ninety-five per cent of the patients succumbed within fourteen days, 86 per cent within ten days, and 48 per cent within six days. No deaths occurred after twenty days. Burwell, Kinney and Finch<sup>7</sup> reviewed 89 cases of oliguria following intravascular hemolysis. Fifty-one of the 55 patients in the fatal cases succumbed within the first two weeks — 26 within six days. The other 4 deaths occurred on the six-

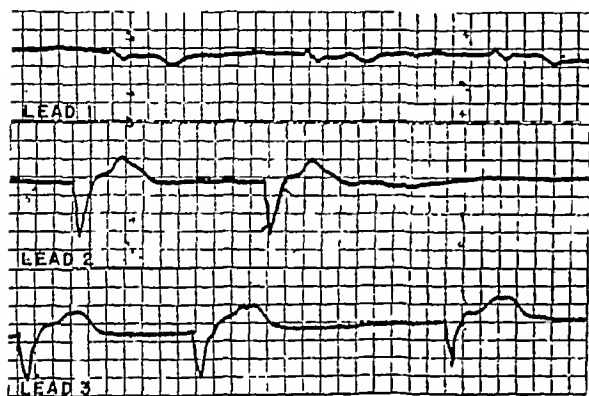


FIGURE 1 *Electrocardiogram in Case 4 Shortly before Death*

teenth, seventeenth, eighteenth and twentieth days respectively.

That factors probably unrelated to the kidney may be of very considerable importance in many fatal cases is suggested by the large number of deaths (50 per cent) within the first six days. It appears highly unlikely that renal insufficiency per se would ever lead to death within such a brief period. There is no doubt that the underlying or precipitating condition is frequently the major cause of a fatal outcome, and it is also probable that in some cases the hepatic damage is significant. Massive generalized edema, as well as pulmonary edema, is a common finding at autopsy,<sup>1, 2, 50</sup> the pulmonary form often being the immediate cause of death. Until the last year all the patients in the fatal cases of hemoglobinuric nephrosis observed by me died with, and probably from, pulmonary edema.

The level of the blood nonprotein nitrogen seems to bear little correlation with the outcome. Lower values are more often encountered in fatal cases than in patients who ultimately recover. The blood nonprotein nitrogen of 2 recently studied patients who recovered reached 225 and 255 mg per 100 cc respectively whereas in 5 fatal cases the highest values were 115, 154, 182, 195 and 240 mg per 100

cc. In Lucké's<sup>1</sup> series the nonprotein nitrogen levels in 10 fatal cases were, in ascending order of magnitude, 109, 114, 150, 175, 188, 218, 225, 240 and 260 mg per 100 cc.

Several investigators<sup>1, 19, 23, 29</sup> have commented on the possible role of potassium intoxication in the fatal outcome through alterations of cardiac function. In 1 case (Case 4) typical electrocardiographic changes of hyperpotassemia preceded death (Fig 1). Winkler and his associates<sup>51</sup> have shown that if potassium salts are injected intravenously in dogs rapidly enough to raise the serum potassium level a reproducible series of electrocardiographic changes occurs, terminating in death from ventricular flutter, fibrillation or arrest when the level reaches 14 to 16 milliequiv per liter. At a serum potassium level of 5 to 8 milliequiv, the T waves become tall and peaked, at 8 to 9 milliequiv, the ST interval is depressed, and the T waves become diphasic. The P waves decrease in size and disappear at 9 to 11 milliequiv per liter, and at the same level intraventricular block occurs. Orally administered potassium salts fail to elevate the serum potassium level significantly in the dog with normal renal function.<sup>52</sup> However, if renal insufficiency has been produced, the same sequence of electrocardiographic changes follows the oral administration of potassium when the serum levels rise.<sup>52</sup> In dogs experimentally rendered anuric, similar electrocardiographic changes follow the increasing concentration of potassium in the blood that occurs as a result of endogenous protein catabolism.<sup>53</sup> There is thus considerable evidence that potassium intoxication is important in certain cases of lower-nephron nephrosis.

### ONSET OF DIURESIS IN SURVIVING PATIENTS

In 34 cases of hemoglobinuric nephrosis reported by Burwell, Kinney and Finch<sup>7</sup> in which the patients recovered diuresis began from the second to the twelfth day in 32 and began on the fourteenth and sixteenth days in 2 cases. In the 4 cases reported by Humphrey and Avery Jones<sup>49</sup> diuresis began on the thirteenth to the fifteenth day after the onset of anuria. The patients in Kugel's<sup>50</sup> cases began passing appreciable amounts of urine on the ninth and tenth days. The 2 patients who recovered in the cases presented below had spontaneous diureses on the tenth and fifteenth days of anuria. Many other cases of spontaneous diuresis in the second and third weeks after the onset of anuria may be found. The evidence, therefore, is suggestive that in lower-nephron nephrosis with anuria or oliguria the damage is not always irreversible, and regeneration of the tubular epithelium is possible and may be anticipated in the majority of cases within the first two or three weeks if the patient can be kept alive long enough for healing to occur.

Once recovery from the acute episode has taken place, complete physiologic restitution may be expected to occur over a period of several months<sup>7, 29, 50</sup>

#### MAXIMUM SURVIVAL PERIOD WITHOUT RENAL FUNCTION

It is currently believed that after complete renal shutdown man can survive at most two or three weeks. This belief has developed during recent years when the parenteral administration of fluids became a routine procedure for a great variety of conditions. In an endeavor to ascertain how long patients with complete anuria survived prior to the days of parenteral fluids the older literature was studied<sup>51-59</sup>. It was not altogether surprising to find that many patients were reported as surviving from three to four weeks, 1 for five weeks, 2 for six weeks, and 3 for seven weeks. Since the possibility exists that certain of these observations were in error it is worth calling attention to 5 of these reported cases in particular in which there appears to be little probability that any urine was formed during the period of observation. In the first of these removal of the right kidney was performed for carcinoma of the kidney twenty-seven and a half days before death<sup>55</sup>. Autopsy revealed the congenital absence of the left kidney. In the second case the patient survived removal of the right kidney for hydronephrosis for twenty-three days before post-mortem examination disclosed the congenital absence of the left kidney<sup>53</sup>. A third patient who died after twenty-five days of anuria was shown at autopsy to have both ureters completely obstructed by cancer<sup>55</sup>. The left kidney was represented by a thin-walled cyst, and the right by a hydronephrotic sac containing a pint of urine. The fourth patient had had chills and fever together with anuria for three days at the age of thirty-two and for eleven days a year later, with recovery associated with the passage of pus-laden urine<sup>56</sup>. At the age of thirty-four, after twenty-two and a half days of anuria during which she was closely observed to make certain that there was no deception, she was operated upon. The left kidney was absent, and 500 cc of thick, foul-smelling pus was evacuated from the right kidney pelvis. Many stones were found in the calyces and one calculus completely occluded the right ureter. Recovery was uncomplicated. The fifth patient succumbed thirty days after the onset of complete anuria due to obstruction of both ureters by pelvic carcinomatosis<sup>57</sup>.

Animal experimentation has been somewhat misleading. It has frequently been observed that guinea pigs and rats die a few days after bilateral ureteral ligation<sup>59</sup> or after anuria has been produced by occlusion of both renal arteries for two hours<sup>60</sup>. The survival of rabbits<sup>61, 62</sup> and of dogs<sup>63-65</sup> is somewhat longer, whereas sheep and goats generally

do not succumb for two weeks<sup>59</sup>. Presumably, elephants might well survive for months. The increased ability of larger animals to survive without functioning kidneys may in part be ascribed to the fact that the rate of formation of metabolic waste products is a function of the rate of total body metabolism, which in turn is correlated with surface area. The amount of body water, however, in which these products may be distributed and thus diluted is almost a linear function of body weight. This penalty of small size has also been noted in infants and children, and has been commented upon by Gamble<sup>66</sup>.

#### THEORETIC CONSIDERATIONS IN TREATMENT

At this point it may be well to consider the course of events that may ensue in an otherwise healthy adult man weighing 70 kg who suddenly lost all function of both kidneys but who did not suffer from "toxic destruction" of body protein<sup>67</sup>. There would be a daily insensible loss of approximately 1000 cc of water by evaporation from the skin and lungs<sup>66</sup>. In the absence of actual sweating no appreciable amount of electrolyte would be lost. Gastric intolerance for food would probably appear and preclude nutrition by mouth, leading to the rapid exhaustion of the scanty body stores of carbohydrate. Approximately 70 gm of body protein would then be broken down daily<sup>68</sup> and the remaining caloric need supplied by the burning of about 200 gm of body fat. In the course of this catabolism of fat and protein, ketone acids, nitrogenous waste products, potassium, sulfate and phosphate would accumulate in the body. Preformed water and water of oxidation in the amount of 470 cc daily would be released, leaving an approximate daily deficit of 530 cc. The nitrogenous waste products would be distributed throughout the entire body water of approximately 50 liters and would rise steadily, as would the level of potassium in the body fluids. The accumulation of ketone acids as well as sulfate and phosphate anions would be followed by a reduction in the carbon dioxide content of the plasma. Rising plasma phosphate may be accompanied by a lowering of the calcium. However, the presence of acidosis should protect the patient from actual tetany. The daily negative water balance, increasing the osmotic pressure of the extracellular fluids, would lead to cellular dehydration. The duration of life under these circumstances is uncertain. It appears likely that the rise in serum potassium would lead to fatal cardiac changes before nitrogen retention or acidosis became threatening.

If isotonic electrolyte solution is given parenterally concentration of the extracellular electrolytes with secondary cellular dehydration will nevertheless occur by virtue of the evaporation of electrolyte-free water from the skin and lungs. If on the other hand, sufficient distilled water is admin-

istered to replace the water loss, concentration of the electrolytes in the body fluids should be kept reasonably constant. If, further, 100 gm of glucose was given daily, ketosis would be prevented and protein breakdown would be reduced by almost half as demonstrated by Butler et al<sup>68</sup> and by Winkler and his co-workers<sup>69</sup> in their studies of fasting man. This would mean that the nitrogenous waste products, potassium, sulfate and phosphate released by protein catabolism would accumulate at only half the rate that they would have accumulated if glucose had not been received. How rapidly should the nonprotein nitrogen rise in this hypothetical person who is now receiving 100 gm of glucose a day and whose insensible loss of water is taken care of? The metabolism of 37.5 gm of protein daily will lead to the formation of 6000 mg of nonprotein nitrogen, which will be distributed throughout the entire body water (amounting roughly to 50 liters), and therefore the blood nonprotein nitrogen should rise at a daily rate of 12 mg per 100 cc. By similar calculations it is possible to determine that the daily rise in serum potassium, sulfate and phosphate will be respectively 0.324, 1.86 and 1.66 milliequiv per liter, on the assumption that the potassium will be distributed in a volume equivalent to the total body water,<sup>63, 70</sup> and that the sulfate and phosphate are distributed only in the extracellular water. Actually since some portion of the phosphate will be deposited in bone or other tissues the rise of serum phosphate will be much slower.

Such data as are available suggest that these rates of increase for nonprotein nitrogen, potassium and sulfate are correct,<sup>29</sup> although the rise in potassium may be slower than expected, possibly owing to an increase in the nonionized fraction of intracellular K-proteinate.<sup>71</sup> Serum sodium levels show no marked deviation from the normal range. Observed serum chloride and bicarbonate values have been lower than those anticipated from the rise in sulfate and phosphate. In a case in which sufficient data were obtained to allow calculation of the electrolyte balance,<sup>29</sup> the sum of the anions— $\text{Cl}' + \text{HCO}' + \text{PO}'' + \text{SO}'' + \text{protein}$ —was consistently lower than that of the cations— $\text{Na} + \text{K} + \text{Ca}$ . No explanation for this discrepancy was apparent.

#### TREATMENT

The treatments that have been suggested in the management of acute anuria or oliguria are many and diverse. They include spinal anesthesia, splanchnic block, diathermy to the kidney region, x-ray irradiation of the kidneys, acetyl-beta-methylcholine injections, irrigation of the renal pelvis, decapsulation or capsulotomy of the kidney, transfusion of compatible blood or plasma, or both, intravenous sodium sulfate, intravenous hypertonic fluids, including glucose and saline solution, massive

intravenous administration of saline or lactate solutions, peritoneal lavage and the use of an artificial kidney. Recently enthusiasm for capsulotomy has been noted.<sup>72, 73</sup> J. T. Peters<sup>74</sup> has advanced the theory that anuria is due to edema of the kidney, which produces an increase in the intrarenal pressure, effectively preventing the flow of urine. The fact remains that in patients who recover diuresis starts at the height of fluid retention and thus at a time when the edema of the kidney may be anticipated to be at its greatest. Furthermore, there is no evidence for the existence of edema of the kidney at the onset when the anuria first occurs. The subject of capsulotomy has recently been reviewed,<sup>75</sup> and the evidence in its favor found wanting. It is to be noted that most of the successes reported in the literature indicate that the operation was performed between the eighth and the tenth day, which is the period in which spontaneous diuresis most often occurs. It is of particular interest that in Talbot's<sup>76</sup> case, in which operation was performed on only one kidney, but catheters placed in both ureters, diuresis began at precisely the same time on each side.

There is no doubt that peritoneal lavage can successfully remove large amounts of nitrogen from the body.<sup>66, 77-82</sup> However, the difficulties involved in maintaining water balance and the frequent development of peritonitis have caused some workers<sup>81</sup> to discard this method of tiding the patient over the period needed for tubular regeneration. The artificial kidneys developed by Kolff<sup>83</sup> and Alwall<sup>61, 62, 84</sup> offer considerable promise for the future. However, evidence available at present indicates that the number of patients with lower-nephron nephrosis who will require such management may be materially reduced by the more widespread use of the conservative therapy of restricted fluids and glucose administration. Although Wakeman et al<sup>85</sup> advocated such a procedure a decade and a half ago, Kugel<sup>86</sup> was unable to find any case of acute toxic nephrosis so treated. He treated 2 patients by rigidly limiting their fluids and obtained uneventful recovery. Since then Muirhead and his associates<sup>81</sup> and Burnett<sup>86</sup> have recommended similar treatment.

The therapeutic regime employed in the treatment of all patients with anuria or oliguria from lower-nephron nephrosis at the Cushing Veterans Administration Hospital has been divided into three phases.

If shock or dehydration is present in the initial phase of this syndrome, whole blood, plasma or saline solution is employed to combat these phenomena.

The second phase of treatment begins when it is observed that the urine volume is markedly diminished or anuria has occurred. Then 750 cc of 15 per cent glucose in distilled water is given

by vein daily, care being taken to run this in slowly, with every precaution to avoid thrombosis of veins. If necessary a vein is cut down upon. Nothing is given by mouth since vomiting appears to be increased by the oral administration of food or liquid. If there is significant vomiting the amount is carefully measured and that much physiologic saline solution is added to the daily infusion of dextrose in water. During the second week of treatment great fortitude is required because of the insistent demands that the patient be drowned with large volumes of intravenous fluid. This must be resisted. If acidosis becomes clinically manifest (as well as being evident on laboratory examination) a liter of one-sixth molar sodium lactate is given, the extracellular fluid volume being thus expanded as the price for combating acidosis.\* Electrocardiograms are made at least every other day for the observance of changes indicative of an excess of potassium. It is my hope at present that it may be possible to combat this if it occurs, by the insertion of a modified Miller-Abbott tube into the small intestine and the perfusion through it into the proximal jejunum of a slightly hypertonic, potassium-free electrolyte and dextrose solution, which is withdrawn from the distal ileum, where its potassium content should be in equilibrium with the blood plasma. With such a procedure Maluf<sup>88</sup> has been able to achieve blood urea clearances of 32 cc per minute. Any loss of sodium is then replaced intravenously with either potassium-free Ringer lactate or one-sixth molar sodium lactate solution.

When the stage of diuresis appears in the second or third week the third phase of treatment is employed, which consists in administration of a volume of water sufficient to make up for the total urine volume in addition to 1000 cc for insensible loss as well as any other losses, together with the amount of sodium chloride found in the preceding day's urine. Frequently, during the phase of diuresis, moderate to severe anemia is noted. This is treated by the transfusion of carefully matched blood. If the patient's anuria has been due to a hemolytic transfusion reaction the greatest of care is exercised in the administration of blood although with proper precautions this is a safe procedure. In the state of diuresis the kidney is producing an only slightly modified glomerular filtrate as urine, which may show only a twofold or threefold concentration of nitrogen and very little ability to conserve sodium chloride. Accordingly, salt

depletion must be avoided. Furthermore, at this time when the urine volume may be well in excess of 2 or 3 liters daily, the danger of drowning the patient has become remote.

### CASE REPORTS

In the following cases the lower-nephron nephrosis was treated by intravenous administration of large volumes of saline solution. Death from pulmonary edema ensued.

**CASE 1 (CVAH 578)** A 40-year-old man, 2 days after drinking with a friend (Case 2) on November 28, suffered nausea and vomiting, followed by a steadily falling urinary output. Approximately 2 liters of 5 per cent dextrose in physiologic saline solution was administered by vein daily. The urine specific gravity was 1.010, with a + test for albumin, and there were a few red and white blood cells in the sediment. The blood nonprotein nitrogen was 72 mg per 100 cc. on December 2 and 115 mg on December 7. The carbon dioxide capacity was 15.3 milliequiv per liter on December 7.

The urinary output during the last 24 hours was 2000 cc.

Autopsy revealed central necrosis of the liver, lower-nephron nephrosis, two 0.6-cm ulcerations in the duodenum, pulmonary edema and bilateral hydrothorax, with 300 cc. of fluid in the left and 400 cc. in the right pleural cavity. The left lung weighed 1300 gm, and the right 1250 gm. Microscopical examination showed the alveoli to be filled with edema fluid. Examination of the viscera was negative for poisons of the heavy-metal group.

**CASE 2 (CVAH 596)** A 36-year-old man, 2 days after drinking with a friend (Case 1) on November 28, noticed nausea and vomiting together with tremulousness and hallucinations. From December 1 to 4, inclusive, 9000 cc. of 5 per cent dextrose in physiologic saline solution was given intravenously in the face of a falling urinary output. Periorbital ecchymoses appeared spontaneously on December 3 and spread over the chest on December 6. Edema of the face and extremities was noted on December 4 and of the lungs on December 5. The urine specific gravity was 1.015, with an acid reaction and a +++ test for albumin and a few red and white blood cells in the sediment. The blood nonprotein nitrogen was 157, 162 and 195 mg per 100 cc. on December 4, 5 and 6. The plasma chloride was 87, and the carbon dioxide capacity 8.5 milliequiv per liter on the day of death (December 6). The blood prothrombin was 30 per cent of normal, the Lee-White coagulation time 19 minutes, and the bleeding time 2 minutes. No fluids were given on December 5. Death occurred 6 hours after intravenous infusion of 1000 cc. of physiologic saline solution in addition to 500 cc. of one-sixth molar sodium lactate.

No autopsy was performed.

In the following case of lower-nephron nephrosis following an extensive brain hemorrhage, pulmonary edema was controlled by rigid restriction of fluids.

**CASE 3 (CVAH, 4601)** A 29-year-old man was subjected to a second craniotomy and exploration of the third ventricle on January 16. Two transfusions of blood were given. During the next 3 days the temperature increased to 106°F, and a period of hypotension lasting 18 hours occurred. Consciousness was never regained after operation. From January 20 to 23 inclusive the patient received 4000 cc. of 5 per cent dextrose in distilled water and 4000 cc. of 5 per cent dextrose in physiologic saline solution intravenously. From operation until January 20 he was incontinent of an unknown amount of urine. Thereafter he was completely anuric. On January 23 both lungs were filled with moist rales. During the next 7 days he received 750 cc. of 15 per cent dextrose in distilled water by vein daily, with the gradual complete clearing of all signs of pulmonary edema. The blood nonprotein nitrogen rose from 96 mg per 100 cc. on January 21 to 182 mg on January 28, the plasma chloride fell to 81.2, and the carbon dioxide capacity to 10.4 milliequiv per liter. Death occurred on January 30 (1 week after the restriction of fluids).

\*If any degree of base dilution has occurred from the excessive intake of 5 per cent sodium bicarbonate solution may be employed. Not infrequently when first seen these patients have already received large quantities of water by mouth or fluids of low salt content parenterally and as a result may exhibit significant hypotonicity of expanded body fluids. Such salt depletion even in the presence of edema may be greatly corrected by the intravenous administration of 3 to 5 per cent sodium chloride with or without bicarbonate. It should be emphasized that in these patients the tonicity of the blood cannot be estimated with accuracy from the serum chloride and bicarbonate.

Autopsy revealed a normal degree of hydration throughout the body. The left lung weighed 450, and the right, 500 gm. There was no evidence of pulmonary edema. Lower-nephron nephrosis was present. A large operative defect in the right frontal lobe of the brain was filled with a blood clot, which extended across the midline to obliterate the basal ganglions on the left and to involve the corpus callosum and insula. The blood clot measured approximately 130 cc. Numerous cysts lined with a single layer of endothelial cells occupied

ination was negative except for hypertension, the blood pressure being 160/110. The lungs were clear. The urine was neutral, with a specific gravity of 1.012, a ++ test for albumin and red and white blood cells in the sediment. The blood nonprotein nitrogen was 185 mg per 100 cc, rising to 240 mg, and the serum chloride 85.5 milliequiv per liter, falling to 80.3 milliequiv, the carbon dioxide capacity was 13.8 milliequiv per liter, falling to 8.5 milliequiv before death on June 11. Treatment was limited to the administration of 1800 cc of 15 per cent dextrose in distilled water intravenously during 40 hours in the hospital. Three electrocardiograms were taken. On June 9 the P waves were low, the QRS complexes widened and slurred, and the ST intervals depressed. The QT interval was 0.36 second. On June 10 the P waves were absent, the T waves were tall and wide, and the QT interval was 0.52 second. Shortly before death on June 11, there was an idioventricular rhythm with a rate of 32, the QRS complexes measured 0.20 second, and the QT interval was 0.92 second (Fig. 1).

Autopsy showed lower-nephron nephrosis and central necrosis of the liver. The pleural cavities each contained 250 cc of fluid. The left lung weighed 660 gm, and the right 600 gm. Microscopical examination disclosed atelectasis

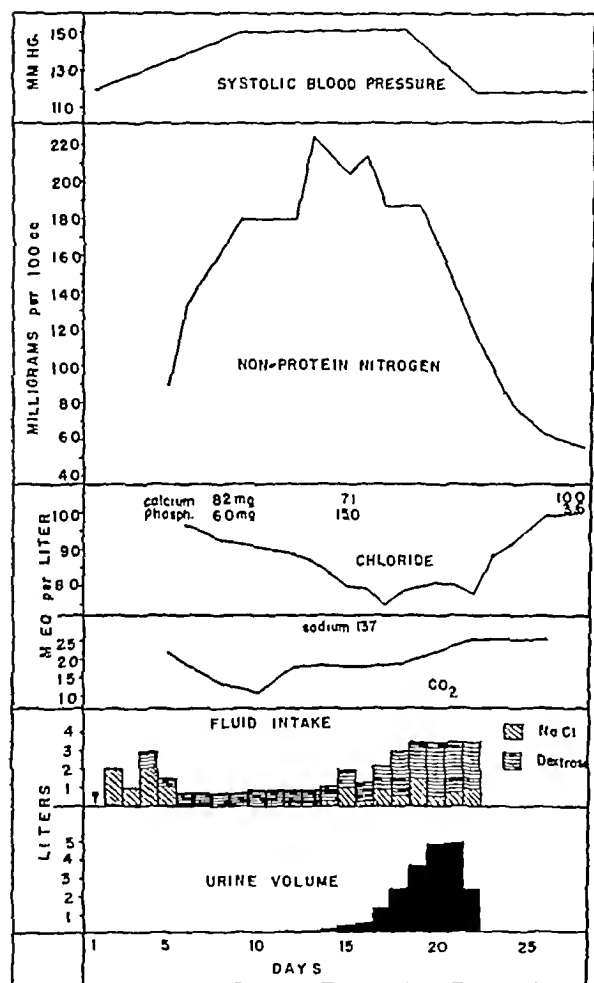


FIGURE 2 Essential Data in Case 6

the right thalamus, hypothalamus, midbrain and pons. Blood was present over both hemispheres and the base of the brain.

In the following case the lower-nephron nephrosis was self-treated by fluid restriction. Death with the electrocardiographic changes of hyperkalemia occurred. There was no pulmonary edema.

**CASE 4 (CVAH 3857)** A 52-year-old man had partaken freely of whisky on May 30. He denied the ingestion of any unusual beverages or foods. On June 2 he felt weak, complained of pain in his back and noted a diminished urinary output. Anorexia, nausea and some vomiting began on June 4. He took no food whatsoever and restricted his fluids to less than 1000 cc daily. The urinary output diminished steadily. When, on June 9, it was less than 2 oz, the patient became alarmed and sought hospitalization. Physical exam-

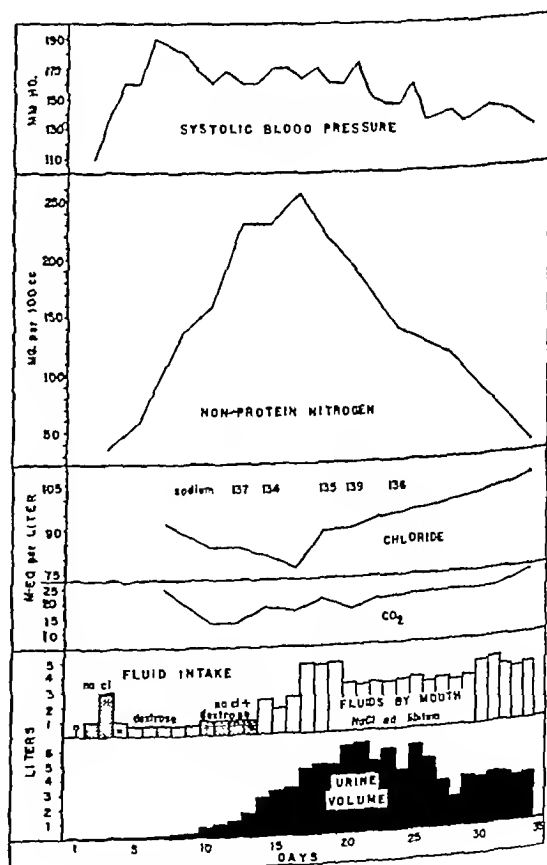


FIGURE 3 Essential Data in Case 7

of the left lower lobe and a small infarct in the right lower lobe but no significant pulmonary edema.

The following case of lower-nephron nephrosis was complicated by severe hypertension and nitrogen retention. The urinary output was normal.

**CASE 5 (CVAH 6331)** A 35-year-old man developed anorexia, nausea and vomiting several days after drinking to excess on October 12, followed by pain in the lumbar region

on October 16 and two convulsive seizures on October 17, after which he was admitted to the hospital.

Two years before admission he had begun to have convulsive seizures occurring at intervals of several months. Eight months after the first seizure his skull was fractured when struck by an airplane propeller. He was unconscious for an unknown period and was hospitalized for a fortnight.

On admission to this hospital the patient was agitated, confused and hallucinated. Numerous ecchymoses were observed over his body. The blood pressure was 220/120. The ocular fundi were normal. All deep tendon reflexes were hyperactive. The urine volume averaged 2000 cc daily. The specific gravity varied from 1.006 to 1.010, a + test for albumin was constantly observed, and red and white blood cells were present in the sediment on all examinations. The spinal fluid was under normal pressure but showed over 5000 red cells per cubic millimeter. On October 22 the blood nonprotein nitrogen was 175 mg per 100 cc., falling to 154 mg 2 days later, when the serum chloride was 73.3 milliequiv and the carbon dioxide capacity 14.7 milliequiv per liter. The blood pressure during his 8 days in the hospital varied from 176/98 to 220/140. A convulsion on October 23 was followed by increased clouding of the sensorium. Several small flame hemorrhages developed in the left retina, and the arteries were observed to be contracted. An electrocardiogram on October 22 was normal. The QRS complexes measured 0.07 second. Two days later the P waves were wider, the PR interval was 0.21 second, the QRS complexes widened and slurred (0.11 second), and the T waves tall and peaked. Death occurred on October 25.

Autopsy revealed central necrosis of the liver and lower-nephron nephrosis, with no evidence of antecedent renal disease. The lungs were free of edema, the left weighing 250 gm and the right 200 gm. There was a depressed fracture of the left parietal region of the skull with an area of brain necrosis 3 cm deep beneath it.

The following cases of lower-nephron nephrosis were treated by fluid restriction and dextrose administration.

**CASE 6 (C\A H 865)** A 28-year-old man, while drinking in a hotel bar on March 9, became nauseated and began to vomit. He continued to vomit during the 5 succeeding days and passed no urine after March 10. From March 11 to 14 inclusive he received intravenously 6000 cc of 5 per cent dextrose in physiologic saline solution and 1500 cc of 5 per cent dextrose in distilled water. On admission to the Medical Service on March 14 the blood nonprotein nitrogen was 90 mg per 100 cc, and the carbon dioxide capacity 22 milliequiv per liter. At this time edema of the face and extremities was present. For the next 2 weeks the patient received nothing by mouth, with the rapid subsidence of excessive vomiting, so that only 100 to 200 cc. was regurgitated daily. Two hundred gm of dextrose was administered by vein daily, dissolved in 750 cc of distilled water with an additional amount equal to the preceding day's loss in vomitus. With the onset of diuresis he received an additional amount of physiologic saline solution approximately equivalent to the preceding day's urinary chloride output. (The frequent thrombosis of veins that occurred with the concentrated dextrose has since caused the use of any solution stronger than 15 per cent to be abandoned, in addition the evidence cited above<sup>1</sup> indicates that 100 gm of dextrose is almost as effective in reducing protein catabolism as 200 gm.) The essential data obtained in this patient are shown in Figure 2. Recovery was uneventful. Urine passed after the onset of diuresis was of a fixed specific gravity at 1.010 and contained albumin and red and white blood cells.

**CASE 7 (C\A H 6969)** A 40-year-old man was drinking on October 18. On the following day he had severe vomiting and weakness of his right arm and leg of a peripheral neuritic type, possibly associated with the fact that he had been lying on the floor for some hours in a comatose state. During the day an unknown amount of urine was passed, the specific gravity of which was 1.010. The sediment contained albumin and red and white blood cells. Subsequently, he was anuric. During the first 2 days of anuria he received 4000 cc. of 5 per cent dextrose in saline solution and 1000 cc. of 5 per cent dextrose in distilled water on the 3rd day. At this time, when first seen, he had moderate generalized edema. For the

next 5 days he received 750 cc. of 15 per cent dextrose in distilled water by vein daily. No thrombosis occurred. With the onset of diuresis on the 9th day he was given 1000 cc of physiologic saline solution containing 100 gm of dextrose daily for 4 days, with the subsequent increase in his generalized edema and the appearance of moist rales throughout both lungs. On the night of the fourth day he had a generalized convulsion in which he fractured his left humerus. The serum calcium at this time was 9.3 mg per 100 cc. After this episode he appeared much improved and was able to take fluid and food by mouth. Although his intake rose to almost 5 liters, his diuresis kept pace with this. The pulmonary and generalized edema subsided, the blood nonprotein nitrogen fell, the serum chloride and carbon dioxide capacity rose, and he made an uneventful recovery. The essential data are shown in Figure 3. Nitrogen clearance was estimated after the onset of diuresis from the 24-hour output of nonprotein nitrogen in the urine and the blood nonprotein nitrogen. From 1.25 cc per minute on the 10th day of illness it rose steadily to 27.6 cc. 4 weeks later. A week after this the standard urea clearance determined in the usual fashion was 70 per cent of normal.

### SUMMARY AND CONCLUSIONS

The precipitating factors, clinical and chemical aspects and pathologic histology of lower-nephron nephrosis are reviewed.

Evidence is presented suggesting that neither nitrogen retention nor acidosis is responsible for the usual fatal outcome.

Fatal cases of lower-nephron nephrosis often exhibit generalized and pulmonary edema at autopsy, the pulmonary edema frequently being the immediate cause of death.

In the absence of pulmonary edema there is evidence that potassium intoxication may lead to a fatal outcome.

Available data indicate that man, unlike small animals, may survive without renal function for four or more weeks, if excessive quantities of fluids are not administered parenterally.

Histologic and clinical evidence indicates that the tubular lesion is often reparable, with spontaneous diuresis to be expected within three weeks if the patient can be kept alive this long.

A review of the many treatments proposed for this condition fails to reveal evidence that any of them speeds the appearance of spontaneous diuresis.

A regime is outlined consisting essentially in the replacement of water loss and the furnishing of 100 gm of dextrose daily, which it is believed may, in many cases, permit the patient to survive long enough to have spontaneous recovery.

Seven cases illustrating various phases of this syndrome and its treatment are reported.

### REFERENCES

- 1 Lucke B. Lower nephron nephrosis: renal lesions of crush syndrome of burns, transfusions, and other conditions affecting lower segments of nephrons. *Mil Surgeon* 99:371-396 1946.
- 2 Mallory T B. Hemoglobinuric nephrosis in traumatic shock. *Am J Clin Path* 17:427-443 1947.
- 3 DeGowin E. L., Warner E. D. and Randall W. L. Renal insufficiency from blood transfusion. II. Anatomic changes in man compared with those in dogs with experimental hemoglobinuria. *Arch Int Med* 61:603-650 1938.
- 4 DeNavasquez S. Excretion of haemoglobin with special reference to transfusion kidney. *J Path & Bact* 51:41-425 1940.
- 5 Daniels W. B., Leonard B. W. and Holtzman S. Renal insufficiency following transfusion: report of 13 cases. *J A M A* 116:1205-1215 1941.

Autopsy revealed a normal degree of hydration throughout the body. The left lung weighed 450, and the right, 500 gm. There was no evidence of pulmonary edema. Lower-nephron nephrosis was present. A large operative defect in the right frontal lobe of the brain was filled with a blood clot, which extended across the midline to obliterate the basal ganglions on the left and to involve the corpus callosum and insula. The blood clot measured approximately 130 cc. Numerous cysts lined with a single layer of endothelial cells occupied

ination was negative except for hypertension, the blood pressure being 160/110. The lungs were clear. The urine was neutral, with a specific gravity of 1.012, a ++ test for albumin and red and white blood cells in the sediment. The blood nonprotein nitrogen was 185 mg per 100 cc., rising to 240 mg, and the serum chloride 85.5 milliequiv per liter, falling to 80.3 milliequiv, the carbon dioxide capacity was 13.8 milliequiv per liter, falling to 8.5 milliequiv before death on June 11. Treatment was limited to the administration of 1800 cc of 15 per cent dextrose in distilled water intravenously during 40 hours in the hospital. Three electrocardiograms were taken. On June 9 the P waves were low, the QRS complexes widened and slurred, and the ST intervals depressed. The QT interval was 0.36 second. On June 10 the P waves were absent, the T waves were tall and wide, and the QT interval was 0.52 second. Shortly before death on June 11, there was an idioventricular rhythm with a rate of 32, the QRS complexes measured 0.20 second, and the QT interval was 0.92 second (Fig. 1).

Autopsy showed lower-nephron nephrosis and central necrosis of the liver. The pleural cavities each contained 150 cc of fluid. The left lung weighed 660 gm, and the right 600 gm. Microscopical examination disclosed atelectasis

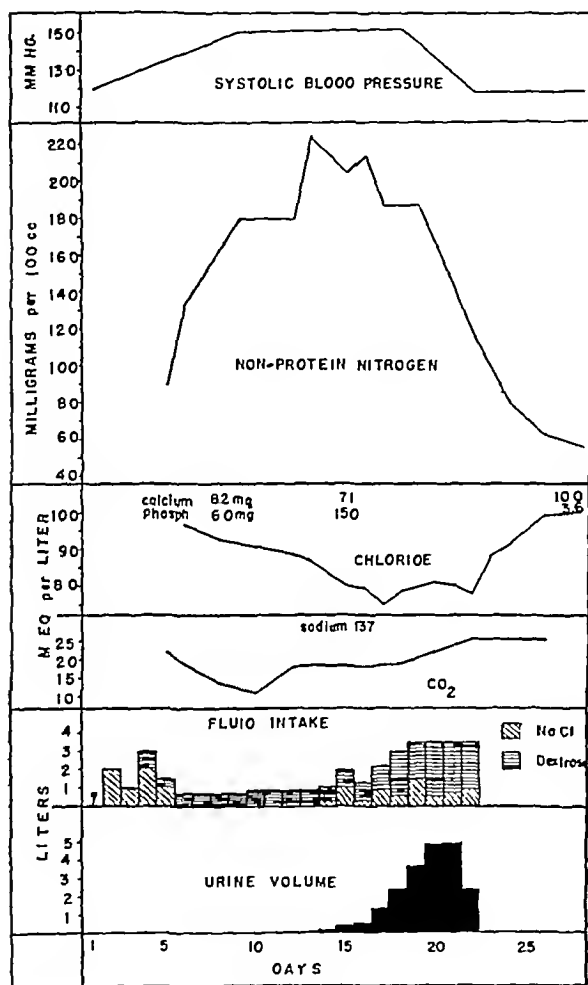


FIGURE 2 Essential Data in Case 6

the right thalamus, hypothalamus, midbrain and pons. Blood was present over both hemispheres and the base of the brain.

In the following case the lower-nephron nephrosis was self-treated by fluid restriction. Death with the electrocardiographic changes of hyperpotassemia occurred. There was no pulmonary edema.

CASE 4 (CVAH 3857) A 52-year-old man had partaken freely of whisky on May 30. He denied the ingestion of any unusual beverages or foods. On June 2 he felt weak, complained of pain in his back and noted a diminished urinary output. Anorexia, nausea and some vomiting began on June 4. He took no food whatsoever and restricted his fluids to less than 1000 cc daily. The urinary output diminished steadily. When, on June 9, it was less than 2 oz., the patient became alarmed and sought hospitalization. Physical exam-

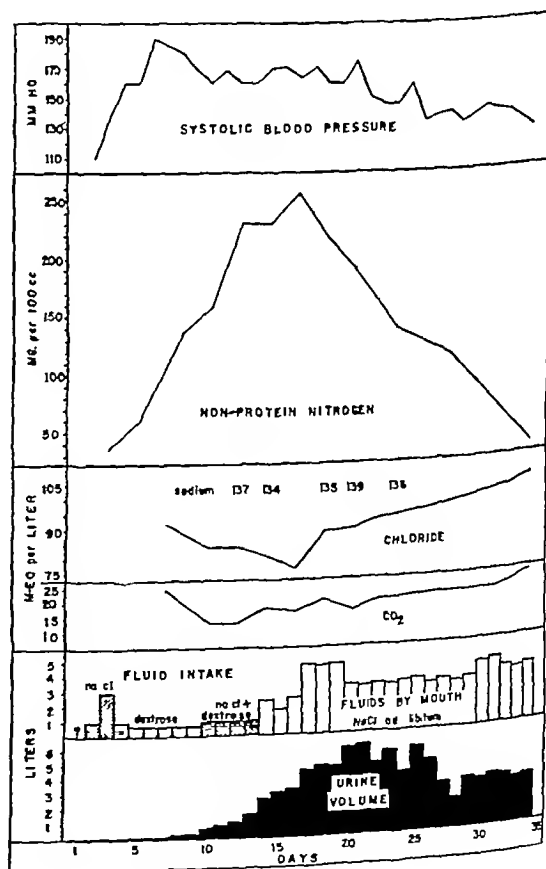


FIGURE 3 Essential Data in Case 7

of the left lower lobe and a small infarct in the right lower lobe but no significant pulmonary edema.

The following case of lower-nephron nephrosis was complicated by severe hypertension and nitrogen retention. The urinary output was normal.

CASE 5 (CVAH 6331) A 35-year-old man developed anorexia, nausea and vomiting several days after drinking to excess on October 12, followed by pain in the lumbar region

## DICUMAROL THERAPY IN CONGESTIVE HEART FAILURE\*

J. H. WISHART, M.D.,† AND CARLETON B. CHAPMAN, M.D.‡

MINNEAPOLIS, MINNESOTA

AMONG the more serious threats to the life of the decompensated cardiac patient are thrombosis and embolism, and some means of combating these phenomena are a very pressing need in cardiovascular therapeutics. Recent work with anticoagulant agents<sup>1, 2</sup> in postoperative patients, in cases of myocardial infarction and in cases of thrombophlebitis suggests that the use of dicumarol offers a safe and effective method of preventing such accidents. To test the effectiveness of this drug, all patients admitted to the Veterans Administration Hospital, Minneapolis, because of cardiac decompensation have been treated with dicumarol since October, 1946. The present report is a preliminary evaluation of the therapy as carried out up to August, 1947.

Although a clear description of hemorrhagic pulmonary infarcts was given by Laennec,<sup>3</sup> it was Virchow<sup>4</sup> who first proposed the view that these lesions were actually due to embolism of branches of the pulmonary artery and who suggested that stasis of the pulmonary circulation was a factor of some pathogenic importance. Experimental support for Virchow's views was supplied by Zahn,<sup>5</sup> who found that sterile mercury emboli, injected into the jugular vein, failed to produce hemorrhagic pulmonary infarcts in rabbits unless the thorax of the experimental animal was tightly bound within two days of the introduction of the embolus. Karsner and Ash<sup>6</sup> reported that obstruction of a branch of the pulmonary artery caused some circulatory changes in the lung tissue supplied by that branch but produced a hemorrhagic infarct only if stasis was effected by simultaneous ligation of the vein from the area.

From these earlier concepts grew the view, now generally accepted, that congestive heart failure predisposes to the development of thrombi in the veins or in the heart itself. These thrombi in time may give rise to infarcts, particularly in the lung, but also in other vital organs such as the brain and kidneys. It is of interest that although Laennec had no adequate concept of the pathogenesis of hemorrhagic infarcts of the lungs, both the illustrative cases he presented in his original description of the lesion were cases of severe congestive heart failure. In recent years a number of surveys

have shown conclusively that pulmonary infarcts occur extremely frequently with congestive heart failure and possibly more frequently with this condition than with any other single disease. Hampton and Castleman<sup>7</sup> reported a series of 370 cases of pulmonary embolism and infarction at autopsy. One hundred and eleven were cardiac cases, and of these, 90 per cent showed infarcts of the lungs. Of the noncardiac medical cases, 62 per cent showed infarcts of the lung, whereas in only 58 per cent of the postoperative cases were pulmonary infarcts found. Hines and Hunt<sup>8</sup> observed that 81 (34.6 per cent) of a series of 234 cardiac cases at autopsy showed gross pulmonary infarcts, although this lesion had been diagnosed clinically in only 2

TABLE 1 Incidence of Pulmonary Infarcts in Series of Kinsey and White<sup>10</sup>

TYPE OF CASE	TOTAL CASES	CASES OF PULMONARY INFARCT
Autopsy performed	45 (24.4%)	18 (40%)
Death but no autopsy	30 (16.3%)	8 (27%)
Survival of patient	107 (59.3%)	14 (13%)
<b>Totals</b>	<b>184</b>	<b>40 (22%)</b>

\*Grades II and III only

of the 81 cases. Greenstein<sup>9</sup> reported pulmonary emboli in 50 per cent of 32 cardiac cases at autopsy. Kinsey and White<sup>10</sup> reviewed 200 cases of congestive heart failure to ascertain the cause of the fever often seen in this disease. They described three grades of cardiac failure: left ventricular failure alone, moderate right ventricular failure (enlarged liver with slight to moderate dependent edema), and marked right ventricular failure with anasarca. Their Grades II and III conform almost exactly with the cases making up the present series for which reason their statistics have been recomputed leaving out their Grade I (left ventricular failure alone). Table 1, constructed from their data, shows the incidence of pulmonary infarcts in the autopsied the dead but not autopsied and the surviving members of the series. In a series such as theirs, and our own, the true incidence of pulmonary infarction probably lies somewhere between the minimum (clinical) figure of 13 per cent and the maximum (autopsy) figure of 40 per cent. That many infarcts of the lungs and of the other organs such as the kidney and spleen are never suspected clinically cannot be denied, yet one cannot accept the incidence of such lesions at autopsy as the true incidence in all cases of congestive heart failure, since not all persons with congestive failure die

\*From the Veterans Administration Hospital and the Department of Medicine, University of Minnesota Medical School.

†Published with the permission of the Medical Director, Veterans Administration, who assumes no responsibility for the opinions expressed or the conclusions drawn by the authors.

‡Instructor in medicine, University of Minnesota Medical School and resident in medicine, Veterans Administration Hospital.

§Clinical assistant professor of medicine and senior staff member, Laboratory of Physiological Hygiene, University of Minnesota Medical School; consultant, Veterans Administration Hospital.

- 6 Ayer, G D and Gault A G Uremia following blood transfusion nature and significance of renal changes *Arch Path* 33 513-532, 1942.
- 7 Burwell, E. L. Kinney, T D and Finch, C A Renal damage following intravascular hemolysis *New Eng J Med* 237 657-665 1947
- 8 Macgrath B G and Findley G M. Oliguria in blackwater fever *Lancet* 2 403 1944
- 9 Terplan, K. L. and Javert C T Fatal hemoglobinuria with uremia from quinine in early pregnancy *J A M A* 106 529-532 1936
- 10 Landsteiner E. K. and Finch C A. Hemoglobinemia accompanying transurethral resection of prostate *New Eng J Med* 237 310-312 1947
- 11 Crevy, C D Hemolytic reactions during transurethral prostate resection *J Urol* 58 125-131 1947
- 12 Beall, D Bywaters E. G L. Belsey R. H R. and Milca J A. R. Case of crush injury with renal failure *Brit M J* 1 432-434, 1941
- 13 Bywaters E G L and Beall D Crush injuries with impairment of renal function *Brit M J* 1 427-432 1941
- 14 Mayon-White R. and Solandt, O M Case of limb compression ending fatally in uraemia *Brit M J* 1 434 1941
- 15 Dunn J S Gillespie M and Niver J S F Renal lesions in two cases of crush syndrome *Lancet* 2 549-552 1941
- 16 Bywaters E G L. Delory G E Rimington C and Smiles J Myohaemoglobin in urine of air raid casualties with crushing injury *Biochem J* 35 1164-1168 1941
- 17 Bywaters E G L. et al Discussion on effects on kidney of trauma to parts other than urinary tract including crush syndrome *Proc Roy Soc Med* 35 321-339 1941-1942
- 18 Bywaters E G L. and Dible J H Renal lesion in traumatic anuria *J Path & Bact* 54 111-120 1942
- 19 Bywaters E G L. Crushing injury *Brit M J* 2 643-646 1942
- 20 Darmady, F M et al Traumatic uraemia reports on 8 cases *Lancet* 2 807-812 1944
- 21 Parsons C G Traumatic uraemia *Brit M J* 1 180-182 1945
- 22 Gollan K R. Lemberg R and Money R A Observations upon crush injury syndrome and Volkmann's contracture associated with severe brain injury and hyperthermia *M J Australia* 2 212-214 1945
- 23 Birnbaum W. Crushing injuries with renal failure *California & West Med* 64 15-18 1946
- 24 Bywaters E G L. and Dible J H. Acute paralytic myohaemoglobinuria in man *J Path & Bact* 55 7-15 1943
- 25 Fischer, H. and Rosier P H Starkstromfälle mit schweren Muskelschädigungen und Myoglobinurie (Befunde Pathologic Prognose und Therapie) *Helvet med acta* 3 212 1947
- 26 Malamud N. Haymaker W. and Custer R P Heat stroke: a clinicopathologic study of 125 fatal cases *Mil Surgeon* 91 397-449 1946
- 27 Young J Renal failure after utero-placental damage *Brit M J* 2 715-718 1942
- 28 Paxson N F. Colub L. J. and Hunter R M Crush syndrome in obstetrics and gynecology *J A M A* 131 500-501 1946
- 29 Humphries J H. and Avery Jones F Oliguria after abortion *Clin Sci* 6 173-186 1947
- 30 McLetchie N G B Renal lesions in case of excessive vomiting *J Path & Bact* 55 17-22 1943
- 31 Goodpastor, W H. Levenson S M. Tagnon H J. Lund C C and Taylor F H L. Clinical and pathologic study of kidney in patients with thermal burns *Surg Gynec & Obst* 82 652-670 1946
- 32 Lund C C. Green R W. Taylor F H L. and Levenson S M Burns: collective review *Surg Gynec & Obst (Internat Abstr Surg)* 82 443-478 1946
- 33 Luetscher J A. Jr and Blackman S S Jr Severe injury to kidneys and brain following sulfathiazole administration high serum sodium and chloride levels and persistent cerebral damage *Ann Int Med* 18 741-756 1943
- 34 Maisel B. Kubik, C S. and Ayer J B Encephalopathy nephrosis and renal granuloma following sulfonamide therapy case with autopsy *Ann Int Med* 20 311-326 1944
- 35 Foy H. Gluckman J. and Konda A Pigment metabolism and renal failure in acute sulphonamide haemolysis resembling blackwater fever *Tr Roy Soc Trop Med & Hyg* 37 303-319 1944
- 36 French A. J. Hypersensitivity in pathogenesis of histopathologic changes associated with sulfonamide chemotherapy *Am J Path* 22 679-701 1946
- 37 Dudley, S F Toxic nephritis following exposure to carbon tetrachloride and smoke fumes *J Indust Hyg & Toxicol* 17 93-110 1935
- 38 Smetana H. Nephrosis due to carbon tetrachloride *Arch Int Med* 63 760-777 1939
- 39 Simon M A. Acute toxic nephritis due to inhalation of carbon tetrachloride fumes *Canad M A J* 41 580-583 1939
- 40 Hammes E. M Jr Carbon tetrachloride as industrial hazard report of two cases *J Indust Hyg & Toxicol* 23 112-117 1941
- 41 Ashe, W F and Sailer S Fatal uremia following single exposure to carbon tetrachloride fumes *Ohio State M J* 38 553-555 1942
- 42 Corcoran A C Taylor R D. and Page I H Acute toxic nephrosis clinical and laboratory study based on case of carbon tetrachloride poisoning *J A M A* 123 81-85 1943
- 43 Forbes J R. Carbon tetrachloride nephrosis *Lancet* 2 590-592 1944
- 44 Kugel, V H. Acute toxic nephrosis in carbon tetrachloride poisoning *J Mt Sinai Hosp* 12 440-447 1945
- 45 Martin W B. Dyke L H Jr, Coddington F L. and Snell A M Carbon tetrachloride poisoning: report of one case with necropsy and one nonfatal case with clinical laboratory studies *Ann. Int. Med* 25 488-497 1946.
- 46 Woods W W Changes in kidneys in carbon tetrachloride poisoning, and their resemblance to those in "crush syndrome" *J Path. & Bact.* 58 767-773 1946.
- 47 Geraghty, F J. and Rogers W A Carbon tetrachloride poisoning with report of case *West Virginia M J* 43 242-246, 1947
- 48 Clinton M Jr Renal injury following exposure to carbon tetrachloride report of case *New Eng J Med* 237 183-185, 1947
- 49 Bywaters E G L. Anatomical changes in liver after trauma. *Clin Sci* 6 19-39 1946
- 50 Kugel, V H Management of acute toxic nephrosis. *Am. J. Med.* 3 188-205 1947
- 51 Winkler A W. Hoff, H E. and Smith P K. Electrocardiographic changes and concentration of potassium in serum following intravenous injection of potassium chloride *Am J Physiol.* 124-478-483 1938
- 52 Winkler A W Hoff H E. and Smith P K. Toxicity of orally administered potassium salts in renal insufficiency *J Clin. Invest.* 20 119-126 1941
- 53 Hoff H E. Smith P K. and Winkler A W Cause of death in experimental anuria *J Clin Investigation* 20 607-624 1941
- 54 Fontaine, A W Suppression of urine for twenty five days. *Virginia M Monthly* 1 407-414 1874
- 55 Gordon S C Cited by Howe H P Unusual case of suppression of urine *New York M J* 84 1186 1905.
- 56 Viningham W D Case of total anuria of twenty three days followed by perfect recovery *J M Soc New Jersey* 5:566-568 1909
- 57 Meyers, W A Obstructive anuria report of remarkable case. *J A M A* 85 10-13 1925
- 58 Farnsworth A H Complete anuria *J A M A* 85 1420 1925
- 59 Meyers W A Long standing anuria certain associated phenomena. *J A M A* 86 1198-1201 1926
- 60 Koletsky S. and Gustafson G E Effects of temporary cessation of renal blood flow in rats *J Clin Investigation* 26 1072-1078 1947
- 61 Alwall N. and Norvitt, L. On artificial kidney II. Effectivity of apparatus *Acta med Scandinavica* Supp 134 250-259 1947
- 62 Alwall N. Norvitt L. and Steins A M Clinical extracorporeal dialysis of blood with artificial kidney *Lancet* 1 60-62, 1945
- 63 Herter C A Results of experimental nephrectomy in dogs as bearing upon uraemic state *M Rec* 54 260-282 1897
- 64 Mosenthal H O. and Hiler A Reaction of nonprotein nitrogen to urea nitrogen of blood *J Urol* 1 75-89 1917
- 65 Abbott W. E. and Shea P Treatment of temporary renal insufficiency (uremia) by peritoneal lavage *Am J M Sc* 211,317-319 1946
- 66 Gamble J L. *Chemical Anatomy Physiology and Pathology of Extracellular Fluid A lecture syllabus* 159 pp Cambridge Harvard University Press 1947
- 67 Peters J P. Nitrogen metabolism in acute and chronic disease *Ann New York Acad Sc* 47 327-344 1946.
- 68 Butler A M et al Cited by Gamble
- 69 Winkler A W. Darowski T S. Eklinton J R. and Peters, J P Electrolyte and fluid studies during water deprivation and starvation in human subjects and effect of ingestion of fish oil carbohydrate and of salt solutions *J Clin. Investigation* 23 807-815 1944
- 70 Winkler A W. and Smith P K. Apparent volume of distribution of potassium injected intravenously *J Biol Chem.* 134 589-598 1938
- 71 Gamble J L. Personal communication
- 72 Reuter F A Anuria tubulo interstitial extravasation 1 Renal capsulotomy Preliminary report *J Urol* 58 97-99 1947
- 73 Lowe E. S Renal decapsulation in treatment of oliguria and anuria. *U S Nav M Bull* 47 959-964 1947
- 74 Peters J T Oliguria and anuria due to increased intrarectal pressure *Ann Int Med* 23 221-236 1945
- 75 Culpepper W S and Findley T Renal decapsulation for oliguria and anuria. *Am J M Sc* 214 100-103 1947
- 76 Talbot, J H Heterogeneous renal disorders *New Eng J Med* 226 228-236 1942
- 77 Seligman A M. Frank, H A. and Fioe J Treatment of experimental uremia by means of peritoneal irrigation *J Clin. Invest.* 25 211-219 1946
- 78 Frank H A. Seligman A M. and Fine J Treatment of uremia after acute renal failure by peritoneal irrigation *J A M A* 130 703-705 1946
- 79 Buckley R W. and Scholten R A Treatment of acute uremia by peritoneal lavage report of case *New Eng J Med* 237 431-434 1947
- 80 Grossman L. A. Ory E M. and Willoughby D H. Anuria treated by peritoneal irrigation *J A M A* 135 273-275 1947
- 81 Muirhead, E E. Small A B. Haley A E. and Hill J M. Peritoneal irrigation for acute renal damage following incompatible blood transfusion discussion based on three cases. *J Lab & Clin Med* 32 988-1001 1947
- 82 Bassett, S H et al Nitrogen and fluid balance in treatment of acute uremia by peritoneal lavage analysis of peritoneal washings for protein nonprotein nitrogen and phosphorus. *Arch Int. Med* 80 616-636 1947
- 83 Kolff W J Artificial kidney *J Mt Sinai Hosp* 14 71-79 1947
- 84 Alwall, N. On artificial kidney I Apparatus for dialysis of blood in vivo *Acta med Scandinavica* 128 317-325 1947
- 85 Wakeman A M. Morrell C A. Eisenman A J. Sprunt, D L. and Peters J P Metabolism and treatment of black water fever *Am J Trop Med* 12 407-1932.
- 86 Burnett, C H. Clinical and therapeutic aspects of acute renal insufficiency due to lower nephron or hemoglobinuria nephrosis *Am Practitioner* 2 6-10 1947
- 87 Peters J P. Personal communication
- 88 Malin N S R. Urea-clearance by perfusion of entire intact small intestine in man *Federation Proc* 7 77 1948

No hemorrhagic complications developed in any of the cases although it was often necessary to suspend dicumarol therapy because of excessive depression of the prothrombin concentration

Vitamin K (30 mg intravenously, three or four times daily) was occasionally used to counteract excessive dicumarol effect, but this measure was rarely necessary

The mortality in the series was 32.8 per cent (20 deaths), and autopsies were done in 12 cases

### RESULTS

Probably the most significant finding in this survey is that there were no deaths definitely attributable to classic pulmonary embolism, and only 1

dence, has been taken to mean probable renal infarction

On the basis of clinical data, definite pulmonary infarcts developed in 2 patients on dicumarol therapy. There is evidence, however, that the dicumarol effect was inadequate before and during the time the embolic phenomena appeared. One of the patients developed thrombophlebitis at a time when dicumarol dosage was adequate, but some days later, when pulmonary infarction occurred, the prothrombin concentration ranged between 30 and 35 per cent. Although these levels are borderline, this case is included in our list of dicumarol failures. The other patient was put on dicumarol therapy because he had previously de-

TABLE 3 *Infarcts Found at Autopsy*

PATIENT	TYPE OF HEART DISEASE	LOCATION OF THROMBI	LOCATION OF INFARCT	OCCURRENCE OF INFARCTION
C A	Isolated myocarditis	Left ventricle	Right kidney	Before dicumarol treatment
C V	Acute myocardial infarct	Left ventricle	Lower lobes of lungs	Before and during dicumarol treatment
C M	Arteriosclerotic	Left auricle	Right kidney and spleen	Before dicumarol treatment
C L	Hypertensive and arteriosclerotic	Left auricle	Lower lobes of lungs	After dicumarol treatment
B G	Rheumatic	Left auricle	Lower lobes of lungs	After dicumarol treatment
J H	Hypertensive and arteriosclerotic	Femoral vein	Lower lobes of lungs	Before and after dicumarol treatment

death might conceivably have been due to such a condition. The patient was an eighty-two-year-old man who had severe arteriosclerotic heart disease and whose electrocardiogram showed left bundle-branch block. His decline was actually gradual but death occurred unexpectedly, and since there was no autopsy one cannot rule out massive pulmonary embolism as the immediate cause of death. In none of the remaining 19 cases was death sudden enough or the terminal symptoms suggestive enough to permit the diagnosis of fatal pulmonary embolism. No such embolus was found in any of the 12 autopsied cases although small emboli were present in several.

The clinical diagnosis of nonfatal embolism and infarction in the lungs is notoriously difficult and in many cases is frankly impossible. Under the best of conditions many infarcts remain silent and undiagnosed. In the present work symptoms and signs were carefully scrutinized for evidence of infarction. In addition, elevations in temperature, pulse rate, white-cell count and sedimentation rate, x-ray films of the chest and urinary-sediment, serum-bilirubin and urinary-urobilinogen determination were specifically studied. Unexplained elevations in temperature, pulse or sedimentation rate probably do not constitute sufficient evidence for the diagnosis of infarction unless accompanied by other evidence such as appropriate symptoms and signs, the visualization of pulmonary lesions by x-ray study or elevation in serum bilirubin or urine urobilinogen. On the other hand, unexplained hematuria, alone or in combination with other evi-

veloped pulmonary infarction. Since there was a rather marked initial drop in the prothrombin concentration, dicumarol was discontinued and was not started again for nine days. During the three days preceding the appearance of fresh infarcts of the lung, the prothrombin concentration ranged between 60 and 70 per cent, and it seems likely that the complication would have been avoided if the dicumarol dosage had been adequate. The case was therefore not included in the group of dicumarol failures. Two patients had transient, microscopic hematuria (2 or 3 red cells per high-power field in a single specimen) while on dicumarol therapy, but in 1 case the infarct, if present, occurred before adequate reduction in the prothrombin concentration had been obtained. In the other case dicumarol therapy was adequate, and the case was accepted as one of dicumarol failure.

At autopsy infarcts (other than myocardial) were present in 6 out of 12 cases. From the ages of the lesions as judged morphologically, it was possible to determine with reasonable certainty whether the infarcts had occurred before, during or after dicumarol therapy. In 5 cases infarcts had developed either before dicumarol had been given or after it had been withdrawn. In the remaining case pulmonary infarction had apparently occurred in spite of adequate doses of dicumarol. The patient, who was suffering from massive myocardial infarction, developed large mural thrombi and multiple pulmonary infarcts but was so ill that the complication did not become clinically

while under observation. In fact, death may occur partly as a result of multiple embolic phenomena so that the incidence at autopsy, as compared with the incidence in a series of this type, is probably unduly high. We believe that the figure 22 per cent is as close as one can come at present to the true incidence of pulmonary infarcts in patients with congestive heart failure, not all of whom die and none of whom are treated with anticoagulants. The true incidence is almost certainly no lower, and may well be somewhat higher.

### MATERIAL

To arrive at a preliminary evaluation of the therapy the records of all patients treated were reviewed. Patients with dyspnea and basal rales as the only indication of decompensation were excluded. Minimum requirements for inclusion in the series comprised such signs as hydrothorax, enlarged tender liver, peripheral edema and elevation of the venous pressure. All except a few pa-

TABLE 2 *Types of Heart Disease*

TYPE	NO OF CASES	PERCENTAGE
Arteriosclerotic	23	38
Rheumatic	16	26
Hypertensive and arteriosclerotic	11	18
Hypertensive	7	12
Myocarditis etiology unknown	2	3
Syphilitic	1	—
Congenital defect with bacterial endocarditis	1	—

tients had peripheral edema, and many had anasarca. The total number of cases exhibiting definite congestive failure was 61. On the basis of the criteria of Kinsey and White 20 of our cases fell into Group II and 41 into Group III.

The ages of the patients in the series varied from twenty-two to eighty-four years, about two thirds being in the group from fifty to fifty-nine years. Ten patients were less than fifty, and 11 were over sixty years of age.

The average stay in the hospital was fifty-three days, the range being from nine to two hundred and ten days. Thirty of the 61 patients were in the hospital from two to six weeks, and 30 for more than six weeks. Only 1 patient was in the hospital for less than two weeks.

The types of heart disease represented in the series are shown in Table 2. There were 7 patients (12 per cent) with acute myocardial infarction and congestive failure, all 7 are included in the arteriosclerotic or hypertensive and arteriosclerotic categories. In 19 cases (31 per cent) auricular fibrillation was present, and there were definite signs of mitral stenosis in 11 (18 per cent). All 3 of these conditions probably predispose, independently of cardiac decompensation, to thrombosis and embolism. In spite of this fact no attempt was made

to rule out patients with any of the 3 conditions. Congestive failure was the only basis for selection.

### METHOD

Before a patient was given dicumarol, a careful search was made for contraindications to the use of the drug. According to Allen et al.,<sup>1</sup> these include renal insufficiency, blood dyscrasias that in themselves cause increased tendency to bleed, hepatic disease associated with a decrease in prothrombin concentration, ulcerative lesions of various sorts and operations on the brain or spinal cord after which bleeding might be fatal. The same authors regard subacute bacterial endocarditis as a probable contraindication. If no contraindications were present, a sample of blood for determination of the prothrombin time was withdrawn, and the initial dose (usually 200 mg) of dicumarol was given orally. In a few cases, small doses of heparin were given intramuscularly in addition to the dicumarol for the first twenty-four or forty-eight hours. Once the administration of dicumarol was begun, the prothrombin time was determined daily, and the dosage of the drug was adjusted accordingly. The aim was to keep the prothrombin concentration below 30 per cent and above 10 per cent, as suggested by Allen and his co-workers.<sup>1</sup> The average initial prothrombin concentration, before dicumarol was started, was 62 per cent of normal, and in 1 case it was only 17 per cent. We interpret this to be further evidence that liver function may be significantly impaired in congestive heart failure. Cotlove and Vorzimer<sup>11</sup> studied the prothrombin time in 20 patients with congestive heart failure and concluded that the disorder does not per se influence the prothrombin time. Their data do not include control prothrombin times and for this reason are difficult to interpret. The present figures provide strong evidence that congestive heart failure may depress the prothrombin concentration (and increase prothrombin time) quite markedly.

The average number of days during which dicumarol was given was twenty-three, the range being from two to fifty-nine. The average duration of adequate dicumarol effect, as judged by the prothrombin time, was thirty-two days, with a range of four to one hundred and two. In most cases the drug was continued until the patient was ambulatory or until death supervened. The average total dose of dicumarol was 2255 mg, and the average daily dose was 105 mg. The latter figure is somewhat misleading in that it is calculated from the number of days on which dicumarol was actually given. Perhaps a more pertinent figure is the average dose per day of adequate dicumarol effect, which was 78 mg. This is in accord with the view that patients in cardiac failure require smaller doses of dicumarol than compensated persons do.<sup>11</sup>

## CLOSED-LOOP OBSTRUCTION OF THE ASCENDING COLON, WITH INCOMPLETE DESCENT OF THE CECUM, SIMULATING ACUTE CHOLECYSTITIS\*

EUGENE A. GASTON, M.D.,† and MAURICE E. COSTIN, M.D.‡

FRAMINGHAM, MASSACHUSETTS

**C**LINICAL findings and laboratory tests frequently fail to indicate accurately the pathologic status of the gall bladder in acute cholecystitis. Gangrene with incipient or actual perforation may exist with minimal physical signs and with normal or only slightly elevated temperature and blood counts. For these reasons and because of the ease and safety of cholecystectomy in the early stages of the disease, early operation is being advocated with increasing frequency.<sup>1-31</sup> The purpose of this communication is to present 2 cases in which acute, closed-loop obstruction of the ascending colon in combination with incomplete descent of the cecum was mistaken for acute cholecystitis, a diagnostic pitfall that may be avoided if both conditions are kept in mind when acute surgical problems involving the right upper quadrant of the abdomen are encountered.

### CASE REPORTS

**CASE 1** A 47-year-old woman was admitted to the hospital on January 7, 1941, complaining of abdominal pain of 5 hours' duration.

Two years before admission she began to complain of intermittent, dull, nagging pain in the right side of the abdomen, which was indefinitely located at the level of the umbilicus and in the right upper quadrant. She also noted flatulence and a feeling of distention following meals, which was relieved by belching. She had always been constipated, requiring a cathartic once or twice a week. Repeated questioning failed to elicit a history of change in bowel habits or abnormal stools. Three months before admission examination by her family physician revealed mild tenderness in the right middle portion of the abdomen. She was placed on a regimen that included milk of magnesia and mineral oil. Thereafter her bowels moved regularly and the abdominal pain disappeared, but gas and indigestion following food, particularly airy and fried food, persisted. She was instructed to take a fat-free diet, and 2 months later her weight had fallen from 150 pounds to 166 pounds. This was believed to be due to the low-calorie intake. A Graham test on December 18, 1940, showed no filling of the gall bladder.

About 2 weeks before admission abdominal pain recurred, at this time located in the right upper quadrant, nonradiating and considerably more severe than that during previous episodes. A bile-salt preparation prescribed at this time caused several watery stools a day but did not relieve the abdominal pain. Five hours before admission the patient was awakened by the sudden onset of excruciating pain in the right upper abdomen radiating to the right scapular region and associated with nausea and vomiting. When she was seen at home by the family physician the entire right side of the abdomen was found to be spastic and tender and she was immediately hospitalized.

Physical examination revealed a well developed, moderately obese woman who complained bitterly of pain in the right upper quadrant. The tongue was dry and furred. The heart was normal and the lungs were clear. The entire right side of the abdomen was tender and spastic, with the point

of maximum tenderness about 4 cm below the costal margin in the midclavicular line. Rebound tenderness was present throughout the abdomen and was referred to the right upper quadrant. No masses were felt. Pelvic and rectal examinations were noncontributory.

The temperature was 98°F, the pulse 90, and the respirations 20.

Each of two urine specimens showed no abnormalities. Examination of the blood disclosed a red-cell count of 4,530,000, with a hemoglobin of 91 per cent, and a white-cell count of 6700, with 61 per cent neutrophils. The icteric index was 9.

An initial diagnosis of acute cholecystitis and cholelithiasis was made, and operation was deferred until the fluid and electrolyte balance could be re-established. During the first 8 hours of hospitalization the abdominal tenderness progressively diminished, her general condition improved, and the white-cell count fell to 5400. At the end of this time she suddenly entered a state of peripheral vascular collapse, with rapid thready pulse and a blood pressure of 80/60. A poorly defined mass could then be felt in the right upper quadrant. Transfusion of whole blood was started at once, with rapid improvement. It was thought that the acutely inflamed gall bladder had perforated and as soon as her condition permitted, she was transferred to the operating room.

At operation the gall bladder was found to be normal. The cecum was incompletely descended and lay in the right upper quadrant. Five centimeters distal to the hepatic flexure was a small annular carcinoma, which completely obstructed the transverse colon. A huge retroperitoneal abscess was found in the right upper quadrant. Its lateral wall, consisting of parietal peritoneum overlaid the colon proximal to this lesion. This abscess was opened, and over a liter of bloody, foul-smelling pus was aspirated. A large area of gangrene was found on the posterior wall of the ascending colon near the hepatic flexure and in the center of this area was a perforation 2 cm in diameter. Since it was impossible to close the perforation satisfactorily, the right half of the colon was resected, the terminal ileum and transverse colon being exteriorized. During the operation the blood pressure fell to dangerously low levels in spite of the continuous administration of whole blood. After operation her condition continued progressively to deteriorate and she died 12 hours later. Permission for autopsy was refused.

**CASE 2** A 70-year-old woman was admitted to the hospital on March 28, 1948, with the chief complaint of abdominal pain.

Four years previously she had experienced an attack of fairly severe right-upper-quadrant pain which radiated to the right scapular region and which persisted for 24 hours. For 2 days thereafter she was mildly jaundiced but could not recall the color of stools or urine. Thereafter, she remained on a low-fat diet and, except for occasional bloating after meals, had no abdominal symptoms until the night before admission to the hospital. At that time she was awakened by the sudden onset of pain in the epigastrium radiating to the right upper quadrant. The pain was constant and associated with increasing tenderness. On the following morning the patient herself noted a mass in the right upper quadrant. There was no nausea or vomiting and she was emphatic in stating that her bowels moved daily and that there had been no change in bowel habits and no abnormal stools.

Physical examination revealed a well developed, well nourished woman in moderate distress. There was marked tenderness in the right upper quadrant of the abdomen associated with muscle spasm and some rebound tenderness. A firm tender mass about 6 cm in diameter, which descended with inspiration and appeared to be contiguous with the liver, was palpable below the right costal margin.

\*From the Surgical Service, Framingham Union Hospital and the Department of Surgery, Boston University School of Medicine.

†Assistant professor of surgery, Boston University School of Medicine, Framingham Union Hospital.

‡Surgeon, Framingham Union Hospital.

manifest Further information on these 6 cases is given in Table 3

With the clinical and post-mortem evidence combined, it seems probable that embolic phenomena developed in 4 (6.5 per cent) of the 61 cases despite adequate dicumarol therapy If the comparison between our data and those of Kinsey and White<sup>10</sup> is valid, the difference in incidence of embolic phenomena in the two series (22 per cent in theirs, and 6.5 per cent in ours) is impressive This difference is statistically significant for samples of these sizes (sigma of the difference =  $\pm 4.4$ , observed difference = 15.5) It should be noted that we included embolic phenomena of all types in our reckoning, whereas Kinsey and White were concerned only with infarcts of the lungs If we exclude the case of renal infarction, the incidence of embolic phenomena in our series becomes 4.9 per cent

### DISCUSSION

That congestive heart failure predisposes to the development of thrombosis and embolic phenomena seems established For this reason the use of anticoagulants in the treatment of the disorder is theoretically fully justifiable In practice, dicumarol is not only effective as an anticoagulant but also safe if certain routine precautions are observed during its administration

To establish the efficacy of dicumarol therapy in congestive failure beyond question will require methodical treatment of many hundreds of cases with the drug Although the present series is not large enough to achieve this result, the fact that there were no deaths attributable with certainty to massive pulmonary embolism is highly suggestive, and the low incidence of embolic phenomena of lesser magnitude is only slightly less so

From our results we believe that dicumarol therapy is probably effective in protecting the patient with congestive heart failure from the danger of embolism and that controlled anticoagulant therapy may become as important in the treatment of the disorder as it already is in that of thrombophlebitis or of postoperative patients The protection it affords is apparently not absolute It seems likely that it retards or prevents the propagation of established thrombi, but it can hardly prevent the breaking off of unorganized projections

of a thrombus lying loose in a vessel or chamber of the heart Ideally, therefore, one should begin dicumarol therapy as early in the disease as possible and should continue it, in the absence of contraindications, as long as signs of cardiac decompensation remain

### SUMMARY AND CONCLUSIONS

Sixty-one patients with definite congestive heart failure were treated with dicumarol in an effort to decrease the incidence of embolic phenomena

Previously published reports indicate that in a group of cardiac patients comparable to our own, one may expect embolic phenomena in the form of infarcts of the lungs in at least 22 per cent In our series, the incidence of such lesions, during the period when dicumarol therapy was effective, was 6.5 per cent There were no deaths attributable with certainty to massive pulmonary embolism, and only 1 death that might conceivably have been due to such an accident

On the basis of these results, it is probable that dicumarol therapy gives protection from thrombosis and embolism to the cardiac patient when he needs it most when he is in congestive failure Further evaluation of the method is under way

### REFERENCES

- 1 Allen E V Hines E A Jr Kvale W F and Barker N W Use of dicumarol as anticoagulant experience in 2,307 cases *Ann Int Med* 27 371-381 1947
- 2 Allen E V Clinical use of anticoagulants report of treatment with dicumarol in 1,686 postoperative cases *J A W A* 134:323 329 1947
- 3 Laennec R T H *A Treatise on the Diseases of the Chest in Which They Are Described according to Their Anatomical Characters and Their Diagnosis Established on a New Principle by Means of Acoustic Instruments* First American edition. 319 pp Philadelphia James Webster 1823 Pp 69-74
- 4 Virchow R *Gesammelte Abhandlungen zur wissenschaftlichen Medizin* 1024 pp Frankfurt a M Medinger Sohn u Co 1856
- 5 Zahn F W Über die Folgen des Verschlusses der Lungenarterien und Pfortaderäste durch Embolie *Verhandl d Gesellsch deutsch Naturforscher u Aerzte* 69: 9-11 1897
- 6 Karsner H T and Ash J E Studies in infarction II Experimental bland infarction of lung *J M Research* 22 205 224 1913
- 7 Hampton A O and Castleman B Correlation of postmortem chest teleroentgenograms with autopsy findings with special reference to pulmonary embolism and infarction *Am J Roentgenol* 43 305 326 1940
- 8 Hines L and Hunt J Pulmonary infarction in heart disease *Ann Int Med* 15 644-647 1941
- 9 Greenstein J Thrombosis and pulmonary embolism. *South African M J* 19 350 and 377 1945
- 10 Kinsey D and White P Fever in congestive failure *Arch. Int. Med* 65 163-170 1940
- 11 Cotlove E and Vorzimmer J J Serial prothrombin estimations in cardiac patients diagnostic and therapeutic implications use of dicumarol *Ann Int Med* 24 648-665 1946

titis In both the cases presented above the cecum had failed to descend and lay in the right upper quadrant of the abdomen

The differential diagnosis between acute, closed-loop colonic obstruction with incompletely descended cecum and acute cholecystitis depends primarily upon keeping the former condition in mind when one is dealing with lesions involving the right upper quadrant of the abdomen It is probable that in a majority of cases a carefully taken history will reveal significant changes in bowel habit preceding the onset of acute symptoms It should be emphasized, however, that such symptoms may be entirely absent as in the cases presented above Simple x-ray study of the abdomen, by demonstrating a distended loop of gas-filled colon in the right upper quadrant, may make the diagnosis obvious Such an examination was not done in Case 1 because of the sudden onset of serious peritonitis associated with shock In Case 2 an x-ray film of the abdomen failed to reveal the distention of the ascending colon and cecum because the closed loop was filled with fluid and contained relatively little gas The diagnosis in Case 1 was further confused by the positive Graham test done three weeks before admission Why the gall bladder failed to fill at this time is not clear

It is evident that the one procedure that will establish the diagnosis of colonic obstruction is x-ray examination with barium enema Because the combination of circumstances causing carcinoma of the colon to resemble acute cholecystitis is not commonly encountered, it is unlikely that routine barium enema is necessary when one is dealing with the clinical picture of acute cholecystitis Since acute obstruction of the colon due to cancer is probably invariably associated with the presence of occult blood in the stool, the guaiac test affords a simple screening method for determining when barium enema is indicated In the absence of obvious anal or rectal disease the presence of occult blood in the stool should serve as a warning that symptoms of acute cholecystitis may be of colonic origin

Since acute, closed-loop obstruction of the colon demands early surgery, just as acute cholecystitis does, the importance of emphasizing an accurate preoperative diagnosis might be questioned Emergency operations are often done at odd hours when operating-room personnel is limited An accurate preoperative diagnosis will point up the necessity for an adequate team before the abdomen is entered

Acute closed-loop obstruction of the ascending colon in the presence of an undescended cecum presents a problem in surgical management when the obstructing neoplasm is at or near the hepatic flexure Since the competent ileocecal valve prevents distention of the terminal ileum in the early stages, primary resection with end-to-end ileotransverse colostomy and proximal decompressing ileos-

tomy, followed by adequate antibiotic therapy, is the choice of many surgeons even in the absence of adequate preoperative preparation of the colon Such a choice proved adequate in Case 2 As an alternate method the ileum and transverse colon may be brought out on the abdominal wall to form an open ileotransverse colostomy, as advocated by Lahey Although such a procedure gives added protection against peritonitis, it has the disadvantage of subjecting the wound and surrounding skin to the digestive action of the ileal discharge If the wall of the cecum is so damaged that it will not withstand the manipulation necessary to a primary resection, a cecostomy for temporary decompression may be necessary although the resulting adhesions will complicate the subsequent resection Under these circumstances appendicostomy may be the operation of choice Such a procedure was rendered impossible in Case 2 by obliteration of the appendiceal lumen

### SUMMARY

Two cases are presented in which acute, closed-loop obstruction of the ascending colon in the presence of an incompletely descended cecum gave clinical pictures closely simulating that of acute cholecystitis

The differential diagnosis depends primarily on keeping the condition in mind when one is dealing with acute problems involving the right upper quadrant of the abdomen Simple x-ray examination of the abdomen may fail to demonstrate the obstructed loop The presence of occult blood in the stool should serve as an indication for barium enema x-ray studies when the clinical picture of acute cholecystitis is encountered

Operative therapy is briefly discussed The possibility of closed-loop obstruction of the colon should give added impetus to an aggressive attitude on the part of the surgeon confronted with the clinical picture of acute cholecystitis

190 Concord Street

### REFERENCES

- 1 Clute H M and Lembright, J F Immediate surgery in acute cholecystitis. *New Eng J Med* 218 72 75 1938
- 2 Fallis L S and McClore R D Acute cholecystitis: review of 320 cases. *Surg Gynec & Obst* 70 1022 1028 1940
- 3 Wallace R H and Allen A W Acute cholecystitis. *Arch Surg* 43 762-772 1941
- 4 Best R R Acute gall bladder. *Surg Gynec & Obst* 73 312 319 1941
- 5 Glenn F Surgical treatment of acute cholecystitis in patients 50 years of age and over. *Surg Gynec & Obst* 73 649-653 1941
- 6 Womack A A and Bricker E M Pathogenesis of cholecystitis. *Arch Surg* 44 658-676 1942
- 7 Glenn F and Moore S W Gangrene and perforation of wall of gall bladder: sequela of acute cholecystitis. *Arch Surg* 44 677-686 1942
- 8 McLanahan S Trout H Jr and Weary W B Acute cholecystitis: review of 140 cases. *Am J Surg* 56 432-437 1942
- 9 Zollinger R and Cutler E C Treatment of acute cholecystitis: evaluation. *J A M A* 121 481-485 1943
- 10 Ellason E L and Stevens L W Acute cholecystitis. *Surg., Gynec & Obst* 78 98-103 1943
- 11 Lester L J Acute cholecystitis with special reference to occurrence of jaundice. *Surgery* 21 675-682 1947

The temperature was 98.6°F, the pulse 84, and the respirations 20. The blood pressure was 185/98.

Examination of the blood disclosed a red-cell count of 4,440,000, with a hemoglobin of 14.5 gm., and a white-cell count of 9850 with 84 per cent neutrophils, of which 2 per cent were stab forms. The urine was normal except for a rare pus cell in the sediment. The blood nonprotein nitrogen was 43 mg., and the total protein 6.3 gm. per 100 cc., with an albumin-globulin ratio of 1:4.1. The serum chloride was 491 mg. per 100 cc.

An x-ray film of the chest showed the lung fields to be clear, the heart and great vessels were normal. X-ray study of the abdomen revealed the presence of an ill defined soft-tissue mass in the right upper quadrant, the nature of which could not be determined. The lower pole of the right kidney was well seen and appeared normal. There were no opaque gall-bladder or urinary-tract calculi and no evidence of intestinal obstruction.

The initial diagnosis was acute cholecystitis, and, because of the evidence of peritoneal irritation, it was feared that perforation was imminent. Immediate surgery was therefore advised.

Operation was performed 3 hours after admission. The mass was found to be an incompletely descended cecum, which was greatly distended, but with its lower border above the level of the umbilicus. The colon was found to be obstructed at the hepatic flexure where there was a small, constricting carcinoma. The serosa of the colon was obviously invaded with cancer at this point, but there were no distinct metastases. The colon distal to the constricting carcinoma was of normal caliber. The ileocecal valve was competent, and the ileum was not distended. The very thin wall of the distended cecum appeared to be viable, and although there was a moderate quantity of cloudy peritoneal fluid in the right gutter, there was no evidence of perforation or peritonitis. Since the ileum proximal to the ileocecal valve and the transverse colon distal to the obstructing neoplasm were both of normal caliber, the entire right half of the colon and the distal 15 cm. of the ileum were resected with an end-to-end anastomosis of ileum to transverse colon. A catheter ileostomy for decompression was placed proximal to the suture line. Primary resection was considered the operation of choice because the incompletely descended cecum did not lend itself well to a cecostomy and, furthermore, cecostomy would have materially interfered with later resection of the neoplasm. An appendectomy was considered but was impossible because the lumen of the appendix was obliterated.

Postoperatively, convalescence was complicated by a period of obstruction of the small intestine, which was probably due to adhesions and which responded well to intubation. The wound healed by first intention, and the patient was discharged from the hospital on the 23rd postoperative day.

## DISCUSSION

Although much has been written on the treatment and prognosis of acute cholecystitis, remarkably little is to be found in the literature on the diagnosis of this condition. This point has been emphasized by Lawrence and Clute<sup>12</sup> in the discussion of 4 cases in which intrinsic diseases of the liver were responsible for the clinical picture usually associated with acute cholecystitis. In 3 of their cases tumors of the liver were found—2 metastatic, and 1 primary. The fourth patient had acute central necrosis of the liver due to carbon tetrachloride poisoning. The cases presented above indicate that lesions of the colon must also be considered in the differential diagnosis.

The diagnostic confusion between lesions of the colon and acute cholecystitis is dependent upon three factors: the site and type of obstruction, competence of the ileocecal valve, and incomplete descent of the cecum.

Colonic obstruction due to carcinoma usually progresses slowly over a period of several months and most commonly results from lesions located in the left half of the colon. In a series of 150 cases of carcinoma of the colon with complete obstruction reported by Gregg and Dixon<sup>13</sup> there were only 5 cases with the obstructing neoplasm in the cecum or ascending colon. In an additional 19 cases the obstruction was in the hepatic flexure or transverse colon. When obstruction of the colon is sudden and complete the resulting symptoms overshadow those of the chronic obstruction, which have usually been present for some time. Symptoms of chronic obstruction are due to the gradual stenosis of the lumen of the colon by the growing neoplasm. As pointed out by Mayo<sup>14, 15</sup> and Collier and Berry<sup>16</sup> this gradual stenosis may give rise to dyspepsia, with sour eructations and postprandial distress. These symptoms are often referred to the upper abdomen and may closely simulate those associated with gall-bladder disease.

Occasionally, symptoms of preceding chronic obstruction are completely absent, and the first indication of abdominal disease is the sudden, unheralded obstruction of the colon. This type of obstruction was present in 5 of 129 cases of carcinoma of the colon reported by Miller.<sup>17</sup>

Competence of the ileocecal valve is said to be present on routine barium-enema x-ray examination in about 10 per cent of cases.<sup>18</sup> If this valve is incompetent, acute obstruction of the colon results in progressive retrograde distention of the small intestine and the clinical picture usually associated with low intestinal obstruction. However, when the ileocecal valve is competent the distention resulting from acute obstruction of the colon is limited to the colon, and, because of its greater diameter and thinner wall, the distention is most marked in the cecum, regardless of the point at which the colon is obstructed. The degree of distention of the cecum under these circumstances frequently becomes so great that it causes areas of necrosis and eventual perforation.<sup>19-21</sup> The perforation of such a necrotic area was the cause of the sudden onset of shock in Case 1. In Case 2 the distended cecum formed an easily palpable, acutely tender mass, which was mistaken for a distended, inflamed gall bladder.

Rankin<sup>22</sup> has emphasized the fact that necrosis and perforation of the normally placed cecum due to closed-loop obstruction of the colon may give rise to a clinical picture resembling that of appendicitis. During the second trimester of intrauterine life the cecum normally descends from the right upper quadrant of the abdomen to the right lower quadrant. When this descent fails to take place and the cecum remains in the right upper quadrant the distention, necrosis and eventual perforation resulting from acute closed-loop obstruction may give rise to the clinical picture of acute cholecys-

Of interest was the development of signs of a pulmonary embolism immediately after full digitalization in Case 2. Such incidents suggest caution in the use of digitalis in patients who have already manifested minor embolic phenomena.

### SUMMARY

Two cases of fatal bacterial endocarditis developing after urethral dilatation are presented. In 1 patient, the history and physical signs gave ample evidence of rheumatic heart disease, in the other, such evidence was found at autopsy. It is pointed

out that chemotherapeutic or antibiotic prophylaxis should be utilized before and after manipulation in such cases.

### REFERENCES

1. Scott, W. W. Blood stream infections in urology: report of eighty-two cases. *J Urol* 21:527-566, 1929.
2. Hyman, A. and Edelman, L. Medical and surgical aspects of hematogenous infections in urology. *J Urol* 28:173-198, 1932.
3. Powers, J. H. Bacteremias following instrumentation of infected urinary tract. *New York State J Med* 36:323-331, 1936.
4. Glaser, R., J. Dankner, A. Mathes, S. B. and Harford, C. G. Effect of penicillin on bacteremia following dental extraction. *Am J Med* 4:55-65, 1948.
5. Clark, W. H., Bryner, S., and Rantz, L. A. Penicillin-resistant non-hemolytic streptococcal subacute bacterial endocarditis. *Am J Med* 4:671-689, 1948.

## MEDICAL PROGRESS

### SARCOIDOSIS (Continued)\*

DAVID G. FREIMAN, M.D.†

BOSTON

**Bone.** Localization of the sarcoid lesions in bone has frequently been described, but the true incidence of such involvement is not known. The incidence of roentgenographically demonstrable involvement, however, has ranged between 15 and 25 per cent of cases in several series<sup>5, 35, 49, 131</sup>, in others it has been considerably lower,<sup>45, 132</sup> and only 1 case of such involvement has been reported from Australia.<sup>115</sup> The tendency of the lesions to appear at any time, to last for indefinite periods, to regress spontaneously and even to reappear at a later date<sup>44</sup> makes it necessary to follow cases for an adequate period by means of serial roentgenograms if such localizations are not to be missed. Furthermore, Schaumann<sup>132</sup> has shown that such localizations may occur, and probably often do without demonstrable roentgenographic or even gross pathologic manifestation, and a reliable estimate is therefore difficult to make even from the autopsied cases.

The radiologically visible bone lesions have a special predilection for the short bones of the hands and feet and, when demonstrable, are of considerable diagnostic significance. A similar appearance, however, has been described in leprosy.<sup>5, 134</sup> Lesions have also been demonstrated in the bones of the carpus and tarsus, in the long bones of the extremities and in the vertebrae.<sup>69, 125-127</sup> rarely they are seen throughout the skeleton, including the skull.<sup>40</sup> Histologic examination of such areas reveals diffuse involvement of the bone-marrow spaces, but only lesions that cause destruction of spongy bone or erosion of the compact bone are likely to be visible.<sup>5</sup>

The bone lesions, originally called "ostitis tuberculosa multiplex cystica (or cystoides)," have been described in great detail by Jüngling,<sup>135, 136</sup> Fleischner<sup>137</sup> and many others.<sup>5, 10, 35, 131, 138-140</sup> The roentgenographic appearance takes two main forms: a circumscribed type with characteristic cystoid areas of rarefaction, usually medullary, and with little or no surrounding reactive change, and a diffuse form in which multiple small areas of rarefaction produce a finely reticulated pattern extending over large portions of the bone, often associated with broadening of the shaft and thinning of the cortex.<sup>35</sup> Both types frequently coexist, however, and there may be transitions from one to the other.<sup>5</sup> External manifestations may be seen as fusiform swellings of the fingers or toes with occasional periarticular subcutaneous nodules or dystrophic nail changes. The swellings are usually symptomless though slight pain may occur in the early stages<sup>35</sup>; lack of pain is probably explained by the fact that periosteum and joints are rarely involved.<sup>5, 9</sup> Occasionally, diffuse, extensive bone destruction causes severe external deformity.

It is difficult to estimate the frequency with which external manifestations are associated with bone lesions. The latter certainly occur in the absence of such manifestations,<sup>5, 9</sup> and in at least one series all 6 cases with bone changes were discovered only by routine roentgenograms of the hands or feet.<sup>47</sup> In Reisner's<sup>25</sup> series, however, all but 1 of 9 cases with visible bone lesions showed external manifestations at the site of involvement. Such manifestations usually mean associated involvement of the skin and subcutaneous tissues of the hands and fingers, and it is of interest that Jüngling<sup>136</sup>

\*From the Department of Pathology and Bacteriology, Massachusetts General Hospital.

†Instructor in pathology, Tufts College Medical School; assistant radiologist, Massachusetts General Hospital.

- 12 Lawrence B K and Clute H M Intrinsic diseases of liver simulating acute cholecystitis *New Eng J Med* 227 701-703 1942
- 13 Gregg R O and Dixon, C F Operable malignant lesions of colon producing obstruction *S Clin North America* 21 1143-1152, 1941
- 14 Mayo C W Carcinoma of right (proximal) portion of colon *S Clin North America* 27 875-884 1947
- 15 Mayo C W Malignant lesions of right colon with particular reference to one stage resection *Postgraduate Med* 1 430-435 1947
- 16 Collier F A and Berry R L Cancer of colon *J A M A* 135 1061-1067, 1947
- 17 Miller, R T, Jr Cancer of colon *Ann Surg* 78 209 225 1923
- 18 Carman R D *Röntgen Diagnosis of Diseases of the Alimentary Canal* Second edition 676 pp Philadelphia W B Saunders Co., 1921
- 19 Saeltzer D V and Rhodes, G K. Diastatic perforation of normal cecum resulting from obstruction of colon *Ann. Surg* 101 1257 1263, 1935
- 20 Tepper G B, and Massell T B Rupture of normal cecum resulting from malignant obstruction of splenic colon *Am. J Surg* 68 142 1943
- 21 Hartwell J A Carcinoma of splenic flexure of colon *Ann. Surg* 66 339 361 1917
- 22 Rankin F W Bergen J A and Buie L A. *The Colon, Rectum and Anus* 846 pp Philadelphia W B Saunders Co., 1935

## BACTERIAL ENDOCARDITIS FOLLOWING URETHRAL MANIPULATION

### Report of Two Cases

JOHN K MENEELY, JR, M D \*

ALBANY, NEW YORK

REVIEWS in the older literature<sup>1-3</sup> and a recent article<sup>4</sup> have commented on the frequent occurrence of bacteremia following manipulation of the genitourinary tract. In one report<sup>3</sup> the complication of bacterial endocarditis in a case is noted, but a perusal of the literature since 1940 revealed no recently reported cases. To emphasize the occurrence of this complication and to stress the need for routine prophylaxis in persons with known valvular defects, the following cases of bacterial endocarditis, developing after urethral dilatation and terminating fatally, are presented.

**CASE 1** A 56-year-old man was admitted to the hospital on July 6, 1945, with the complaint of chills, fever and vomiting. A few hours previously, sounds had been passed for the relief of urethral strictures. Physical examination was negative, no cardiac murmurs were noted. A retention catheter was inserted, and 20,000 units of penicillin was given intramuscularly every 2 hours for ten doses. The temperature promptly fell to normal, and the patient was discharged 2 days after admission.

Two days later, the patient was readmitted to the hospital with a history of having developed severe chills and fever almost immediately after leaving the hospital. Physical examination revealed a soft, grating systolic murmur at the apex and a few posterior basal rales. He was catheterized, penicillin was given intramuscularly every 2 hours for 2 days in a dosage of 20,000 units and every 3 hours for 2 days in a dosage of 10,000 units. The temperature quickly fell, and the patient was discharged on the 4th hospital day.

Ten days later he was readmitted with complaints of continued chills, fever, malaise and severe headaches since arrival at home. At this time, no murmur was noted, but a gallop rhythm was present at the apex. No petechiae were observed, and the spleen was never felt. No organic defects were found on cystoscopy and retrograde pyelography on the 3rd hospital day, but colon bacilli were recovered from the bladder and both ureters. On the 9th hospital day several blood cultures were positive for colon bacilli, and purpuric spots appeared over the body. Intramuscular injections of penicillin (20,000 units every 3 hours) were begun at that time, but the patient became moribund and died on the 12th hospital day.

Autopsy disclosed old, inactive rheumatic inflammation of the mitral and aortic valves, with superimposed acute, ulcerative endocarditis of the left auricular endocardium and mitral valve. Post-mortem blood cultures from the heart were positive for colon bacilli. Focal embolic infarctions were seen in the kidney and spleen, and there were chronic, inflammatory changes in the urinary bladder and urethra.

\*Assistant in medicine, Albany Medical College clinical assistant in medicine Albany Hospital.

**CASE 2** A 56-year-old man was admitted to the hospital on November 7, 1947, with the complaint of shaking chills and fever for 1 week prior to admission. Three weeks before entry, he had undergone urethral dilatation for strictures, and a few hours later he had an episode of violent shaking chills and fever.

The past history revealed an attack of rheumatic fever as a child, necessitating bed rest for 11 months. Since that time, however, there had been no cardiac complaints.

Physical examination revealed a loud systolic and a harsh diastolic murmur at the aortic area, with much fainter replicas at the apex. No external stigmas of embolization were noted at that time, and the spleen was not felt. The remainder of the physical examination was noncontributory.

On the following day, numerous petechiae were noted on the abdominal wall, and several hemorrhagic bullae appeared on the toes of the right foot. Cultures of these bullae were positive for *Staphylococcus aureus* and were mannite and coagulase positive. Three cultures of blood drawn in the first 2 days were positive for the same organism. Intramuscular injection of penicillin (100,000 units every 4 hours) was begun. New bullae appeared on the hands, but the patient improved clinically. Seven days after entry, because of developing cardiac decompensation, the patient was digitalized a few hours later, the clinical picture of pulmonary embolism was evident. The patient rallied briefly at this point, but 2 days later became comatose and remained so until the time of death, 18 days after admission. Terminally, uremia was present. The penicillin was increased to 100,000 units every 2 hours on the 3rd hospital day, and to 200,000 units every 2 hours on the 5th day. All blood cultures taken after the initial three were negative. No autopsy was performed.

### DISCUSSION

The sequence of events in both cases and the similarity of the organism in the blood stream and urinary tract in 1 case make it evident that the endocarditis had a direct relation to the urethral manipulation. Although urethral dilatation is a common office procedure, such complications make it mandatory to consider the use of prophylactic agents in all persons subjected to these procedures. Persons with a clear history and definite signs of rheumatic heart disease must receive vigorous prophylaxis. The method of choice is not yet certain, but the use of penicillin, with or without sulfadiazine, for two days before and after manipulation, has been advised by Glaser et al<sup>4</sup> and Clark and his associates.<sup>5</sup>

Of interest was the development of signs of a pulmonary embolism immediately after full digitalization in Case 2. Such incidents suggest caution in the use of digitalis in patients who have already manifested minor embolic phenomena.

### SUMMARY

Two cases of fatal bacterial endocarditis developing after urethral dilatation are presented. In 1 patient, the history and physical signs gave ample evidence of rheumatic heart disease; in the other, such evidence was found at autopsy. It is pointed

out that chemotherapeutic or antibiotic prophylaxis should be utilized before and after manipulation in such cases.

### REFERENCES

1. Scott, W. W. Blood stream infections in urology: report of eighty-two cases. *J Urol* 21:527-566, 1929.
2. Hyman A., and Edelman L. Medical and surgical aspects of hematogenous infections in urology. *J Urol* 28:173-198, 1932.
3. Powers J. H. Bacteremia following instrumentation of infected urinary tract. *New York State J Med* 36:523-531, 1936.
4. Glaser R. J., Danziger A., Mathes S. B. and Harford C. G. Effect of penicillin on bacteremia following dental extraction. *Am J Med* 4:55-65, 1948.
5. Clark W. H., Bryner S. and Rantiz, L. A. Penicillin resistant non hemolytic streptococcal subacute bacterial endocarditis. *Am J Med* 4:671-689, 1948.

## MEDICAL PROGRESS

### SARCOIDOSIS (Continued)\*

DAVID G. FREIMAN, M.D.†

BOSTON

**Bone.** Localization of the sarcoid lesions in bone has frequently been described, but the true incidence of such involvement is not known. The incidence of roentgenographically demonstrable involvement, however, has ranged between 15 and 25 per cent of cases in several series<sup>5, 8, 9, 131</sup>, in others it has been considerably lower,<sup>45, 132</sup> and only 1 case of such involvement has been reported from Australia.<sup>116</sup> The tendency of the lesions to appear at any time, to last for indefinite periods, to regress spontaneously and even to reappear at a later date<sup>44</sup> makes it necessary to follow cases for an adequate period by means of serial roentgenograms if such localizations are not to be missed. Furthermore, Schaumann<sup>7, 133</sup> has shown that such localizations may occur, and probably often do, without demonstrable roentgenographic or even gross pathologic manifestation, and a reliable estimate is therefore difficult to make even from the autopsied cases.

The radiologically visible bone lesions have a special predilection for the short bones of the hands and feet and, when demonstrable, are of considerable diagnostic significance. A similar appearance, however, has been described in leprosy.<sup>8, 134</sup> Lesions have also been demonstrated in the bones of the carpus and tarsus, in the long bones of the extremities and in the vertebrae.<sup>69, 125-127</sup> rarely they are seen throughout the skeleton, including the skull.<sup>40</sup> Histologic examination of such areas reveals diffuse involvement of the bone-marrow spaces, but only lesions that cause destruction of spongy bone or erosion of the compact bone are likely to be visible.<sup>5</sup>

The bone lesions, originally called "ostitis tuberculosa multiplex cystica (or cystoides)," have been described in great detail by Jüngling,<sup>125, 126</sup> Fleischner<sup>127</sup> and many others.<sup>5, 10, 38, 131, 138-140</sup> The roentgenographic appearance takes two main forms: a circumscribed type with characteristic cystoid areas of rarefaction, usually medullary, and with little or no surrounding reactive change, and a diffuse form in which multiple small areas of rarefaction produce a finely reticulated pattern extending over large portions of the bone, often associated with broadening of the shaft and thinning of the cortex.<sup>38</sup> Both types frequently coexist, however, and there may be transitions from one to the other.<sup>5</sup> External manifestations may be seen as fusiform swellings of the fingers or toes, with occasional periarticular subcutaneous nodules or dystrophic nail changes. The swellings are usually symptomless though slight pain may occur in the early stages<sup>35</sup>; lack of pain is probably explained by the fact that periosteum and joints are rarely involved.<sup>5, 9</sup> Occasionally, diffuse, extensive bone destruction causes severe external deformity.

It is difficult to estimate the frequency with which external manifestations are associated with bone lesions. The latter certainly occur in the absence of such manifestations,<sup>5, 9</sup> and in at least one series all 6 cases with bone changes were discovered only by routine roentgenograms of the hands or feet.<sup>47</sup> In Reisner's<sup>38</sup> series, however, all but 1 of 9 cases with visible bone lesions showed external manifestations at the site of involvement. Such manifestations usually mean associated involvement of the skin and subcutaneous tissues of the hands and fingers, and it is of interest that Jüngling<sup>126</sup>

\*From the Department of Pathology and Bacteriology, Massachusetts General Hospital.

†Instructor in Pathology, Tufts College Medical School; Assistant Pathologist, Massachusetts General Hospital.

- 12 Lawrence, B. K., and Clute, H. M. Intrinsic diseases of liver simulating acute cholecystitis. *New Eng J Med* 227 701 1942
- 13 Gregg, R. O., and Dixon, C. F. Operable malignant lesions of colon producing obstruction. *S Clin North America* 21 1143-1152 1941
- 14 Mayo, C. W. Carcinoma of right (proximal) portion of colon. *S Clin North America* 27 875 884 1947
- 15 Mayo, C. W. Malignant lesions of right colon with particular reference to one-stage resection. *Postgraduate Med* 1 430-435, 1947
- 16 Collier, F. A., and Berry, R. L. Cancer of colon. *J A M A* 135 1061-1067, 1947
- 17 Miller, R. T., Jr. Cancer of colon. *Ann Surg* 78 209 225 1923
- 18 Carman, R. D. *Röntgen Diagnosis of Diseases of the Alimentary Canal*. Second edition. 676 pp. Philadelphia: W. B. Saunders Co., 1921
- 19 Saeltzer, D. V., and Rhodes, G. K. Diastatic perforation of normal cecum resulting from obstruction of colon. *Ann. Surg* 101 1257 1263 1935
- 20 Tepper, G. B., and Massell, T. B. Rupture of normal cecum resulting from malignant obstruction of splenic colon. *Am. J. Surg.* 64 142 1943
- 21 Hartwell, J. A. Carcinoma of splenic flexure of colon. *Ann. Surg* 66 339 361 1917
- 22 Rankin, F. W., Bergen, J. A., and Buie, L. A. *The Colon, Rectum and Anus*. 846 pp. Philadelphia: W. B. Saunders Co., 1933

## BACTERIAL ENDOCARDITIS FOLLOWING URETHRAL MANIPULATION

### Report of Two Cases

JOHN K. MENEELY, JR., M.D.\*

ALBANY, NEW YORK

REVIEWS in the older literature<sup>1-3</sup> and a recent article<sup>4</sup> have commented on the frequent occurrence of bacteremia following manipulation of the genitourinary tract. In one report<sup>3</sup> the complication of bacterial endocarditis in a case is noted, but a perusal of the literature since 1940 revealed no recently reported cases. To emphasize the occurrence of this complication and to stress the need for routine prophylaxis in persons with known valvular defects, the following cases of bacterial endocarditis, developing after urethral dilatation and terminating fatally, are presented.

**CASE 1** A 56-year-old man was admitted to the hospital on July 6, 1945, with the complaint of chills, fever and vomiting. A few hours previously, sounds had been passed for the relief of urethral strictures. Physical examination was negative, no cardiac murmurs were noted. A retention catheter was inserted, and 20,000 units of penicillin was given intramuscularly every 2 hours for ten doses. The temperature promptly fell to normal, and the patient was discharged 2 days after admission.

Two days later, the patient was readmitted to the hospital with a history of having developed severe chills and fever almost immediately after leaving the hospital. Physical examination revealed a soft, grating systolic murmur at the apex and a few posterior basal rales. He was catheterized, penicillin was given intramuscularly every 2 hours for 2 days in a dosage of 20,000 units and every 3 hours for 2 days in a dosage of 10,000 units. The temperature quickly fell, and the patient was discharged on the 4th hospital day.

Ten days later he was readmitted, with complaints of continued chills, fever, malaise and severe headaches since arrival at home. At this time, no murmur was noted, but a gallop rhythm was present at the apex. No petechiae were observed, and the spleen was never felt. No organic defects were found on cystoscopy and retrograde pyelography on the 3rd hospital day, but colon bacilli were recovered from the bladder and both ureters. On the 9th hospital day several blood cultures were positive for colon bacilli, and purpuric spots appeared over the body. Intramuscular injections of penicillin (20,000 units every 3 hours) were begun at that time, but the patient became moribund and died on the 12th hospital day.

Autopsy disclosed old, inactive rheumatic inflammation of the mitral and aortic valves, with superimposed acute, ulcerative endocarditis of the left auricular endocardium and mitral valve. Post-mortem blood cultures from the heart were positive for colon bacilli. Focal embolic infarctions were seen in the kidney and spleen, and there were chronic, inflammatory changes in the urinary bladder and urethra.

\*Assistant in medicine, Albany Medical College clinical assistant in medicine Albany Hospital.

**CASE 2** A 56-year-old man was admitted to the hospital on November 7, 1947, with the complaint of shaking chills and fever for 1 week prior to admission. Three weeks before entry, he had undergone urethral dilatation for strictures, and a few hours later he had an episode of violent shaking chills and fever.

The past history revealed an attack of rheumatic fever as a child, necessitating bed rest for 11 months. Since that time, however, there had been no cardiac complaints.

Physical examination revealed a loud systolic and a harsh diastolic murmur at the aortic area, with much fainter replicas at the apex. No external stigmas of embolization were noted at that time, and the spleen was not felt. The remainder of the physical examination was noncontributory.

On the following day, numerous petechiae were noted on the abdominal wall, and several hemorrhagic bullae appeared on the toes of the right foot. Cultures of these bullae were positive for *Staphylococcus aureus* and were man- nite and coagulase positive. Three cultures of blood drawn in the first 2 days were positive for the same or- ganism. Intramuscular injection of penicillin (100,000 units every 4 hours) was begun. New bullae ap- peared on the hands, but the patient improved clinically. Seven days after entry, because of developing cardiac decompensation, the patient was digitalized, a few hours later, the clinical picture of pulmonary embolism was evident. The patient rallied briefly at this point, but 2 days later became comatose and remained so until the time of death, 18 days after admission. Terminally, uremia was present. The penicillin was increased to 100,000 units every 2 hours on the 3rd hospital day, and to 200,000 units every 2 hours on the 5th day. All blood cultures taken after the initial three were negative. No autopsy was performed.

### DISCUSSION

The sequence of events in both cases and the similarity of the organism in the blood stream and urinary tract in 1 case make it evident that the endocarditis had a direct relation to the urethral manipulation. Although urethral dilatation is a common office procedure, such complications make it mandatory to consider the use of prophylactic agents in all persons subjected to these procedures. Persons with a clear history and definite signs of rheumatic heart disease must receive vigorous prophylaxis. The method of choice is not yet certain, but the use of penicillin, with or without sulfadiazine, for two days before and after manipulation has been advised by Glaser et al.<sup>4</sup> and Clark and his associates.<sup>5</sup>

and attributed to mumps<sup>166 167</sup> Actually, fever occurs in considerably less than half the cases and is usually of low grade, constitutional symptoms are minimal, and evidence of other sarcoid manifestations is noted both clinically and at autopsy<sup>91-94</sup> Enlargement of the lacrimal glands may be associated, or may occur with salivary-gland enlargement alone as one form of the Mikulicz syndrome<sup>4 164 165 169</sup> Any of these localizations, however, may develop independently of the others

*Nervous and endocrine systems* Diffuse involvement of the central nervous system has been described on a number of occasions both clinically and at autopsy<sup>89 164 170 171</sup> Lethargy simulating that of encephalitis lethargica may occur and has cleared up with improvement of other manifestations<sup>164</sup> Evidence of peripheral-nerve affection may be noted in the form of pareses and paresthesias or loss of deep reflexes Such findings are rare, however, and may be due to spinal-cord involvement, they constitute a point of differentiation from tuberculoid leprosy in which peripheral-nerve invasion is common<sup>172</sup> Involvement of the cranial nerves, frequently transient may also occur, often in association with the uveoparotid syndrome The facial nerve is most commonly affected, and the resultant palsy is usually of the peripheral type It tends to follow enlargement of the parotid gland, though occasionally it precedes it and may even be an initial symptom<sup>173</sup> Involvements of the auditory, glossopharyngeal and oculomotor nerves may also occur, with resultant deafness, palatal paralysis and varying degrees of cycloplegia<sup>45 92 164 165 174</sup> A case of Adie's syndrome with tonic pupils and absent tendon reflexes has been attributed to sarcoidosis<sup>175</sup> The hypoglossal nerve has been affected on at least one occasion<sup>176</sup> Dysarthria and dysphagia have also been noted but may at times be due to marked dryness of the mouth resulting from salivary-gland involvement<sup>163</sup>

Localization in the hypothalamic region and pituitary gland may be associated with the syndrome of diabetes insipidus, and such localizations have on several occasions been confirmed at autopsy<sup>24 40 70 177</sup> This has not been invariable, however<sup>38</sup> A number of these cases have also been associated with salivary-gland involvement, and in the presence of thirst due to dryness of the mouth, symptoms of polydipsia and polyuria, like dysarthria and dysphagia, must be evaluated with caution

Other stigmas of pituitary-gland involvement have occasionally been noted Kraus<sup>71</sup> has described a case in which polyuria, genital dystrophy, cessation of menses and hypertrichosis were associated with involvement of the pituitary gland and its stalk but this case was unfortunately complicated by a chromophobe adenoma In

another case with panhypopituitarism, the granuloma in the pituitary gland may well have been a tuberculoma<sup>178</sup>

Lesions have been observed in the testis and epididymis,<sup>24 80 94 179</sup> prostate,<sup>24</sup> and thyroid gland<sup>94 100</sup> usually without disturbance Hyperthyroidism in the presence of demonstrable sarcoid lesions in the thyroid gland has been described,<sup>150</sup> but a causal relation seems unlikely In contradistinction to caseating tuberculosis, involvement of the adrenal glands appears to be quite rare

*Gastrointestinal and isolated sarcoid manifestations* Involvement of the stomach and intestines is recorded very infrequently in association with generalized sarcoidosis Occasionally, however, localized lesions have occurred in the stomach,<sup>151</sup> small intestine appendix and colon<sup>29 152-155</sup> and in the regional lymph nodes draining such areas in the absence of manifestations elsewhere

The occurrence of epithelioid and giant cells in some cases of regional enteritis has raised the possibility that the two diseases are related In occasional cases these granulomas are clearly of sarcoid type to the point of massive formation of noncaseating tubercles without evidence of tubercle bacilli even on animal inoculation,<sup>156</sup> but, with one possible exception,<sup>157</sup> such sarcoid lesions have been strictly isolated manifestations In most cases the scattered granulomas seen in the bowel wall in regional enteritis bear only a superficial resemblance to the lesions of sarcoidosis They tend to be small, widely scattered, rather indistinct collections of histiocytes and epithelioid cells, often containing one or two giant cells, and most authors have been content to attribute such findings to foreign-body reaction<sup>158</sup> In at least one case surgical removal of the affected bowel revealed no sarcoid lesions, although evidence of disseminated sarcoidosis existed elsewhere<sup>159</sup> It seems highly unlikely, therefore, that any considerable number of cases of regional enteritis belong in the sarcoid group<sup>40 190</sup>

Isolated sarcoid lesions have also been described in various lymph-node groups, the skin, the spleen and other organs Occasionally, these findings represent temporary localized phases of the disease stabilized in the process of progression or regression In most cases, however, a diagnosis of generalized sarcoidosis is totally unwarranted As pointed out below in the discussion of etiology, a large number of bacterial and chemical agents seem capable of reproducing the histologic features of sarcoidosis For this reason it seems wise to distinguish the *sarcoid lesion* as a descriptive histologic term from *sarcoidosis*, a disseminated disease associated with such lesions<sup>191</sup>

*Miscellaneous manifestations* Occasional localizations have been described in the pancreas,<sup>50</sup> breast<sup>4 35 109</sup> and skeletal muscle<sup>10 47 142</sup> The

noted bone lesions in 29 of 30 cases of lupus pernio, which often involves these areas. Reisner notes a high incidence of skin involvement, disseminated as well as local, in cases with bone lesions. Spontaneous regression of bone lesions appears more likely to take place in the diffuse than in the circumscribed form.<sup>38</sup>

Sarcoid lesions have been demonstrated by sternal-marrow biopsy.<sup>141 142</sup> Dressler<sup>141</sup> also observed some depression of hematopoiesis. Lucia and Aggeler,<sup>143</sup> on the other hand, failed to find granulomas in their biopsies, and the marrow in these areas showed evidence only of mild myelopoietic stimulation as might be seen in any chronic infection.

*Skin and mucous membranes* The incidence of skin manifestations, the oldest and best known of the regional localizations, varies widely with the source of material. In the old dermatologic literature, the incidence of skin lesions is very high,<sup>5</sup> but they have been noted in only 40 to 50 per cent of cases in some more recent series<sup>24 33</sup> and considerably less in others.<sup>47 96</sup> Many forms have been described, including the miliary and nodular sarcoids of Boeck,<sup>2, 3 144</sup> the diffuse, plaque-like lupus pernio of Besnier,<sup>13</sup> the rare erythrodermic form of Schaumann,<sup>145</sup> the subcutaneous sarcoid of Darier and Roussy<sup>146 147</sup> and their variants. All show, on histologic examination, infiltration of the skin with the characteristic granulomas and differ only in the nodularity or diffuseness of the infiltrate, the degree of vascular engorgement and the variable involvement of corium and subcutaneous tissues. They represent, in fact, visible manifestations of the same polymorphism characterizing the roentgenographic pattern in lung and bone, and for this reason, retention of many of the earlier descriptive subtypes has little point. Even the subcutaneous lesions of the "Darier-Roussy" type have been so frequently confused with other conditions, such as erythema induratum and the nodular panniculitis of Weber-Christian, that retention of the term is of little value.<sup>66</sup>

The various skin lesions are described in great detail by various authors<sup>7 8 10</sup> and in textbooks of dermatology. The lesions may persist for long periods or may spontaneously regress in the course of a few months. Regression in one area is associated with a new eruption elsewhere in some cases.<sup>38</sup> Healing may leave no residue or may result in an atrophic scar.

Erythema nodosum occasionally occurs as an early skin manifestation.<sup>5 29 148-151</sup> Since this condition appears to be a more or less nonspecific manifestation of hypersensitivity and is often seen in association with such diseases as rheumatic fever, tuberculosis and coccidioidomycosis, its occurrence with sarcoidosis is particularly interesting. Furthermore, a pulmonary roentgenographic picture identical with that seen in sarcoidosis occurs in

association with erythema nodosum alone,<sup>119 12 13</sup> raising the possibility that some common allergic basis underlies at least part of this clearly non-specific radiologic picture.

Mucous-membrane lesions, essentially similar in character to those in the skin, are described in only 10 to 20 per cent of cases.<sup>5, 10 144 154</sup> but have probably been frequently overlooked. Involvement of the nasal mucosa may produce a stenosis, and involvement of the larynx may produce hoarseness. Lesions have also been noted in the oral mucosa, pharynx, epiglottis and lower respiratory tract, and on at least two occasions, involvement of the bronchial mucosa has been established by bronchoscopic biopsy.<sup>32 99</sup>

*Eye (lachrymal and salivary glands)* Involvement of the eye and its related structures is reported in 25 to 50 per cent of cases in recent series,<sup>24 38 42 47 155</sup> with incidence figures again varying widely with the sources of the material. These figures are substantially higher than older estimates of 5 to 10 per cent<sup>156 157</sup> and clearly represent the now general acceptance of the uveoparotid syndrome as a manifestation of sarcoidosis. Ocular localizations have no special temporal relation to other manifestations,<sup>9 155</sup> but since the attendant discomfort or visual disturbance is more readily noted by the patient than other relatively asymptomatic localizations, they have frequently constituted a presenting complaint.

Eye involvement usually manifests itself as a painless iritis or iridocyclitis, either bilateral or, less commonly, unilateral.<sup>31 155</sup> It occurs in two forms: a benign serous type, and a more severe nodular variety, which may be associated with corneal involvement. Although the lesions may resorb completely—and this has been described even in large nodules<sup>157</sup>—synechiae, corneal opacities, glaucoma and even phthisis bulbi and loss of sight in one or both eyes have been frequently reported and represent serious complications of the disease.<sup>38 155</sup> Conjunctival involvement probably occurs in not more than 5 per cent of cases and may not be associated with other ocular lesions.<sup>40 158 159</sup> Involvement of the posterior uveal tract is rare,<sup>31 155</sup> but choroiditis, retinitis, retinal perivasculitis and optic-nerve involvement have been described.<sup>21, 155 159-162</sup> An occasional complete recovery is reported,<sup>163</sup> but usually the sequelae are serious. Optic-nerve involvement has been associated in most reported cases with involvement of the brain.<sup>91 161 162</sup> and sometimes with diabetes insipidus.<sup>70</sup>

Uveitis, usually bilateral, may be associated with bilateral enlargement of the parotid gland, and frequently of the submaxillary and submental salivary glands as part of a syndrome that has been termed uveoparotid fever.<sup>47, 92 151 164</sup> This complex was first described by Heerfordt<sup>165</sup> in 1909, though similar cases had been reported earlier.

usually tending to be weak.<sup>8 10 205</sup> In Reisner's<sup>38</sup> series, 60 per cent of patients failed to react to doses as high as 10 mg, and 10 of these tested with 100 mg also failed to react. These figures are significantly higher than the expected incidence of nonreactors in an urban population such as the one from which this series was drawn. Unfortunately, however, the majority of reported cases were inadequately tested in the higher and more significant concentrations, and few of the autopsied cases have had an adequate work-up in this regard. Focal reactions to tuberculin have also been negative in such cases.<sup>59</sup>

**Kveim reaction** Intradermal injection of extracts of sarcoid tissue have produced characteristic skin reactions in a number of patients with sarcoidosis.<sup>204-205</sup> The antigen, prepared after the manner of the Frei antigen for lymphogranuloma inguinale, is extremely thermostable<sup>206-208</sup> and seems to be ineffectual unless injected with a large-bore needle in grossly particulate form.<sup>208</sup> The typical reaction, in the form of an indurated and later crusted, occasionally necrotic papule, is slow to evolve, often requiring weeks to reach maximum size and persisting for many months; histologic examination of the sites of the positive tests reveals a granulomatous structure entirely consistent with that of spontaneous sarcoid lesions in the skin. Evanescent early responses first described by Williams and Nickerson,<sup>209</sup> are apparently nonspecific.<sup>206</sup>

The incidence of positive reactions in different series varies. Danbolt and Nilssen<sup>205</sup> produced a positive reaction in 34 of 36 patients tested. Puttkonen<sup>206</sup> found the test positive in 33 of 42 patients and such cases were practically always in an active phase with lesions demonstrable in the skin, lymph nodes or tonsils; the test was almost always negative when the lesions had healed. Nelson,<sup>205</sup> testing a series of 17 American Negroes with sarcoidosis produced characteristic reactions in 7 of 11 active cases, whereas the reactions in 6 inactive cases remained negative. Tests in apparently normal controls have been entirely negative or of low order and negative tests have also been obtained in patients with a variety of skin lesions including leprosy, tuberculosis and lymphogranuloma inguinale.<sup>206</sup>

The typical Kveim reaction, therefore, seems to be rather specific for cases of sarcoidosis, particularly cases with demonstrable activity. The antigen itself, however, is far less specific. Nelson<sup>205</sup> was able to produce identical reactions both clinically and histologically, and in the same patients, using antigens prepared from various sarcoid lesions and from normal human spleen. Similar reactions have also been produced with antigens prepared from the lesions of lymphatic leukemia.<sup>206-208</sup> The histologically characteristic lesions produced in some sarcoid patients with living BCG<sup>210 211</sup> living<sup>212</sup>

or heat-killed<sup>213</sup> human tubercle bacilli and even nonspecific substances such as India ink<sup>214</sup> may well be of a similar nature, and such reactions may also explain the appearance of subcutaneous granulomas following exposure to beryllium compounds and other substances in apparently normal persons. The findings to date suggest an obvious parallel with the history of the Wassermann antigen.

As a diagnostic test, the Kveim reaction is markedly limited by the slow evolution, long duration and occasional severity of the lesions produced. The test also sheds little light on the etiology of the disease but offers a challenging approach to the problem of the pathogenesis of sarcoid lesions.

### *Course and Prognosis*

Sarcoidosis tends to run a prolonged, low-grade, chronic and unpredictable course, ranging in duration from several months to many years. Occasionally, the onset is abrupt and febrile, and a case has been reported in which such an acute onset occurred thirty-six hours after childbirth.<sup>215</sup> Often, however, it is exceedingly difficult to determine the exact time of onset so that estimates of average duration are not too reliable; these have varied in different series from two and two-tenths<sup>20</sup> to eight or more years.<sup>5</sup> In some series individual cases have been followed for fifteen years or more.<sup>38 41</sup> Residual lesions were found at autopsy in 1 of Boeck's early cases twenty-nine years after the original diagnosis had been made,<sup>84</sup> and another case was followed clinically for thirty-four years.<sup>216</sup> The benignity of the course and the generally good prognosis have been repeatedly stressed and it is certain that a considerable number of patients recover completely. In a group of 37 cases with adequate follow-up study reported by King,<sup>30</sup> half of which were confirmed by biopsy, 23 cleared completely or almost completely within three years, 8 showed no change in periods up to four years, and the remaining 3 showed extension. On the other hand, in a series of 28 cases followed by Reisner<sup>38</sup> for an average period of five years, all confirmed by biopsy, regression of lesions to the point of disappearance occurred in only a third. In an additional third the disease was essentially stationary or consisted of alternate periods of progression and regression, and in the final third the disease was progressive to the point of death in 7 cases. In Thomas's<sup>44</sup> series of 15 cases, the results were approximately the same. It is possible that a great many of the published cases have been followed for an insufficient period so that the general excellence of the outlook may have been overemphasized. The high incidence of Negroes in the series of Reisner<sup>38</sup> and Thomas<sup>44</sup> (86 and 80 per cent respectively) may also have had some bearing on the course of these cases, and sarcoidosis in the Negro may in fact, represent a special problem.<sup>217</sup>

serous membranes are infrequently involved, though pleural or pericardial effusion is occasionally seen.<sup>47</sup>

A wide variety of conditions has been described in association with sarcoidosis including Hodgkin's disease,<sup>43</sup> hemolytic anemia<sup>47, 192</sup> and polyarthritides,<sup>142, 193</sup> but coexistence in most of these cases does not necessarily imply causal relation. On the other hand, thrombocytopenic purpura has been recorded with sufficient frequency to be significant,<sup>29, 71, 194-196</sup> and the same observation applies to such an associated syndrome as diabetes insipidus.

**Blood** The white-cell count tends to be within normal limits or low in the large majority of cases, and definite leukopenia has been recorded in a third to a half of the cases in some series.<sup>9, 33</sup> The differential count often shows a mild monocytosis, occasionally as high as 15 per cent, but this is not constant and may even vary from time to time in the same case.<sup>42</sup> However, if monocytosis is accepted as a manifestation in the circulating blood of the reticuloendothelial activity giving rise to epithelioid granulomas, this finding might be expected to occur only during the active phases of the disease if it occurs at all.<sup>4, 23</sup> Mild eosinophilia (counts rarely over 10 to 15, but occasionally as high as 35 per cent<sup>24</sup>) is another inconstant finding, it has been noted in a fourth to a half of the cases in some series.<sup>24, 25, 38</sup>

Changes in the red-cell count or hemoglobin are of little significance. There may be a mild anemia, or polycythemia may occur in association with pulmonary fibrosis.<sup>4</sup> The sedimentation rate is frequently increased,<sup>24, 42, 47</sup> and this has been observed not only in patients in the active phases of the disease<sup>24, 42</sup> but also in patients whose lesions appear well stabilized.<sup>38</sup>

Elevation of the total serum protein, a fact to which Salvesen<sup>123</sup> first called attention in 1935, has since been noted in many cases. The rise may be considerable so that the value may exceed 9.0 gm per 100 cc, and is exclusively in the globulin fraction. The rise in globulin may occur at the expense of the albumin so that reversals of the ratio may be observed even in cases in which the total protein shows little or no increase.<sup>24, 38</sup> Again, these changes are inconstant and, when present, are usually associated with an active phase of the disease, in the healed phases the total protein and albumin-globulin ratio tend to be normal.<sup>41, 43, 197</sup> Electrophoretic studies on the serum proteins have shown that the rise is primarily in the gamma-globulin fraction.<sup>197, 198</sup> The findings are consistent with those seen in other chronic infections, such as lymphogranuloma inguinale and kala azar, and have suggested antibody formation to several investigators.<sup>198, 199</sup> Although Harrell<sup>42, 200</sup> has reported a substance resembling Bence-Jones protein in the urine in 2 cases it has been shown that the

proteins in multiple myeloma present a different electrophoretic pattern.<sup>199</sup>

Elevations in serum calcium, with values as high as 16.5 mg per 100 cc, have also been noted. The hypercalcemia has, on rare occasions, been associated with renal calculi,<sup>29, 130</sup> renal insufficiency<sup>137</sup> and even diffuse metastatic calcification.<sup>128</sup> Hypercalcemia, when it occurs, is often associated with hyperglobulinemia, and some relation between the two has been suggested on the basis of the calcium-binding power of serum protein. The calcium level does not vary in proportion with the protein, however, and may be higher than can be accounted for by the globulin elevation.<sup>34, 200</sup> Furthermore, most of the serum calcium is bound to the albumin fraction, with the globulin increment in hyperglobulinemia binding very little calcium.<sup>201, 202</sup> This suggests that the calcium increment in these cases is in an unbound state and, as such, independent of the hyperproteinemia except so far as each is a manifestation of disease activity. In the inactive phase, the calcium, like the protein, returns to normal levels. The relation of calcium levels to bone involvement is not certain. Hypercalcemia has been noted in both the presence and the absence of roentgenographically demonstrable bone lesions, but it is known that bone involvement may occur in the absence of roentgenographic changes.<sup>7, 123</sup>

In spite of the elevated calcium, serum phosphorus tends to be normal or at most very slightly elevated, the low phosphorus values observed in hyperparathyroidism are not seen. Moderate elevations in the serum alkaline phosphatase have been recorded, but the phosphatase values cannot be correlated with the extent or activity of the bone lesions or with the calcium content of the blood.<sup>200</sup> Cholesterol values in the neighborhood of 130 mg per 100 cc have occasionally been noted.<sup>24</sup> In the absence of renal insufficiency, non-protein nitrogen values are within normal limits.

The various serologic reactions that have been reported have been noncontributory. Serologic reactions for syphilis have been positive in some cases, Gravesen<sup>6</sup> reports only 13 positive findings among 433 patients in the literature so tested, but this figure seems rather low. In this country a higher incidence has been noted, probably owing in part to the high proportion of Negroes in the various series. In several cases positive blood Wassermann reactions have been inconstant, or have persisted in spite of intensive antisyphilitic therapy, suggesting the possibility that some reactions are nonspecific.<sup>38, 164</sup>

**Tuberculin reaction** The high incidence of sarcoid patients who either fail to react to tuberculin or react weakly to concentrations as high as 10 mg or more is a fact upon which practically all authors are agreed. Most estimates of the incidence of such nonreactors range between 60 and 70 per cent of cases, the remaining positive reactions

even in some postprimary disseminated lesions.<sup>120</sup> Whether the organisms are capable of being killed and so completely altered or removed from practically all the lesions that microscopical search and animal inoculations are negative in the great majority of cases is another matter, however, this point has still to be proved, especially since it has been demonstrated that even killed organisms may persist in tissues for some time, retaining recognizable shape and staining qualities.<sup>225</sup>

Several investigators have been attempting to produce specific lesions in sarcoid patients by the use of tubercle bacilli or their products. Positive results have been obtained in some cases with BCG<sup>210, 211</sup> and living or heat-killed tubercle bacilli,<sup>212, 213</sup> but the results are inconstant.<sup>226</sup> As noted above similar responses can be produced by extracts of sarcoid tissue or even leukemic tissue and normal spleen (Kveim antigens). An attempt to invoke characteristic lesions in sarcoid patients with tuberculophosphate has been unsuccessful.<sup>227</sup>

### (To be concluded)

### REFERENCES

- 151 Neilson J Recherches radiologiques sur les lésions des os et des poumons dans les sarcoides de Boeck. *Bull Soc franç dermat et syph* 41 1187 1218 1934
- 152 Wyatt G M Discussion of Garland<sup>44</sup>
- 153 Schaumann J Notes on histology of medullary and osseous lesions in benign lymphogranuloma and especially on their relationship to radiographic picture. *Acta radiol* 7 358-364 1926
- 154 Mordock J R and Hunter H J Leprosy roentgenologic survey. *Am J Roentgenol* 28 598-621 1932
- 155 Jungling O Ostiitis tuberculosa multiplex cystica (eine eigenartige Form der Knochentuberkulose). *Fortschr a d Geb d Röntgenstrahlen* 27 375 383 1919 21
- 156 Idem. Über Ostiitis tuberculosa multiplex cystoides zugleich ein Beitrag zur Lehre von den Tuberculiden des Knochens. *Beitr z klin Chir* 143 401-475 1928.
- 157 Fleischer F Die Erkrankung der Knochen bei Lupus pernio und Boecks Miliarlupoid. Ostiitis tuberculosa multiplex cystoides (Jungling). *Fortschr a d Geb d Röntgenstrahlen* 32 193 218 1924
- 158 Jordae J W and Osborne E D Besnier-Boeck's disease report of 2 cases of extensive involvement. *Arch Dermat & Syph* 35 663-684 1937
- 159 Doh H P and Menagh F R Bone lesions in sarcoid roentgen and clinical study. *Am J Roentgenol* 21 149-155 1929
- 160 Connolly A E Osteitis tuberculosa multiplex cystoides and sarcoid lesions. *Brit J Radiol* 11 25-27 1938
- 161 Dreiser M Über einen Fall von Splenomegalie durch Sternalpunktion aus Boecksche Krankheit verifiziert. *Klin Wchnsch* 2 1467-1471 1938
- 162 Castellanos A and Galan E Sarcoidosis (Besnier-Boeck-Schaumann's disease) report of case in child simulating Still's disease. *Am J Dis Child* 71 515-529 1946
- 163 Lucia S P and Aggeler P M Sarcoidosis (Boeck) lymphogranulomatosis benigna (Schaumann) observations on bone marrow obtained by sternal puncture. *Acta med Scandinavica* 104 351-365 1940
- 164 Boeck C Nachmalis zur Klinik und zur Stellung des benignen Miliarlupoids. *Arch f Dermat u Syph* 121 70-741 1916
- 165 Schaumann J Sur une forme erythrodermique du lymphogranulome benign. *Ann de dermat et syph* 1361-374 1920
- 166 Dancr J. and Roussy G Un cas de tumeurs benignes multiples (sarcoides sous-cutanées ou tuberculides nodulaires hypodermiques). *Arch de dermat et syph* 5 144-149 1904
- 167 Idem Des sarcoides sous-cutanées contribution à l'étude des tuberculides ou tuberculose atteintes de l'hypoderme. *Arch de med exper et dermat syph* 18 130 1906
- 168 Berkelund C J Boeck's sarcoid with erythema nodosum as initial symptom report of case. *Acta med Scandinavica* 128 338 50 1947
- 169 Lofgren S Erythema nodosum studies on etiology and pathogenesis in 185 adult cases. *Acta med Scandinavica* Supp 174 1 197 1946
- 170 Freeman O Tuberculin negative cases of erythema nodosum or erythema exudativum multiforme. *Acta med Scandinavica* 126 39-410 1946
- 171 Savin L H Analysis of signs and symptoms of 66 published cases of veeo-parotid syndrome with details of additional case. *Tr Oph Soc U Kingdom* 54 349 366 1934
- 172 Slöid N Erythema nodosum study of its clinical features and origin. *Acta med Scandinavica* Supp 157 1-176 1945
- 173 Kerley P Significance of radiological manifestations of erythema nodosum. *Brit J Radiol* 15 155-165 1942
- 174 Lombolt S Sur des lésions manquées dans les sarcoides. *Bull Soc franç de dermat et syph* 41 1142 1144 1934
- 175 Levitt J M Boeck's sarcoid with ocular localization survey of literature and report of case. *Arch Ophthalm* 26 358 388 1941
- 176 Blegvad O Boeck's sarkoid der conjunctiva. *Acta ophthalm.* 9 180-199 1931
- 177 Osterberg G Intus Boeck (sarkoid of Boeck in iris). *Brit J Ophthalm.* 23 145 160 1939
- 178 Seefelder R Ein weiterer Beitrag zu den Augenveränderungen bei der Besnier-Boeck'schen Krankheit (Lupus pernio — Besnier Boeck'sches Sarkoid bzw benignes Miliarlupoid benigne Lymphogranulomatose — Schaumann). *Arch. f Augent* 110 415-425 1937
- 179 Goldberg S and Newell F W Sarcoidosis with retinal involvement report of 2 cases. *Arch Ophthalm* 32 93-96 1944
- 180 von Bahr G Case of veeoparotitis with perivascularitis and other rare symptoms. *Acta ophthalm* 16 101-108 1938
- 181 Walsh F B Ocular importance of sarcoid its relation to veeoparotid fever. *Arch Ophthalm* 21 421-438 1929
- 182 Reis W and Rothfeld J Tuberkulide des Sehnerven als Komplikation von Hantsarkoiden vom Typus Daner-Roussy. *Arch. f Ophthalm* 126 357 366 1931
- 183 Roos B Über das Vorkommen der Schaumannschen benignen Lymphogranulomatose (des Boeck'schen benignen Miliarlupoids). *Ztschr f Kinderh* 59 280-302 1937
- 184 Waldenström J Some observations on veeoparotitis and allied conditions with special reference to symptoms from nervous system. *Acta med Scandinavica* 91 53-68 1937
- 185 Heerfordt C F Über eine Fehls veeoparotidea subchronica an der Glandula parotis und der Uvea des Auges lokalisiert und häufig mit Parotitis cerebrosplanter Nerven kompliziert. *Arch. f Ophthalm* 70 254-275 1909
- 186 Daireaux P Paralysie faciale et intus d'origine ourlienne des nerfmes ourliennes. *Bull med Paris* 13 227 1899
- 187 Pechin A Complications oculaires des oreillons (intus et keratites). *Rev gen. Ophthalm* 20 455 1901
- 188 Ferne J and Grynfeldt J Étude anatomo-clinique de certaines formes de la maladie de Besnier-Boeck-Schaumann. Essai de pathogenèse. *Ophthalmologica* 112 195 224 1946
- 189 Heaton T G and Shannon E H Mieschitz disease. *Cared M J* 58 568-570 1948
- 190 Zollinger and von Meyenburg Über eigenartige perivaskuläre Granulomatose des Gehirns. *Schweiz. med Wchnsch* 23 825 1942
- 191 Roos B Cerebral manifestations of lymphogranulomatosis benigna (Schaumann) and veeoparotid fever (Heerfordt). *Acta med. Scandinavica* 104 123 130 1940
- 192 Pardo-Castello V Tiant, F R. and Pineyro R. Nerve lesions of leprosy. *Arch Dermat & Syph* 55 785 792 1947
- 193 Feilich A and Viner G Indocyclitis parotitis polynervitits new clinical syndrome. *J Neurol & Psychopath* 2 357-358 1922
- 194 Levin P M Neurological aspects of veeo-parotid fever. *J Nerv & Ment Dis* 81 176-191 1935
- 195 Lewis G E Sarcoidosis some speculations as to stages of infection in general. *Brit. M J* 1 532-534 1941
- 196 Curtis A C Taylor H. Jr., and Grekin R H Sarcoidosis I Results of treatment with varying amounts of calceferol and dihydrotachysterol. *J Invest Dermat* 9 131-150 1947
- 197 Leitner St J Diabetes insipidus bei der epitheloidziffligen Granulomatose. *Schweiz. med Wchnsch* 26 311-320 1945
- 198 Glass S J and Davis S Granuloma of pituitary associated with pan hypopituitarism. *J Clin Endocrinol* 4 489-492 1944
- 199 van Hosen J Ein Beitrag zur Kenntnis des Boeck'schen Miliarlupoids und seiner Beziehung zu Erkrankungen anderer Organe. *Dermat. Ztschr* 28 1-27 1919
- 200 Oldberg S Morbus Schanmann-Morbus Basedow (Ein Fall von Morbus Schanmann mit Lokalisation u. a. in Glandula thyroidea mit Hyperthyreose). *Acta med Scandinavica* 115 165-176 1943
- 201 Gore I and McCarthy A M Boeck's sarcoid report of case involving stomach. *Surgery* 16 865-877 1944
- 202 Lewandowsky F Zur Kenntnis der Boeck'schen Sarkoide. *Arch f Dermat u. Syph* 123 287-293 1921
- 203 Watson C J Ripley L G Wangensteen O H and McCartney J S Isolated sarcoidosis of small intestine simulating non-specific ileo-jejunitis. *Gastroenterology* 4 30-32 1945
- 204 Homans J and Hiss G M Regional ileitis clinical not pathological entity. *New Eng J Med* 209 1315 1324 1933
- 205 Moschcowitz E. and Wilensky A O Non-specific granulomata of intestine. *Am J M Sc* 166 48-66 1923
- 206 Case records of the Massachusetts General Hospital (Case 2702). *New Eng J Med* 224 120-122 1941
- 207 Nemert F R Posterior uveitis in case of sarcoidosis. *Brit J Ophthalm* 30 724-728 1946
- 208 Wilensky A O Essential nature of non-specific granulomatous lesions of gastrointestinal tract. *Surgery* 6 288-305 and 472-467 1939
- 209 Morland A Case of sarcoidosis of lung with regional ileitis. *Tubercle* 28 22 1947
- 210 Watter S and Sommers S C Cicatrizine enteritis (regional ileitis) as pathologic entity analysis of 120 cases. *Am J Path.* 24 475 501 1948

Death, when it occurs, is usually due to pulmonary fibrosis, with resultant respiratory and cardiac insufficiency, or to superimposed cascating tuberculosis. Extensive localizations in vital areas such as the heart, and perhaps the kidney and brain, may also be fatal in some cases. Other serious complications include glaucoma and phthisis bulbi resulting from ocular involvement, and the occasional mutilating effects of bone and skin lesions.

### Treatment

The evaluation of therapeutic measures has been enormously complicated by the marked tendency of the disease to regress spontaneously. A wide variety of agents, including salts of gold and arsenic, chaulmoogra oil, antileprol and others far too numerous to mention, have been tried with equivocal results. Simple measures such as fresh air, sunlight, good diet and rest have been equally satisfactory if not more so.

X-ray therapy has been tried with beneficial effects in a few cases,<sup>43 82 218</sup> and little or no effect in others.<sup>47</sup> More recently, the successful use of calciferol in the treatment of lupus vulgaris has suggested its use in sarcoidosis as well. Curtis and his coworkers<sup>176</sup> report considerable improvement following the use of large doses of both calciferol and dihydrotachysterol. Toxic reactions were present in all cases, however, though no recognized permanent damage was noted, and Lomholt<sup>219</sup> believes that patients with sarcoidosis tolerate calciferol less well than those with lupus.

### ETIOLOGIC ASPECTS

At some time or other practically every agent capable of producing a granulomatous reaction or of diffusely affecting the reticuloendothelial system has been suggested as a possible cause of sarcoidosis. The arguments usually consist in accenting similarities between sarcoidosis and the known disease produced by such agents, at the same time ignoring or minimizing differences. The greater part of the discussion has centered about the possible etiologic role of the tubercle bacillus, most authors since the time of Boeck going on record either for or against. The repeated failures, except on a very few occasions, to identify this organism in the lesions either microscopically or by animal inoculation, as well as the high incidence of weak reactors or nonreactors to tuberculin in the group, have provided the greatest stumbling block to the general acceptance of this theory—though, paradoxically enough, both sides use these findings as their strongest arguments.

### Tuberculosis

The case for tuberculosis has been presented in detail by Pinner<sup>191</sup> whose arguments are essentially those of the many other proponents of this theory. The arguments, both factual and theoret-

ical, that have been mustered on both sides of the question can be conveniently grouped into four categories: bacteriologic, anatomic, immunologic and epidemiologic.

**Bacteriologic arguments.** The identification of acid fast bacilli in sarcoid lesions has been sporadically reported since the time of Boeck.<sup>2</sup> The various positive findings have been listed by Pinner<sup>4</sup> and others,<sup>10 25</sup> and several more have been reported since.<sup>168, 195 220</sup> However, these represent only a minute fraction of cases in which such organisms have not been found, often after exhaustive microscopical search and inoculation into a wide variety of animals.

Attempts to explain this phenomenon on the ground that the organisms are in a filterable form, or have dissociated into nonacid-fast or partially acid-fast forms, are highly theoretical and unconvincing.<sup>102 220 221</sup> On the other hand, if the lesions are actually due to the usual form of the tubercle bacillus, it is necessary to assume that the organisms are quickly killed and disintegrated at their points of focalization under the influence of the local immune forces. Under these circumstances, the lipids of the bacillus might be capable of inducing tubercle formation, as has been demonstrated experimentally,<sup>77 78</sup> whereas the proteins of the bacillus, in the absence of hypersensitivity, produce no significant necrosis or constitutional reaction. Thus, the same immunologic situation responsible for the prompt killing of the bacilli might explain the morphologic character of the lesion.<sup>4 120 222</sup>

If this is true, organisms might be expected to be identified only in very early lesions. Kyrle,<sup>223</sup> in a frequently quoted and controversial case, reported a series of biopsies on a very early skin lesion. Abundant tubercle bacilli were seen on the tenth day together with a nonspecific infiltration of lymphocytes and histiocytes, but a guinea-pig inoculation was negative. By the twenty-first day, the infiltrate was composed largely of epithelioid cells with some giant cells, and the bacilli were much reduced in number, guinea-pig inoculation was again negative. By the thirty-sixth day, the epithelioid-cell foci were free of organisms, contained numerous giant cells and were being encapsulated by fibrous tissue. By the ninety-fourth day, the infiltrate had disappeared. One of two guinea pigs inoculated with blood from the patient during a febrile episode developed tuberculosis. This case is exceedingly difficult to evaluate since it is both unique and atypical.

There is plenty of experimental evidence that acquired resistance to tuberculosis can increase the ability of the body to destroy tubercle bacilli, and the decrease in organisms may be sufficiently marked to render it very difficult to find them even on serial section.<sup>224</sup> It is also known that bacilli may be impossible to find in many primary foci and

murmur heard only in the left lateral decubitus position. The aortic second sound was equal to the pulmonic. The lungs were clear, except for a few crackles at the left base posteriorly. The abdomen was normal. Neurologic examination was negative.

The temperature was 104°F, the pulse 112, and the respirations 28. The blood pressure was 110 systolic, 70 diastolic.

Laboratory studies showed a urine with a specific gravity of 1.018, a + test for albumin, but no sugar or bile, the sediment contained 2 or 3 white cells and 2 or 3 red cells per high-power field. There were no casts. The hemoglobin was 16 gm, and the white-cell count was 13,300, with 83 per cent neutrophils. A stool was guaiac negative. The nonprotein nitrogen was 37 mg and the total protein 6 gm per 100 cc. Six flasks were inoculated with blood, and all grew coagulase-positive *Staphylococcus aureus*. A spinal tap was attempted, but only blood was obtained.

The patient was placed on penicillin, 2,000,000 units a day, digitalized with purodigin and given 75 mg of heparin. On this regime the blood cultures became sterile on the fifth hospital day and remained so. The temperature gradually subsided from daily levels of 103° to 104°F to 99° to 101°F in the course of two weeks. Despite these improvements he remained drowsy, had occasional bouts of hiccuping, but complained only of poor appetite. Approximately two weeks after admission the nonprotein nitrogen was found to be 160 mg per 100 cc. Additional laboratory studies showed the urinary specific gravity to be 1.008, with a ++ test for albumin and rare white cells and red cells in the sediment. The urine culture showed *Bacillus pyocyaneus* (*Pseudomonas aeruginosa*). The blood sodium was 123.4 milliequiv, the chloride 90 milliequiv, and the carbon dioxide 25.8 milliequiv per liter, and the calcium was 8.7 mg and the phosphorus 6.4 mg per 100 cc. The blood pressure was 190 systolic, 110 diastolic. Repeated blood cultures were negative. Four days later rapid breathing, increase in the pulse to 140 and moist rales in the lungs suddenly developed, clearing rapidly with morphine and tourniquets. In spite of therapy he showed little improvement in his general condition, and the urinary output, which had been maintained at 1500 to 2000 cc a day, dropped sharply to less than 500 cc a day, averaging about 350 cc. The urine specific gravity was 1.005. There was a ++++ test for albumin and many white cells and rare red cells in the sediment. The white-cell count rose to 22,000, with 86 per cent neutrophils, 9 per cent lymphocytes and 5 per cent eosinophils.

The course was steadily downhill, and approximately one month after admission the lungs suddenly became filled with bubbling rales, and the patient became sweaty and apprehensive. The

blood pressure was 210 systolic, 130 diastolic, the pulse 160, and the respirations 10. He failed to rally and expired soon after the onset of this episode.

#### DIFFERENTIAL DIAGNOSIS

DR ALFRED KRANES: May we know when this diminution in the urinary output took place? It is not quite clear from the record. I wondered whether the nonprotein nitrogen rose in the presence of a normal urinary output during the first weeks and with a normal specific gravity.

DR RITA M. KELLEY: The nonprotein nitrogen rose while the output was still adequate, but the specific gravity became low, only in the last few days was the output poor. The nonprotein nitrogen rose steadily and was elevated for about ten days before death.

DR KRANES: The nonprotein nitrogen began to rise at the end of two weeks, but the patient lived a month.

DR KELLEY: That is right, but the decrease in output came only a few days before death.

DR KRANES: Therefore it rose in spite of a normal urine output, with a low specific gravity. Might I ask whether the specific gravity rose?

DR KELLEY: It never rose.

DR KRANES: We are faced with a man who came in with an acute fulminating *Staph. aureus* septicemia, which was promptly recognized and treated, and who died one month later with one of the complications of renal insufficiency—namely, acute pulmonary edema.

As I see the problem we are asked to try to guess what was the trouble with the kidneys. So far as the acute episode that brought him in is concerned, the record is fairly clear-cut, although exactly what the portal of entry for the staphylococcus was is not at all clear. Very often we do not know just how invasion took place. In this case, since the man was a carpenter, he may have had what seemed to be an insignificant skin infection, and from that, very virulent organisms entered the blood stream, producing the picture described. He may have had an acute sinusitis or ethmoiditis. I do not see how we can possibly guess the origin of the septicemia. Whether or not he had a bacterial endocarditis is also a guess. He probably did, although not primary. The chances that the organisms landed on one of the heart valves are certainly fairly great in this particular case, in which we have reason to believe mitral rheumatic heart disease existed, probably mitral stenosis. There is a fairly good probability that he had an acute bacterial vegetation engrafted on the mitral and possibly on some of the other valves. Do we know any more about the murmur?

DR KELLEY: The mitral diastolic murmur remained the same. There were no new murmurs.

DR KRANES: Presumably mitral stenosis and possibly acute bacterial endocarditis.

- 191 Pinner M. On etiology of sarcoidosis *Am Rev Tuberc* 54:582-584, 1946
- 192 Crane A. R. and Zetlin, A. M. Hemolytic anemia, hyperglobulinemia and Boeck's sarcoid *Ann Int Med* 23:882-889 1945
- 193 Zweifel E. Gleichzeitiges Vorkommen eines Boeckschen Sarkoids mit einer primären chronischen Polyarthritus (beginnendes Sjögren-Syndrom) *Helvet paediatr Acta* 1:475-484 1946
- 194 Jersild M. Syndrome of Heerfordt (necroparotid fever), manifestation of Boeck's sarcoid *Acta med Scandinav* 97:322-328 1938
- 195 Berhlinger, W. (Cited by Rubin and Pinner <sup>49</sup>)
- 196 Nordland M., Ylvisaker, R. S. Larson P. and Reiff R. Pregnancy complicated by idiopathic thrombocytopenic purpura and sarcoid disease of spleen, splenectomy and subsequent normal delivery case report *Minnesota Med* 29:166-170 1946
- 197 Fisher A. M. and Davis B. D. Serum proteins in sarcoid electrophoretic studies *Bull Johns Hopkins Hosp* 71:364-374 1942
- 198 Seibert, F. B. Seibert M. V. Atro A. J. and Campbell H. W. Variation in protein and polysaccharide content of sera in tuberculosis sarcoidosis and carcinoma *Am J M Sc* 213:247 1947
- 199 Gutman A. B., Moore D. H., Gutman E. B., McClellan V. and Kahat E. A. Fractionation of serum protein in hyperproteinemia with special reference to multiple myeloma *J Clin Investigation* 20:765-783, 1941
- 200 Harrell G. T. and Fisher S. Blood chemical changes in Boeck's sarcoid with particular reference to protein calcium and phosphatase values *J Clin Investigation* 18:687-693 1939
- 201 Jaffe H. L. and Bodansky A. Serum calcium clinical and biochemical considerations *J Mt Sinai Hosp* 9:501-920 1943
- 202 Gutman A. B. and Gutman E. B. Relation of serum calcium to serum albumins and globulins *J Clin Investigation* 16:903-919 1937
- 203 Lomholt, S. Discussion of Reunion dermatologique der Strasbourg 10 Pp 1350 1353
- 204 Kveim A. En ny og spesifikk kutan reaksjon ved Boeck's sarcoid. *Nord med* 9:169-172 1941
- 205 Danbolt N. and Nilssen R. W. Investigations on course of Kveim's reaction and its clinical value *Acta dermat venerol* 25:489-502 1945
- 206 Putkonen, T. Über die Intrakutanreaktion von Kveim (KvR) bei Lymphogranulomatosis benigna und über das Bild dieser Krankheit im Lichte der Reaktionsergebnisse *Acta dermat-venereol* 25 (Supp 10) 1-194 1943
- 207 Lomholt S. Beitrag zur Kveimreaktion bei Lymphogranulomatosis benigna *Acta dermat-venereol* 24:447 1943
- 208 Nelson C. T. Observations on Kveim reaction in sarcoidosis of American Negro *J Invest Dermatol* 10:15-26 1948
- 209 Williams, R. H. and Nickerson D. A. Skin reactions in sarcoid *Proc Soc Exper Biol & Med* 33:403-405 1935
- 210 Lemming R. Attempt to analyze tuberculin energy in Schumann's disease (Boeck's "sarcoid") and necroparotid fever by means of BCG vaccination *Acta med Scandinav* 103:400-429 1940
- 211 Lemming R. Development of Boeck's sarcoid at place on skin where BCG vaccination had been made in case of Schumann's disease *Acta med Scandinav* 110:151-160 1942
- 212 Warfvinge L. E. Boeck's sarcoid experimentally produced by virulent, human tubercle bacilli in case of Schumann's disease *Acta med Scandinav* 114:259-270 1943
- 213 Idem Über eine von abgetöteten Tuberkelbazillen hervorgerufene Hautreaktion bei Lymphogranulomatosis benigna (vorläufige Mitteilung) *Acta tuberc Scandinav* 19:126-141 1945
- 214 Volk, R. *Tuberkulose der Haut* In *Handbuch der Haut und Geschlechtskrankheiten* Edited by J. Jadassohn Vol. 10: 879 pp. Berlin Julius Springer 1931 P 111
- 215 Taschman M. Pulmonary sarcoidosis acute onset. *J Mt Sinai Hosp* 14:648-652 1947
- 216 Vidal J. Guihart H. L. and Girard M. Maladie de Boeck-Boeck-Schumann Lesions cutanées et pulmonaires d'apparence tuberculeuse *Rev de la tuberc* 8:58 1943
- 217 Michelson H. E. Sarcoidosis review and appraisal. *J A M A* 136:1034-1039 1948
- 218 Pohle E. A., Paul L. W. and Clark, E. A. Roentgen therapy of Boeck's sarcoid *Am J M Sc* 209:503-513 1945
- 219 Lomholt, S. Discussion of disorders of chest sarcoidosis. *Lancet* 2:445 1947
- 220 Schumann J. and Hallberg V. Koch's bacilli manifested in tissue of lymphogranulomatosis benigna (Schumann) by using Hallberg's staining method. *Acta med Scandinav* 107:499-501, 1941
- 221 Mellon R. R. and Beinhaber L. G. Pathogenesis of noncaseating tuberculosis of skin and lymph glands *Arch. Dermat. & Syph* 36:515-533 1937
- 222 Sulzberger M. B. *Dermatologic Allergy* Springfield Charles C. Thomas 1940 Lecture 9 Pp 211-249
- 223 Kyrle J. Die Anfangsstadien des Boeck'schen Lupoides Beitrag zur Frage der tuberculösen Ätiologie dieser Dermatose *Arch f Dermat u Syph* 131:33-79 1921
- 224 Rich A. R. <sup>50</sup> P 457
- 225 Ocott, C. T. Reaction to killed tubercle bacilli in normal and immunized (sensitized) rabbits *Am J Path* 15:287-293 1939
- 226 Forssman O. Some notes on value of percutaneous BCG vaccination according to Rosenthal together with some experiments aiming at obtaining specific cutaneous reaction in Schumann's disease by means of this method. *Acta tuberc Scandinav* 20:123-135 1946
- 227 Harrell G. T. Reactions in humans to phosphatid. fraction of human tubercle bacilli *J Clin Investigation* 23:943 1944.

## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., Editor

BENJAMIN CASTLEMAN, M.D., Associate Editor

EDITH E. PARRIS, Assistant Editor

### CASE 34451

#### PRESENTATION OF CASE

A forty-one-year-old carpenter entered the hospital because of fever and delirium.

The patient had been well and active until two days before admission, when he developed a slight cough, a feeling of tightness in the chest and a mild headache. The next day he refused his breakfast but reported for work only to return home shortly, complaining of cough and headache. He went to bed with a shaking chill and a temperature of 103.5°F. Sixteen grams of sulfadiazine was prescribed and taken in divided doses during the next

twenty-four hours. Despite this he grew gradually less responsive and became delirious, with continuance of the high fever. He was then given 300,000 units of penicillin in oil and sent to the hospital.

The past history revealed an episode several years previously of ankle pains, which were severe enough to cause him to stay in bed a month. A few years later he was told that he had a heart murmur. He had had frequent colds and a chronic, non-productive cough. Since his father's death from cardiac disease five months previously, he had been considerably concerned about heart disease and began to complain of pain in the anterior chest and mild exertional dyspnea although there was no orthopnea, ankle edema or palpitation.

Physical examination showed a well developed, obese man who was semistuporous, warm, flushed and sweating. There were a few questionable petechiae on the arms, neck and buccal mucosa, and small, blotchy, pink macules on the trunk and legs. The eyes were not remarkable although the fundi were not seen. The throat was slightly injected. The ears were normal. The neck was supple, and there was no venous distention. The heart was enlarged, the border of cardiac dullness extending 2 cm beyond the midclavicular line. There was tachycardia with frequent extrasystoles. There was a Grade II, rumbling, diastolic, apical

would be the most likely etiology, although there are certain aspects of the picture that are atypical. The other possibilities that I have mentioned cannot be ruled out.

DR MERRILL SOSMAN: Was the brain removed at autopsy, Dr Mallory?

DR TRACY B MALLORY: No.

DR SOSMAN: Then there is no use speculating about that. I might ask Dr Kranes what he expects to find in the heart—whether or not it will be an acute bacterial endocarditis.

DR KRANES: An enlarged heart with rheumatic mitral disease and probably some acute bacterial vegetations containing *Staph aureus*.

DR SOSMAN: Do you think that the renal lesions could have been embolic?

DR KRANES: You mean the type of embolic glomerulonephritis found with *Streptococcus viridans*? There is no evidence in this case that *S viridans* was found. I hesitate to make a diagnosis of two organisms when only one is presented to me.

DR MALLORY: Will you tell us about the impressions of the clinicians on the ward, Dr Kelley?

DR KELLEY: Most of us thought that it was probably an acute nephritis. We did not know the amount of sulfonamide administered until later when the patient's physician came in. At that point we inclined to acute diffuse nephritis on the basis of the maintenance of the penicillin blood level, ten times the sensitivity of the organism. We believed that the infecting organism had been controlled by the penicillin.

DR MALLORY: How did you explain the fever?

DR KELLEY: He also had a slightly infected urine because he was maintained on constant catheterization since he was unable to void spontaneously.

DR JOHN B QUINBY: Are the urinary findings, the first ones, adequate to rule out the thought of a pre-existing element of renal failure based on old pyelonephritis?

DR KRANES: No, that is always possible in a perfectly healthy man. One must remember that a patient can have renal disease and maintain excellent health. I think it is possible but not probable.

#### CLINICAL DIAGNOSES

Acute glomerulonephritis  
Acute pulmonary edema  
Acute bacterial endocarditis  
Rheumatic heart disease  
Cystitis

#### DR KRANES'S DIAGNOSES

Rheumatic heart disease  
*Staph aureus* septicemia  
Acute bacterial endocarditis  
Acute nephritis caused by sulfonamide nephritis

#### ANATOMICAL DIAGNOSES

Endocarditis, acute bacterial (*Staph aureus*),  
mitral and aortic valves, healing  
Endocarditis, rheumatic, old, mitral and aortic  
valves  
Glomerulonephritis, acute  
Arteriosclerosis, coronary, severe, aortic, mild  
Myocardial infarct, old  
Infarcts, recent, kidney and spleen  
Cystitis, acute hemorrhagic

#### PATHOLOGICAL DISCUSSION

DR MALLORY: Autopsy showed a very much enlarged heart, weighing over 500 gm, with evidence of old rheumatic damage to both mitral and aortic valves. The mitral valve had, in addition, a very large, friable vegetation, measuring nearly 3 cm in diameter, and there were a few, very small, acute vegetations on the aortic valve. There was a large area of scarring in the myocardium, and on examining the coronary arteries we found that they were reduced to almost pinpoint lumens. So we had two possible sources for the myocardial scars: emboli from the acute endocarditis and coronary sclerosis. The microscopical sections suggest that both played a part. A portion of the scarring was very old, obviously many months if not several years in age—completely healed, fibrous scars with no trace of the necrotic muscle cells. In fact, there was slight replacement of the scar by adipose tissue. These scars must have long antedated the endocarditis, and I ascribe them to the coronary-artery disease. There were also, however, many small foci of acute myocardial necrosis scattered throughout the heart, which I think were undoubtedly due to emboli. The kidneys were the major point of interest. They were extremely enlarged, with very thick, pale cortices, and showed typical acute diffuse glomerulonephritis. There were infarcts in the spleen and in one of the kidneys, evidently secondary to the endocarditis, and a very severe terminal pulmonary edema with old, calcified scars in the pleura near the base, the etiology of which I am uncertain about, but they were probably tuberculous.

Glomerular lesions can occur in the ordinary type of *S viridans* endocarditis in two forms: involvement of scattered glomeruli or of portions of individual glomeruli, which is ordinarily called embolic glomerulonephritis. That is the common type and does not usually lead to renal insufficiency, although generally associated with red cells in the urine. In about 10 per cent of endocarditis cases a diffuse glomerulonephritis develops. I think that this is the first case of diffuse glomerulonephritis that I can remember in which the nephritis was associated with staphylococcal rather than strepto-

Were there any x-ray films, and are they helpful at all?

DR JOSEPH HANELIN The patient was too ill to have conventional films. The films were obtained with the patient recumbent, this being an anteroposterior instead of the usual posteroanterior projection. The heart is large. Despite the magnification it looks larger than one would expect to see it in this position. There is a density superimposed on the right side of the heart, which may represent an enlarged left auricle. The lung fields are probably clear, and these little circular densities throughout the lung probably represent vascular shadows rather than metastatic abscesses. The spleen is perhaps just visible — if that is the spleen, it does not appear enlarged. The bone structures are normal.

DR KRANES When, during the course of the illness, was this film taken?

DR KELLEY On admission.

DR KRANES In the days before intensive chemotherapy, the patient probably would have died within a few days or a week after admission, and the chances are that at autopsy many metastatic abscesses would have been found in various parts of the body, most commonly in the kidneys, brain and myocardium — the sites most commonly affected. Whether, despite the intensity of treatment, residual abscesses remained is impossible to say on the evidence. There is no evidence of myocardial involvement except for two attacks of acute pulmonary edema. There was certainly no evidence of cardiac tamponade. The patient ran a temperature of 101°F in the hospital, so presumably the infection may not have been completely healed.

The real problem is not so much the bacterial infection as the nature of the renal lesion. Time was when in a case of this sort we would be satisfied to make a diagnosis of acute nephritis and let it go at that, but nowadays we are expected to try to predict what the microscopical lesion will be. I find that quite impossible, but I see no reason why we should not look over the possibilities. In this particular case there were many factors operating that may have produced renal damage. In many cases of kidney disease we are hard put to find the cause. There are many possible causes here. The first and most obvious one is the large dose of sulfadiazine that he received on the day before admission — 16 gm in twenty-four hours. One wonders what role sulfonamides played in the production of this picture. As you know, sulfonamides may produce renal damage in any one of four ways. They can plug up the tubules, they can produce a lower-nephron nephrosis, they can cause an acute interstitial nephritis involving neither the tubules nor the glomeruli, and they can produce acute necrotizing arterial lesions similar to those found in periarteritis nodosa. These were first described

by Rich\* several years ago, and since then isolated case reports have appeared in which periarteritis-like lesions are found following sulfonamide administration, the patients frequently dying in uremia. Which one of these may have been operating in this case I find it difficult to say. I think we can rule out the first one — that is, plugging of the tubules, since there was no anuria. Lower-nephron nephrosis, also, usually leads to striking oliguria or anuria, which this patient did not have. I think it would be unusual for a person with lower-nephron nephrosis to have an adequate urinary output for so long and to develop azotemia. The other two types I cannot rule out. It is conceivable that he had a periarterial lesion or interstitial nephritis due to sulfonamide. As for acute glomerulonephritis, one would expect a good deal more hematuria than described here. I think we must assume that this patient did have an acute lesion, since there is no evidence that the kidneys had previously been involved in any way. On the law of chances I think that glomerulonephritis is very unlikely.

One naturally wonders whether the kidney disease could possibly be linked to the primary illness. Can the staphylococcus be incriminated in this case? As I said before, in the prepenicillin and pre-sulfonamide era this patient would have died in several days with evidence of septic emboli in the kidneys, either several discrete abscesses or miliary abscesses of the cortexes. As I read this, I wondered to myself, although I have never seen it described, whether if such a patient were kept alive with chemotherapy and the septic element controlled, he might live long enough to develop renal insufficiency from these lesions. I have never heard of it, but I think it is not improbable. One might find diffuse miliary abscesses throughout the cortexes of the kidney interfering with renal function. We are dealing here with a virulent organism that was coagulase positive and may not have been reached by penicillin.

While on the subject of the staphylococcus, I suppose it is not too far-fetched to bring up one other possibility, although again I hesitate to mention it because of its rarity. That is bilateral cortical necrosis. These cases are described chiefly in women, the majority of them occurring after delivery. A few cases have been described in men, however. The reason I mention it here is that lesions like bilateral cortical necrosis have been produced experimentally in animals by the injection of staphylococcus toxin. Since this patient suffered from a severe staphylococcal septicemia, one wonders if it could possibly have been a source for the renal lesion.

I have no way of choosing among these various possibilities. I am forced to make a guess. On the law of probabilities I should think that sulfonamides

\*Rich A. R. Role of hypersensitivity in periarteritis nodosa as indicated by 7 cases developing during serum sickness and sulfonamide therapy. *Bull. Johns Hopkins Hosp.* 71:123-140, 1942.

this patient became distended very promptly as soon as the enema was given, it might mean that the enema fluid escaped from the colon into the peritoneal cavity, especially if the distention was attended by sudden, severe, abdominal pain. On the other hand, perforation of the colon is rare as a result of enemas. It is a very unusual occurrence in my experience, with the exception of instrumental perforations, which occur while a colostomy is being irrigated or something of that sort or in the presence of a lesion in the wall of the colon itself. Carcinomas of the colon rarely perforate. On the other hand, perforation of the colon, proximal to an obstructing carcinoma, is not infrequent. We have seen such things occur with an overdistended colon when a perforation of the cecum may occur as a result sometimes of an enema given in the X-Ray Department. Lymphomas sometimes perforate and diverticula of course do.

The cervical lymph node must have been pathologic. It was apparently a single mass, suggestive of involvement of one of the lymph nodes with carcinoma or some other malignant tumor, possibly lymphoma. Could it have been related to anything within the abdomen? The Virchow node, which we read about in textbooks but rarely see, does occur in carcinoma of the stomach and esophagus, sometimes occasionally from other abdominal carcinomas but not very frequently.

No peristalsis was heard except during paroxysms of pain, when a few, scattered, high-pitched sounds were audible. That is an important observation. After twenty-four hours of peritonitis it is a little bit unusual for a patient still to have peristalsis detected by auscultatory methods. One occasionally hears it, but it is distinctly unusual.

The tender mass in the pelvis is of interest. The average malignant tumor in the pelvis arising from the genital tract is not particularly tender. On the other hand, if one has a carcinoma arising in the bowel, it may well be tender because of secondary inflammation from infection. This could have been, I presume, a purely inflammatory mass.

This patient died, obviously of peritonitis, sixty-four hours after the sudden episode of pain and distention. Can we connect this whole history and try to make one diagnosis, or do we have to make several diagnoses? I am inclined to make more than one, but I must confess I do not know what exactly was wrong with her. I think it is fair to say, on the basis of the history, that she must have had gallstones and difficulty with the gall bladder because of certain aspects of the history, such as intermittent colicky pain in the upper abdomen. The fact that this followed a period of jaundice and that when it occurred the jaundice disappeared lends a certain amount of weight to the possibility of gallstone ileus. She may have had a large stone, which had entered the intestinal tract and passed down slowly, causing intermittent attacks of pain, and had ultimately lodged. I cannot remember a

case of gallstone ileus in which a stone of sufficient size to obstruct the small bowel had passed through the common duct. Those that I am familiar with had ulcerated through into the abdominal cavity from the common duct across an abscess or an area of necrosis into the duodenum or from the gall bladder directly into the duodenum. Dr Mallory perhaps would like to comment on that as a generality. But it seems to me that if we are dealing with gallstone ileus, which should be thought of, a more definite, acute, inflammatory process in the right upper quadrant should have been observed at some time or other in the past. We have no such observation. The only symptoms and signs that point toward the gall bladder are those of obstruction and not inflammation. So, although it possibly should be mentioned, on the basis of the history it seems to me that that diagnosis does not have sufficient weight.

Another important question to decide is whether the peritonitis that the patient died of arose as a result of the enema. One would think so from the way the history reads. She was all right except that the bowels did not move for twenty-four hours, which does not seem unusual, but she was given an enema and then the abdomen immediately became distended and she developed pain, which suggests perforation. Let us assume that the peritonitis did arise from perforation of the colon. I do not believe it came from perforation of the small bowel by the way of an enema. If the perforation and the peritonitis were the result of an enema, it must have been from the colon. Therefore, one would have to assume that there was some intrinsic lesion in the colon. The gall-bladder disease with jaundice, with some of the other things the patient had, and the type of pain, which was entirely in the upper abdomen, suggest either small-bowel obstruction or pancreatitis or perhaps gall-bladder colic. She probably had a mass in the pelvis. This mass was tender and irregular. It could have been malignant in the sense that it was a malignant neoplasm and it could of course have arisen in the bowel, in the sigmoid or in some other loop that lay within the pelvis. There is nothing to suggest that it arose from the retained cervix, which felt normal, though on motion of the cervix the patient experienced pain.

That is as far as I can go with a situation such as this. If we assume that the peritonitis, which she died of, arose as a result of the giving of an enema, I think we must also assume that she had some lesion of the colon, possibly the sigmoid, and that it probably was inflammatory, either primarily inflammatory or a growth of some kind that was secondarily inflamed. If we assume that that was the case we have to neglect some of the important aspects of the history that have to do with the gall bladder.

DR DANIEL S. ELLIS: I should like to ask Dr Sweet if he would consider the possibility of a malignant lesion perhaps involving the pancreas or the

coccal infection. There can be no doubt about the organism, however. It was grown repeatedly.

DR KRANES: How about the absence of hematuria? Or was there hematuria in this case? Is that not a bit unusual?

DR MALLORY: There may have been more than was apparent in the record.

DR KELLEY: No, there was never very much

## CASE 34452

### PRESENTATION OF CASE

A sixty-nine-year-old woman was admitted to the hospital because of abdominal distention and lower suprapubic pain.

Thirty-eight years before admission a hysterectomy had been performed because of fibroids. Ten years before admission during a routine physical checkup including x-ray examination, a nonfunctioning gall bladder was discovered. The patient at this time admitted an intolerance to fried and fatty foods of thirty years' duration. Eight months before admission the patient was awakened in the early morning by a sharp, excruciating, right-upper-quadrant pain, which radiated to the scapula. The acute episode passed off after several hours, leaving residual soreness. There was no associated nausea or vomiting, dark urine, acholic stools, jaundice or chills and fever. During the six weeks that followed she had several recurrent attacks of right-upper-quadrant pain. Five months before admission she noted failing appetite, loss of weight, weakness and lethargy. Two months before admission she became jaundiced and complained of itching. She could not report on the color of stools and urine. Chills and fever were absent. She did have daily nausea and vomiting until admission. The weight loss by now had amounted to 24 pounds. Two weeks before admission it was discovered that the blood sugar was 390 mg per 100 cc, whereas the value had been normal two weeks before. The jaundice subsided in the four weeks preceding admission. During the two weeks before admission the patient complained of epigastric pain radiating through to the back and she noticed a lump in the neck. Twenty-four hours before admission an enema was given because she had had no bowel movement for twenty-four hours. The enema was not expelled, and she suddenly became distended and complained of lower abdominal, suprapubic pain. The vomiting continued without change. At the time of admission she had passed no gas by rectum.

Physical examination showed a left supraclavicular lymph node that was enlarged, firm and freely movable. The heart was not enlarged, and there was a Grade II systolic murmur at the apex transmitted to all areas. The abdomen was distended and

diffusely tender. No peristalsis was heard except during the patient's rare paroxysms of pain, when a few scattered, high-pitched sounds were audible. On pelvic and rectal examination there was a large, retained cervix, which could not be visualized. There was a very tender mass in the cul-de-sac, which felt lobulated. This mass was continuous with the cervix, motion of which caused severe pain. There was a small amount of soft feces in the rectum that was guaiac positive. The white-cell count was 24,000.

The temperature was 97°F, the pulse 90, and the respirations 20. The blood pressure was 118 systolic, 70 diastolic.

Shortly after admission the patient rapidly went into shock, the blood pressure was unobtainable, and the pulse was 140. Distention and generalized tenderness were increased. Rigidity and rebound tenderness were present. The temperature at this time was 101°F. In spite of blood transfusion the patient never recovered from shock, and the temperature reached 107°F terminally. She died thirty hours after admission.

### DIFFERENTIAL DIAGNOSIS

DR RICHARD H. SWEET: This woman had a long history of encounters with the medical profession. The hysterectomy done thirty-eight years before admission undoubtedly was a supravaginal hysterectomy, leaving the cervix.

The episode eight months before admission is rather characteristic of gallstone colic. It is very frequent for a patient to have gallstone colic in the absence of nausea and vomiting. If infection is absent, one need not see changes in the temperature, pulse and white-cell count. If the stone does not pass through the cystic duct, there is, of course, no jaundice. One can relate all these symptoms to gall-bladder disease except the lump in the neck. She could have had, to explain the later difficulties, increasing trouble with the gall bladder, a mild or moderate degree of infection and passage of the stone into the duct, with jaundice and all the characteristic signs of obstruction — perhaps subsequent release of the obstruction because of passage of the stones into the intestinal tract.

I do not know why she developed a high blood sugar. There is nothing else to suggest that she had pancreatitis, although she complained of pain radiating to the back, which might go with it.

How can the lump in the neck be connected with gall-bladder disease? It may have been a metastasis from carcinoma of the gall bladder. Anyone who has had gallstones for a period of many years is likely to develop a carcinoma. Conversely I at least have never seen a carcinoma of the gall bladder develop in the absence of stones, although it may, of course, be found. The lump in the neck which developed out of a clear sky, is an important finding. Of course one should not place too much emphasis on the wording of these histories, but if

# The New England Journal of Medicine

Formerly  
The Boston Medical and Surgical Journal  
Established 1828

Official Organ of

THE MASSACHUSETTS MEDICAL SOCIETY  
and

THE NEW HAMPSHIRE MEDICAL SOCIETY

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND  
PUBLISHED WEEKLY UNDER THE JURISDICTION OF THE  
COMMITTEE ON PUBLICATIONS

Richard M. Smith, M.D., *Chairman*  
James P. O'Hare, M.D. Conrad Westelboeck, M.D.  
Oliver Cope, M.D. John Fallon, M.D.  
Joseph Garland, M.D. *Editor*

ASSOCIATE EDITORS  
Thomas H. Lanman, M.D. Donald Munro, M.D.  
Henry Jackson, Jr., M.D.

Clara D. Davies, *EXECUTIVE EDITOR*  
Robert O. Leary, *ASSISTANT EDITOR*

EDITORIAL BOARD  
C. Gay Lane, M.D. Maxwell Finland, M.D.  
Henry R. Vietz, M.D. James M. Faulkner, M.D.  
Robert M. Green, M.D. Carroll B. Larson, M.D.  
Dwight O'Hara, M.D. Francis D. Moore, M.D.  
Fletcher H. Colby, M.D. C. Stuart Welch, M.D.  
Robert L. Goodale, M.D. Vernon F. Williams, M.D.  
Chester M. Jones, M.D. Benjamin Castleman, M.D.  
Harvey R. Morrison, M.D. Hugh R. Leavell, M.D.

SUBSCRIPTION TERMS \$7.00 per year in advance, postage paid for the  
United States (medical students \$4.00 per year) Canada \$8.00 per year  
(Boston funds) \$9.50 per year for all foreign countries belonging to the  
Postal Union

MATERIAL should be received not later than noon on Thursday three  
weeks before date of publication

THE JOURNAL does not hold itself responsible for statements made by any  
contributor

COMMUNICATIONS including those concerning classified advertising but  
without regard to other advertising should be addressed to the *New England  
Journal of Medicine* 8 Fenway Boston 15 Massachusetts Telephone  
RE 6-2094

NEW ENGLAND ADVERTISING REPRESENTATIVE (except for classified  
advertising) Edwin B. Tyler 89 State Street Boston Massachusetts  
Telephone LA 3 5316

## FAMILY REUNION

MASSACHUSETTS, the Mother of many outstanding figures and accomplishments in public health, will be able to view her children and see how they have developed when the American Public Health Association celebrates its seventy-sixth birthday with a meeting in Mechanics Hall, Boston, from November 8 to 12.

Just a hundred years ago the Massachusetts Medical Society was joining the American Statistical Association in petitioning the Legislature to establish a commission to survey sanitary conditions within the Commonwealth. The immediate result was the masterly report of Lemuel Shattuck and his associates, submitted April 25, 1850, and ultimately the first state board of health, with which

Massachusetts set the pattern for the whole country nineteen years later.

The continued Massachusetts contribution is highlighted in the current presiding officers of the American Public Health Association. The president and first woman to hold this office, Dr. Martha Eliot, associate chief of the Children's Bureau, comes of a distinguished Boston family to which she adds lustre. The president-elect is Dr. Charles F. Wilensky, an authority who has made himself indispensable locally and nationally in both public-health and hospital fields. His official positions as director of the Beth Israel Hospital and deputy commissioner of the Boston Health Department give only an indication of his broad community service.

The American Public Health Association has become a very influential and representative organization of twelve thousand members including professional workers in all branches of public health. Twelve sections will be holding scientific sessions, and a great many discussions will vitally interest practicing physicians. A special session honoring Lemuel Shattuck will be held on November 10.

During the twenty-five years since the American Public Health Association last met in Boston public health has developed enormously. As the mother of so much of the best in public health, Massachusetts has a tremendous interest in seeing what manner of men her children have become. Her cordial greeting will be heightened by a maternal interest in how the offspring have fared in other environments and, as children returning from far places, in the new ideas they will doubtless introduce into the "home."

## DIAMOND ANNIVERSARY OF NURSING

Nursing Progress Week, beginning on November 14, has long been in preparation. In planning for it the American Nurses' Association has done a truly admirable piece of work, organizing a nationwide demonstration that will reach its peak on Linda Richards Day, November 16. It deserves the nation's attention.

Nursing, in one form or another, is an ancient calling, devoted to the care of those who cannot

ampulla of Vater as a cause of the pain rather than stone

DR SWEET I neglected to mention it, though it ran through my mind as I read the history over I tried to explain the pain in the back and also the change in the picture that was characteristic of the appearance of that pain and prolonged nausea, which often occurs in pancreatic disease Carcinoma of the pancreas may cause intermittent jaundice, so we need not exclude the diagnosis of carcinoma of the pancreas because of the fact that the jaundice cleared Of course the lymph node in the neck, if it was malignant, could have been secondary to carcinoma of the pancreas as well as to other things — the lymphatic channels intercommunicate

DR ELLIS One might also explain the hyperglycemia on that basis

DR SWEET That was a rather sudden development, was it not?

DR ELLIS I thought it was carcinoma of the pancreas or even of the ampulla of Vater, causing the onset of diabetes along with the onset of the original symptoms In 2 cases that I know of, disappearance of symptoms, including the diabetes, was noted when the major lesion was detected

DR W PHILIP GIDDINGS We had this patient as a private case for a short period She was brought here from another hospital, where the enema had been given She had a normal gastrointestinal series and a negative barium enema, both within a few weeks According to the patient, the interval between the enema and the distention and discomfort was very brief But according to those who gave the enema and the doctor in the other hospital, there had been a distinct interval, and the onset of the change was by no means sudden or agonizing On that basis I was inclined to believe that it was not perforation of the colon We all thought that she had a perfectly good history of gall-bladder disease, and we thought that stones were present The lymph node in the neck, which was a little above the supraclavicular area, actually was very hard, and there was no question in our minds that it represented a metastatic cancer We questioned gallstone ileus as Dr Sweet did, but it did not seem to fit She had been under continuous medical observation for eight months, and we were informed that the diabetes had developed suddenly, on that basis and because of the node in the neck, we thought that we were dealing with carcinoma of the pancreas The presence of peristalsis when she first came in did not seem compatible with peritonitis of twenty-four hours' duration, as it did not to Dr Sweet Our original impression was that she had abdominal carcinomatosis from carcinoma of the pancreas The terminal event that started four hours after admission was rather dramatic The passage into shock was very rapid The increase in abdominal tenderness was very marked, and the rebound tenderness and so forth described did not appear until the final severe episode, but at that time it became

apparent to us that she obviously had peritonitis as well and we were unable to state its source

#### CLINICAL DIAGNOSES

Rupture of abdominal viscus  
General peritonitis  
Carcinoma of stomach?  
Carcinoma of pancreas?

#### DR SWEET'S DIAGNOSIS

Generalized peritonitis from perforation of colon at site of inflammatory, malignant lesion

#### ANATOMICAL DIAGNOSES

*Adenocarcinoma of pancreas, with metastases*  
*Perforation of metastatic carcinoma of ileum forming pelvic abscess*  
*Peritonitis, acute generalized*

#### PATHOLOGICAL DISCUSSION

DR TRACY B MALLORY When the peritoneal cavity was opened there was obvious diffuse peritonitis, which, because of the slight turbidity of the fluid, appeared quite fresh In the pelvis there was a partially localized collection of pus that seemed to have been present for a rather longer time, perhaps for weeks even On examining the bowel we found multiple tumor nodules, all of which, however, seemed to be involving the bowel from the serosa inward The distribution was rather peculiar One of these nodules had almost completely encircled the pylorus, producing quite marked pyloric stenosis A second was in the ileocecal valve and likewise was quite stenotic She had a Meckel diverticulum, but it was not perforated About halfway between the Meckel diverticulum and the ileocecal valve was a perforation about 0.5 cm in diameter in one of these multiple neoplastic areas Further search showed that the primary carcinoma was in the pancreas Approximately three quarters of the organ was destroyed by tumor The gall bladder was dilated and thin-walled, and we found no stones in the gall bladder or bile duct So we believe everything is explained by carcinoma of the pancreas and the metastases I cannot say whether or not the enema had anything to do with the perforation in the small bowel, which was a considerable distance above the ileocecal valve — probably not

DR GIDDINGS I believe, Dr Mallory, that there was one more interesting feature about the autopsy — the site of the perforation in the ileum was in a loop that was fairly adherent in the right pelvis as the result of an old, fibrous band, which was pretty obviously a result of the hysterectomy

DR MALLORY Yes The bowel was sharply angulated, and the tumor nodule was in the site of the angulation, with the perforation in that knuckle Whether that mechanical fixation had anything to do with the metastasis at that point is questionable.

on, Dr James A. Spalding, who presented the collection to the Boston Medical Library

The Library has also been the recipient of many outstanding gifts from public-spirited citizens who believed in placing valuable documents in local institutions where they could be properly safeguarded and preserved for posterity

In this connection there may be noted the receipt book, dated 1643, of Governor John Winthrop of Massachusetts, a collection of medical letters, written between 1652 and 1663, of his son, John Winthrop, governor of Connecticut, the documents of Dr James Thacher, of Plymouth, covering the years from 1754 to 1844, and recently supplemented by a collection of twenty-three letters, the original records of the secretary of the Milton Vaccination Committee, dated 1809, giving in detail the story of the famous experiment of inoculation and vaccination of the children of the town, the records of inoculations and vaccinations from 1775 to 1800, at Rainsford Island, in Boston Harbor, and the original depositions of various prominent physicians and other persons given in Suffolk Superior Court in 1853 on the petition of William T G Morton, regarding his right to use ether as a surgical anesthetic, and other valuable documents that have found a permanent abode in the Library

Where material of local value cannot be obtained by gift, every effort should be made to acquire it by purchase. Booksellers and book scouts occasionally come into possession of such material and usually offer it to local libraries or societies. It is regretted that some institutions do not recognize the necessity of owning all documents of local interest and, rather than spend a few dollars, permit the material to go elsewhere

Dr Spalding was a good friend of the Boston Medical Library, and it was through his efforts that the collection of original sketches and drawings of the anatomist, Alexander Ramsey, made between 1721 and 1824, were rescued from a closet in a New Hampshire farmhouse. The director of the Library recalls driving one brisk October morning to Portland, Maine, to see Dr Spalding, and then driving another hundred miles into the mountains and having to listen to a broadcast of a world-series game before any business could be transacted,

reminding one of tea-time and the Saturday holiday in London, where likewise business cannot be considered during these sacred hours. However, negotiations were conducted satisfactorily, and the drawings are now in Boston

Dr Frederick C Shattuck, 1847-1929, a prominent physician of Boston, with a national reputation, saved all the letters received by him from other physicians throughout the country and from time to time turned them over to the Library. Such letters are valuable for their contents or their signatures, and all such current correspondence unless privileged should be preserved and presented to local institutions

Dr H Winnett Orr, the eminent orthopedic surgeon of Lincoln Nebraska, who invented the Orr method of treating osteomyelitis, is also historically minded. He systematically assembled in fifteen folio scrapbooks a mass of material on his personal and family affairs, on the history of orthopedics and on osteomyelitis, wound treatment and fractures. Volume Six constitutes a history of the first American orthopedic unit to England and France from 1917 to 1919. In 1921 Dr Orr wrote an interesting pamphlet entitled *An Orthopedic Surgeon's Story of the Great War*. The scrapbook of 365 pages contains a mass of documentary and photographic material relating to the unit. In the back there is a long manuscript by Dr Orr on the history of the orthopedic service of Base Hospital No 8, American Expeditionary Forces. Dr Orr, recognizing the outstanding local importance of his scrapbook, very generously presented it to the Boston Medical Library. It is hoped that in the future all documentary material relating to the medical profession in any way will be preserved and deposited with appropriate libraries or institutions

## LO, THE POOR ESKIMO

A BCG-vaccination program among the Eskimos at Point Barrow, Alaska, has been completed, according to the Bureau of Indian Affairs. The initiation of a medical survey on Navajo-Hopi reservations in Arizona and New Mexico, conducted by a team selected by the American Medical Association, under the leadership of Dr Louis J Moorman of

care for themselves. It was a group activity, semi-organized, and largely on a religious basis before the Middle Ages. It was not until the early nineteenth century that the roots of modern training struck into fertile soil at Kaiserswerth, under the guidance of Pastor Fliedner, and it was here that Florence Nightingale found the inspiration that was to be her own lifelong guiding influence. Nursing became a profession when she later organized the school at St. Thomas' Hospital in London.

In America the first professional school for nursing was established in 1872 in Boston, at the New England Hospital for Women and Children. Linda Richards was its first matriculant and in the following year became America's first graduate nurse. In 1873 schools for nurses were established at Bellevue Hospital in New York, where Linda Richards, after her graduation, became night superintendent, at the Massachusetts General Hospital, and at New Haven, Connecticut, where the Connecticut Training School for Nurses came into existence.

The "Boston Training School" as it was first called, which had been established at the Massachusetts General Hospital, welcomed Linda Richards as its own superintendent in 1874. In 1877 she went to England to study nursing methods in the school at St. Thomas', returning in the same year to organize the training school at the Boston City Hospital.

So it is that in 1948, seventy-five years after the first trained nurse was graduated and these three eminent schools of nursing were founded, the Diamond Jubilee of Nursing in America is appropriately celebrated.

There must be other purposes for a jubilee than the recapitulation, however proudly, of seventy-five years of progress by a profession. The American Nurses' Association, with 162,000 of the 320,000 registered nurses in America in its membership, has set itself to the recruitment of the 40,000 additional students needed for approved schools. It is directing attention to the necessity for the extension and improvement of nursing service to all through the improvement of schools of nursing. It is promoting "economic security for all nurses, adequate licensure laws and more effec-

tive counseling and placement of both prospective students and graduate nurses."

Thus the struggle goes on for all groups, seeking higher standards of achievement and better standards of working and living. The problem that still defies solution is the basic economic one of payment and where it is to come from.

---

## MANUSCRIPTS AND MEDICAL HISTORY

MANUSCRIPTS are the source material of medical history. Occurring in the form of diaries, account books, case records, biographical collections and single items, letters, bills, recipes, treatises and miscellaneous documents of all periods, including the present, they should be preserved and deposited in permanent sanctuaries for the benefit of scholars and other interested persons.

The correspondence and other documents of eminent physicians of the twentieth century will be valuable to the people of the succeeding centuries, throwing light upon medicine of today in its economic, social and clinical aspects.

Single letters may be of the greatest importance, such as the letter of Dr. Zadok Howe, written in 1814 to Dr. Nathaniel Miller on the prospectus of the cancer hospital at Franklin, Massachusetts, and the three letters of Dr. Oliver Wendell Holmes written in 1861 and 1863, relating to the injury received by his son, later Justice Holmes, at Keedysville during the Civil War. Recently the Boston Medical Library has acquired a collection of twenty-two letters of Dr. Howe that throw considerable light upon his personality and character.

Physicians from time to time have collected letters of eminent medical men and have eventually deposited their collections in medical and historical libraries. Dr. Ernest B. Young, of Boston, made such a collection and gave it to the Boston Medical Library before his death in 1923. Dr. Lyman Spalding, of Maine, who lived from 1775 to 1821, was an eminent physician of his time and corresponded with the outstanding physicians of the country. He wrote the first edition of the *Pharmacopoeia of the United States of America*, published in Boston in 1820. His letters and scrapbook and the manuscript of the *Pharmacopoeia* descended to his grand-

## BOOK REVIEWS

*The Treatment of Rheumatism in General Practice* By W S C Copeman, O B E, M A, M D (Cantab), F R C P (London) Fourth edition 8°, cloth, 258 pp Baltimore Williams and Wilkins Company, 1946 \$4.00

This small volume, written for the general practitioner has the virtue of brevity and clarity. It presents the accepted British teaching on rheumatism, which differs somewhat from the American point of view. Although treatment is discussed fully there is too much of a recital of remedies without any critical evaluation of these remedies. The book would have been greatly improved by tables or outlines of treatment that the author advocates. Illustrations would also have added to the teaching value of the work.

*Case Histories in Clinical and Abnormal Psychology* Edited by Arthur Burton 8°, cloth, 680 pp New York and London Harper and Brothers, 1947 \$4.00

This book, although primarily intended as a case book to accompany courses in abnormal psychology, might be of interest to others, such as psychiatrists, general practitioners and certain laymen. The work consists of case histories of varying importance indicative of prevailing psychologic methods in the United States.

Besides the value of the case histories themselves, one gets a vivid example of the usefulness of psychologic testing so far as diagnosis, prognosis and treatment are concerned.

The various papers are an excellent example of scientific reporting, and although each has some special merits, the usefulness of the Rorschach test in depicting various tendencies even when overt signs are absent was of particular interest to the reviewer.

To the general reader this book will undoubtedly demonstrate the importance of the clinical psychologist in evaluating emotional problems—a fact long recognized by psychiatrists.

*Hormones and Behavior: A survey of interrelationships between endocrine secretions and patterns of overt response* By Frank A. Beach With a foreword by Earl T. Engle 8°, cloth, 368 pp New York Paul B. Hoeber, Incorporated, 1948 \$6.50

This work is a detailed, encyclopedic account of the problems concerning the interrelation of hormones and overt behavior. The author has gone to considerable lengths to include a great number of experimental data and has compiled a volume that may be considered unique of its kind. He has included most of the important work done on this subject and has presented it in a well systematized manner. Because of the peculiar nature of the studies, the author has limited himself in great part to a recitation of the known facts and has only attempted to draw general conclusions therefrom.

The major interest of this work is for those who are especially concerned with experimental approach to the problem of hormonal influence on behavior; however, it can be classed among books that will always be of value in any library as a reference work for anyone concerned with behavior in general.

## BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

*Interesting and Useful Medical Statistics* Edited by William H. Kupper, M D 8°, cloth, 528 pp Dubuque, Iowa William C. Brown Company, 1948 \$6.50

In this unusual book the compiler has presented numerous statistical tables on morbidity and mortality, on the incidence of symptoms, signs, results of treatment of disease and on miscellaneous subjects of medical interest, such as absen-

teism, atomic bomb victims, contraception, dicumarol, drivers, farm and Fourth of July accidents, life expectation, male climacteric, medical education, Negro physicians, smoking, state hoards, UNRRA personnel and weights of men. The tables have been selected from the literature of the past ten years and comprise two hundred and twenty-five topics arranged alphabetically. Full acknowledgment is given to the original publisher. The volume is recommended as an essential reference tool for all medical and general libraries.

*Epilepsy: Proceedings of the Association held jointly with the International League against Epilepsy, December 13 and 14 1946, New York* 8°, cloth, 654 pp, with 167 illustrations and 56 tables Baltimore Williams and Wilkins Company 1947 \$12.00

This volume comprises the twenty-sixth of the *Research Publications of the Association for Research in Nervous and Mental Disease*. Eighty-two persons have contributed to the volume, comprising forty-five papers. The text is divided into seven parts: historical, heredity and pathology, experimental studies, electroencephalography, medical treatment, war and epilepsy, and psychological-social. A good index concludes the text. The publishing is excellent. The book should be in all medical libraries and in the collections of all physicians interested in the subject.

*Physical Treatment of Injuries of the Brain and Allied Nervous Disorders* By K. M. Hern, M C S P, diplomate of Liverpool Physical Training College, in charge of physiotherapy, Department of Military Hospital for Head Injuries Oxford. With a foreword by Air Vice-Marshal Sir Charles P. Symonds, K B E, C B, D M, F R C P 8°, cloth, 96 pp with 83 illustrations Baltimore Williams and Wilkins Company, 1947 \$4.00

This monograph describes the method of treatment employed in the Military Hospital for Head Injuries, Oxford, England. In this method the patient and physiotherapist co-operate. The monograph is well printed and should prove useful to all persons interested in the subject.

*Noah Webster: Letters on yellow fever addressed to Dr. William Currie* With an introductory essay by Benjamin Spector M D 8°, paper, 110 pp, with one portrait Baltimore Johns Hopkins Press, 1947 \$2.00 Supplements to the *Bulletin of the History of Medicine*

Dr. Spector in this monograph has made a noteworthy contribution to American medical history. Noah Webster, generally thought of as a lexicographer, was an epidemiologist of no mean stature and the author of a two-volume treatise on epidemic and pestilential diseases published at Hartford in 1799. Dr. William Currie was a highly respected physician of Philadelphia. He became interested in yellow fever prevalent in his city in 1797 and wrote a series of letters to Benjamin Wyncoop that were published in a local newspaper. The series of twenty-five letters by Webster were addressed to Dr. Currie and likewise published in a newspaper, the *Commercial Advertiser*, New York, during the months of October to December, 1797. In his introductory essay Dr. Spector discusses Webster's contribution to American medical thought and progress and analyzes his work on infectious diseases. A table of contents summarizes the various letters. The monograph is well published in every way. An index, although difficult to compile, would have been a valuable addition to the text. The volume is recommended for all medical and general history collections.

*Identification of Tumors: Essential gross and microscopic pathologic features systematically arranged for easier identification* By N. Chandler Foot, M D, professor of surgical pathology, Cornell University Medical College and surgical pathologist to New York Hospital 8°, cloth, 397 pp, with 241 illustrations and 26 tables Philadelphia J. B. Lippincott Company, 1948 \$6.00

In this volume Dr. Foot has presented a guide to the identification of tumors, malignant and benign, illustrated with photomicrographs. The text is divided into two parts: neo-

Oklahoma City, is also reported from the same source

Other medical surveys under similar federal and American Medical Association auspices have been completed in Alaska and on Indian reservations of the Northwest, the *Washington Report on the Medical Sciences* announces. Another is planned for Puerto Rico. Since the incidence of tuberculosis among Alaskan natives is recorded as sixteen times as high as the rate for the continental United States, it is comforting to know that the continent's oldest inhabitants currently receive more tangible evidence of their adopted country's esteem than souvenir canes.

## MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

### COMMUNICABLE DISEASES IN MASSACHUSETTS FOR SEPTEMBER, 1948

DISEASE	REFERENCE		SEVEN-YEAR MEDIAN
	SEPTEMBER 1948	SEPTEMBER 1947	
Chancroid	2	2	1*
Chicken pox	135	123	110
Diphtheria	28	10	10
Dog bite	1005	942	924
Dysentery, bacillary	9	13	13
German measles	58	43	49
Gonorrhea	303	393	410
Granuloma inguinale	0	0	0*
Lymphogranuloma venereum	1	0	0*
Malaria	1	7	13
Measles	203	69	150
Meningitis, meningococcal	5	3	8
Meningitis, Pfeiffer bacillus	2	0	0
Meningitis, pneumococcal	1	1	1†
Meningitis, staphylococcal	0	0	0†
Meningitis, streptococcal	1	1	0†
Meningitis, other forms	0	0	0†
Meningitis, undetermined	6	12	3†
Mumps	351	148	194
Pneumonia, lobar	276	31	66
Polio myelitis	55	147	121
Salmonellosis	2	26	20
Scarlet fever	107	130	241
Syphilis	141	206	361
Tuberculosis, pulmonary	203	217	217
Tuberculosis, other forms	15	16	16
Typhoid fever	1	1	3
Undulant fever	4	10	2
Whooping cough	268	644	546

\*Four-year median.  
†Six year median.

#### COMMENT

Diseases with an incidence above the seven-year median were chicken pox, diphtheria, German measles, measles, mumps, lobar pneumonia and undulant fever.

Diseases with an incidence below the seven-year median were bacillary dysentery, meningitis, poliomyelitis, scarlet fever and whooping cough.

Mumps was again at the highest level since it was made reportable in 1916. Poliomyelitis was at the lowest since 1942.

There is still too much diphtheria. The majority of the cases were in unimmunized persons. Some were in persons who had failed to have booster doses.

#### GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Actinomycosis was reported from Everett, 1, total, 1.  
Diphtheria was reported from Arlington, 4, Athol, 1, Boston, 19, Brookline, 1, Cambridge, 1, Lawrence, 1, Montague, 1, total, 28.

Dysentery, bacillary, was reported from Boston, 1, Fitchburg, 1, Holyoke, 1, Lowell, 3, Worcester, 2, Wrentham, 1, total, 9.

Encephalitis, infectious, was reported from Worcester, 1, total, 2.

Lymphocytic choriomeningitis was reported from Cambridge, 1, Danvers, 1, Fitchburg, 7, total, 9.

Malaria was reported from Swansea, 1, total, 1.

Meningitis meningococcal, was reported from Boston, 1, Brookline, 1, Cambridge, 1, Lynn, 1, Quincy, 1, total, 5.

Meningitis, Pfeiffer bacillus, was reported from Holyoke, 1, South Hadley, 1, total, 2.

Meningitis, pneumococcal, was reported from Boston, 1, total, 1.

Meningitis, streptococcal, was reported from Groton, 1, total, 1.

Meningitis, undetermined, was reported from Ashburnham, 1, Brockton, 1, Cambridge, 1, Chicopee, 1, Plainville, 1, Stoughton, 1, total, 6.

Poliomyelitis was reported from Agawam, 1, Arlington, 1, Barnstable, 1, Belmont, 1, Boston, 6, Cambridge, 2, Carver, 1, Chicopee, 1, Dartmouth, 1, Everett, 2, Framingham, 1, Hinsdale, 1, Leominster, 1, Lexington, 1, Mansfield, 1, Marblehead, 1, Marlboro, 1, Millbury, 1, New Bedford, 1, Newton, 2, Northampton, 1, Pittsfield, 1, Princeton, 1, Rockport, 1, Salem, 1, Salisbury, 1, Springfield, 9, Walpole, 1, Watertown, 2, West Boylston, 2, West Springfield, 7, Woburn, 1, Worcester, 4, total, 55.

Salmonellosis was reported from Beverly, 1, Worcester, 1, total, 2.

Septic sore throat was reported from Boston, 2, Chelsea, 1, Newton, 1, total, 4.

Trichinosis was reported from Methuen, 1, Swansea, 1, Watertown, 1, total, 3.

Typhoid fever was reported from Fall River, 1, total, 1.

Undulant fever was reported from Bridgewater, 1, Marblehead, 1, Rehoboth, 1, Templeton, 1, total, 4.

## MISCELLANY

### TRAINED FISH

Scientists at the University of Wisconsin, according to a recent news release, are training fish to smell. Such a course would be considered unnecessary on the Atlantic seaboard—classified with carrying coals to Newcastle.

Actually, the bluntnose minnow, in contradiction to its descriptive name, has been found to have an unusually keen sense of smell. It can detect phenols in water in low concentrations and, with the use of electric shocks to condition its reflex, has been taught to react in an agitated manner when the offending substance is encountered.

### MEDICAL DIRECTOR OF NEW ENGLAND TELEPHONE AND TELEGRAPH COMPANY

Dr. George F. Wilkins, of Brookline, a native of Kinderhook, New York, and a graduate of Holy Cross College and Harvard Medical School, has been appointed medical director of the New England Telephone and Telegraph Company.

### OLD MAN OF THE SEA

If the Federal Security Administration figures on births and longevity are reasonably reliable, 21,500,000 of the nation's population will be sixty-five years of age or over by a century's end, *Insurance Economics Surveys* reports. With a steadily decreasing number of employable citizens the social security burden of the future can be left to the imagination.

### NATIONAL MENTAL HEALTH ACT

In the year since funds were made available under the National Mental Health Act of 1946, Government supported programs have been activated in forty-two states and four territories, according to a report from *Scientific American*. The six remaining states are in process of setting up their programs.

## NOTICES (Concluded from page 728)

- OCTOBER 1-MAY 20 Metropolitan State Hospital Page 418 issue of September 9
- NOVEMBER 4-6 American Society of Anesthesiologists Page 418 issue of September 9
- NOVEMBER 6 and 7 American Cancer Society Incorporated Page 644 issue of October 21
- NOVEMBER 8 Massachusetts Public Health Association Page 692 issue of October 28
- NOVEMBER 8 New England Heart Association Page 692 issue of October 28
- NOVEMBER 8-12 American Public Health Association Page 420 issue of March 18
- NOVEMBER 9 Harvard Medical Society Page 728
- NOVEMBER 9-12 Interstate Postgraduate Medical Association of North America Page 644 issue of October 21
- NOVEMBER 10 New England Conference of Industrial Physicians and Surgeons Page 728
- NOVEMBER 10-15 Association of Military Surgeons of the United States Page 722 issue of May 13
- NOVEMBER 12 The Use of Hormones in Breast Cancer Dr. Ira T. Nathanson Penetruck Association of Physicians 8:30 p.m. Haverhill
- NOVEMBER 17 Middlesex East District Medical Society Page 644 issue of October 21
- NOVEMBER 20-25 American Academy of Pediatrics Annual Meeting Chalfonte-Haddon Hall Hotel Atlantic City New Jersey
- NOVEMBER 30 Hampden District Medical Society Page 492 issue of September 23
- DECEMBER 2 Suffolk Centors Meeting Page 492 issue of September 23
- DECEMBER 4 American Federation for Clinical Research Page 644 issue of October 21
- DECEMBER 4-9 American Academy of Dermatology and Syphilology Page 728
- DECEMBER 7-9 Southern Surgical Association Annual Meeting Page 543 issue of April 8
- DECEMBER 9 and 10 New York State Society of Anesthesiologists Page 34 issue of July 1
- FEBRUARY 4 1949 American Board of Obstetrics and Gynecology Inc. Page 244 issue of August 5
- MARCH 7-9 1949 American Academy of General Practice Page 728
- MARCH 28-APRIL 1 1949 American College of Physicians Page 156 issue of July 22
- MAY 16-19 1949 American Urological Association Baltimore Hotel Los Angeles California
- MAY 26-28 1949 American Gynecological Association Hotel Loraine Madison Wisconsin
- NOVEMBER 11 17 1949 Third Inter-American Congress of Radiology Page 155 issue of July 22

## DISTRICT MEDICAL SOCIETIES

## RAMPDEN

NOVEMBER 30 8:30 p.m. Academy of Medicine Springfield Carooms of the Breast Dr. Grandley W. Taylor

## MIDDLESEX EAST

NOVEMBER 17  
JANUARY 19  
MARCH 23  
MAY 11

## SUFFOLK

DECEMBER 2 Suffolk Centors Meeting

## WORCESTER NORTH

NOVEMBER 10 Henry Heywood Memorial Hospital Gardner  
DECEMBER 15 Leominster Hospital Leominster  
FEBRUARY 25 Burbank Hospital Fitchburg  
APRIL 27 Annual Meeting

## Announcing . . .

A NEW EFFICIENT  
24-HOUR TELEPHONE  
ANSWERING SERVICE

If your telephone is unattended during the day or night — the PHYSICIANS SERVICE EXCHANGE will answer all calls and relay any message desired. Our office is equipped with Soundscribers and Gray Electronic Transcribers. This enables physicians to dictate from their office or home telephone and have the transcriptions dictated promptly.

**PHYSICIANS SERVICE EXCHANGE**  
264 BEACON ST. Copley 7-4040 BOSTON

THE GEORGE WASHINGTON UNIVERSITY  
SCHOOL OF MEDICINE

## Announces

FOURTH ANNUAL SERIES OF INTENSIVE  
POSTGRADUATE COURSES

1	Ocular Pathology	Motility and Orthoptics	January 10-14 1949
2	Psychosurgery		January 24-28 1949
3	Psychiatry	January 31-February 11 1949	
4	Therapeutics	January 31-February 4 1949	
5	Gastrointestinal Problems in Pediatrics	February 7-11 1949	
6	Obstetrics	February 14-18 1949	
7	Gynecology	February 21-25 1949	
8	Anesthesiology	February 28-March 4 1949	
9	Surgical Physiology	March 7-11 1949	
10	Abdominal Surgery	March 14-25 1949	
11	Bone and Joint Surgery	March 28-April 1 1949	
12	Neoplastic Diseases	April 4-8 1949	
13	Metabolic Diseases	April 11-15 1949	
14	Thoracic Diseases	April 18-22 1949	
15	Cardiovascular Diseases	April 25-May 6 1949	
16	Gastroenterology	May 9-13 1949	

By appropriate combinations of the above the following longer courses can be arranged:  
For the Psychiatrist (Courses No. 2, 3) January 24-February 11 1949  
For the General Physician (Courses No. 4, 5, 6) January 31-February 18 1949

For the Obstetrician (Courses No. 6, 7) February 14-25 1949  
For the Surgeon (Courses No. 7, 8, 9, 10, 11, 12) February 21-April 8 1949

For the Internist (Courses No. 13, 14, 15, 16) April 11-May 13 1949  
Other combinations can also be arranged.

A Distinguished Guest Faculty Will Supplement the Local Staff  
Registration in each course is limited.

Hotel accommodations are available.  
Veterans can use their benefits under the G. I. Bill.

For further details write

DIRECTOR OF POSTGRADUATE INSTRUCTION  
The George Washington University School of Medicine  
1335 H Street N.W., Washington 5 D.C.

## CHARLES B. TOWNS HOSPITAL

Established 1901

FOR ALCOHOLISM, NARCOTIC  
AND BARBITURATE ADDICTIONS

Exclusively

THE TOWNS TREATMENT is a medical and psychiatric procedure.

Withdrawal of narcotics, either opiates or synthetics, is by gradual reduction and specific medication.

After 47 years, this treatment is generally accepted as standard.

Physicians and psychiatrists in residence. Trained nursing, physio- and hydrotherapy staff.

Patients are assured of complete privacy if desired.

Length and cost of treatment are pre-determined.

Advantageously situated facing Central Park. Solarium and recreation roof. Excellent cuisine and service.

Literature on Request

W. D. SILK WORTH  
Medical Sup't

EDWARD B. TOWNS  
Director

293 CENTRAL PARK WEST NEW YORK 24 N.Y. Schuyler 4-0770

Member American Hospital Association  
Our ad also in J. A. M. A. and other leading medical journals

plasms of general distribution, and neoplasms of special systems and organs, including a chapter on the ear and eye. The text is concluded with two special chapters on the technical methods of value in the diagnosis of tumors and a tabular locator for tentative identification of neoplasms. A good index concludes the volume. The illustrations are excellent, clear and well defined. The type is large and clear, and the printing well done. The book should prove valuable to students, surgeons and physicians.

*Handbook of Treatment and Medical Formulary.* By Charles M. Gruber, M.D., professor of pharmacology, Jefferson Medical College, Philadelphia 8<sup>th</sup>, cloth, 585 pp. Philadelphia: F. A. Davis Company, 1948. \$7.00.

Dr. Gruber has written this manual for the general practitioner and under each disease gives condensed methods of treatment and dosages in metric and apothecaries' measures, of the recommended remedies. The material is arranged alphabetically. A valuable appendix of sixty pages lists important drugs, galenic preparations and chemicals with average doses. There is a good index. The manual should prove valuable to the practicing physician as a quick reference source.

*Synopsis of Pediatrics.* By John Zahorsky, M.D., professor of pediatrics and director, Department of Pediatrics, St. Louis University of Medicine, and pediatrician-in-chief to the St. Mary's Group Hospitals. Assisted by T. S. Zahorsky, M.D., senior instructor in pediatrics, St. Louis University School of Medicine, and assistant pediatrician to the St. Mary's Group of Hospitals. Fifth edition. 12<sup>th</sup>, cloth, 449 pp., with 158 text illustrations and 9 color plates. St. Louis: C. V. Mosby Company, 1948. \$5.50.

This edition of a standard manual, intended primarily for students, first published in 1934, has been thoroughly revised and enlarged to some extent. Material on the newer drugs has been incorporated in the text. A good index concludes the volume. The manual should prove useful to students and general practitioners. The publishing is excellent, although the type is of a small size necessitated by the size of the volume and the amount of text.

## NOTICES

### HARVARD MEDICAL SOCIETY

A meeting of the Harvard Medical Society will be held in the amphitheater of Building D, Harvard Medical School on Tuesday, November 9, at 8 p.m. The Department of Biological Chemistry, Harvard Medical School, will present the following program:

The Production of Radioactive Cystine by Direct Bombardment in the Pile. Eric G. Ball, Arthur K. Solomon and Octavia Cooper.

Ascorbic Acid and the Biologic Action of Adrenal Cortical Hormones. Ralph W. McKee, Theodore S. Cobbe, Jr., and Quentin M. Geiman.

Metabolism of  $C^{14}$ -Labeled Glucose by the Rat Diaphragm in Vitro. Claude A. Villee.

Isotopic Studies of the Origins of Glycogen Carbons. A. Baird Hastings and Yale J. Topper.

Localization of Cerebral Tumors Employing  $P^{32}$ . Bertram Selzerstone, Arthur K. Solomon and William H. Sweet.

Subsequent meetings will be held on December 14, January 11, February 8, March 8, April 12 and May 10.

### NEW ENGLAND CONFERENCE OF INDUSTRIAL PHYSICIANS AND SURGEONS

The yearly dinner meeting, with election of officers, of the New England Conference of Industrial Physicians and Surgeons will be held at the University Club, Boston, on November 10, at 6:00 p.m. Colonel W. C. Knott, M.C., U.S.A., will speak after the dinner on the subject "What the United States Army is doing in Industrial Medical Work."

### AMERICAN ACADEMY OF GENERAL PRACTICE

The first annual scientific assembly of the American Academy of General Practice will be held at the Netherlands Plaza Hotel, Cincinnati, Ohio, March 7 to 9. The program will include essays by eighteen outstanding medical teachers, a dinner for secretaries and presidents of constituent state chapters and a banquet for members and their wives and guests.

Nonmembers of the Academy may attend the assembly as guests on payment of a registration fee of \$5.00 (only doctors of medicine may register). There is no registration fee for members. Banquet tickets will be sold at \$5.00 a plate.

Members wishing to make hotel reservations may apply to the chairman, Sub-Committee on Hotels, American Academy of General Practice, Dixie Terminal Building, Cincinnati 2, Ohio.

### AMERICAN ACADEMY OF DERMATOLOGY AND SYPHILOLOGY

The seventh annual meeting of the American Academy of Dermatology and Syphilology will be held in Chicago December 4 through 9.

The principal sessions will be held at the Palmer House, with special courses in histopathology and mycology scheduled for Saturday and Sunday, December 4 and 5, at the Medical Schools of the University of Illinois and Northwestern University. As in the past two years, teaching clinics will be held on the afternoons of Monday, Tuesday and Wednesday, December 6, 7 and 8. A new feature this year consists of informal discussion groups, which will be held at noon and 5:00 p.m.

Extensive scientific and technical exhibits will be set up. Dr. Samuel M. Bluefarb is chairman of the committee on scientific exhibits, and Dr. Clyde L. Cummer is in charge of the technical exhibits.

Special courses in histopathology, mycology, x-ray and radium therapy, mucous-membrane lesions, bacteriology of the skin, industrial dermatoses, specific granulomas and dermatoscleroses will be held under leaders in these various fields.

Special lectures will be given on "Certain Aspects of Blood Dyscrasias of Special Interest to Dermatologists," by Dr. Cyrus C. Sturgis, chairman, Department of Internal Medicine, Medical School, University of Michigan; "The Relation of Endocrines to Cutaneous Diseases," by Dr. Arthur A. Hellbaum, professor of pharmacology, School of Medicine, University of Oklahoma; and Dr. E. C. Keaty, research associate of pharmacology and dermatology, School of Medicine, University of Oklahoma.

### SOCIETY MEETINGS AND CONFERENCES

#### CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, NOVEMBER 11

##### FRIDAY, NOVEMBER 12

\*9-00 a.m.-12:00 m. Combined Medical and Surgical Staff Rounds. Peter Bent Brigham Hospital.

\*12-00 m. Clinicopathological Conference. Margaret Jewett Hall. Mt. Auburn Hospital. Cambridge.

12-00 m.-1:00 p.m. Clinicopathological Conference (Boston Floating Hospital). Joseph H. Pratt Diagnostic Hospital.

##### MONDAY, NOVEMBER 15

\*12:15-1:15 p.m. Clinicopathological Conference. Main Amphitheater. Peter Bent Brigham Hospital.

##### TUESDAY, NOVEMBER 16

\*12:15-1:15 p.m. Clinicoradiological Conference. Peter Bent Brigham Hospital.

\*1:30-2:30 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children. Massachusetts General Hospital.

##### WEDNESDAY, NOVEMBER 17

\*11:00 a.m.-12:00 m. Medical Rounds. Amphitheater. Children's Hospital.

\*12:00 m.-1:00 p.m. Clinicopathological Conference (Children's Hospital). Amphitheater. Peter Bent Brigham Hospital.

\*2:00-3:00 p.m. Combined Clinic by the Medical Surgical and Orthopedic Services. Amphitheater. Children's Hospital.

\*Open to the medical profession.

(Notices concluded on page 77)

# The New England Journal of Medicine

Copyright 1948 by the Massachusetts Medical Society

Volume 239

NOVEMBER 11, 1948

Number 20

## THE RELATION OF VASCULAR DISEASE TO THE HYPERTENSIVE STATE\*

### II The Adequacy of the Renal Biopsy as Determined from a Study of 500 Patients

BENJAMIN CASTLEMAN, M.D.,† AND REGINALD H. SMITHWICK, M.D.‡

BOSTON

IN APRIL, 1943, the anatomic findings observed in renal biopsies removed from 100 hypertensive patients subjected to bilateral dorsolumbar sympathectomy were reported.<sup>1</sup> The biopsies were graded according to the severity of the vascular disease without knowledge of any clinical data about the patient, and it was found that there were enough differences in the degree of vascular disease to classify the group into five grades of advancing severity (Grades 0, 1, 2, 3 and 4). In this first series 7 per cent of cases were Grade 0, 21 per cent Grade 1, and 25 per cent Grade 2—that is, 28 per cent and possibly 53 per cent of the cases showed renal vascular systems so slightly damaged that it seemed unlikely that the blood flow could have been embarrassed sufficiently to be the one factor responsible for the hypertension. We therefore concluded “that in many of these cases and probably others the hypertensive state antedated the renal vascular lesions, which once established, probably aggravated the hypertension.”

Since the publication of this paper, those who believe that renal vascular disease antedates the hypertensive state have objected that a small biopsy is not an adequate sample of the entire kidney and that no definite conclusions should be drawn from these biopsies.<sup>2</sup> We admit that in some cases the biopsy may not have been truly representative of the entire kidney, although an attempt was made to select a region that seemed on gross inspection an accurate sample. It is true that the biopsies are small, averaging 6 by 5 by 4 mm, but each microscopical section contains about fifty cross-sections of arterioles and small arteries. Furthermore, although vascular disease may be segmental in the large vessels and although not every arteriole is necessarily involved in kidneys removed

at autopsy from hypertensive patients, arteriolar disease, when present in a kidney, is by and large a generalized process. It is perhaps possible in a small series of cases to strike a biopsy that is not an adequate sample, but it does not seem likely that this could have occurred in a series of 500 patients, which forms the basis for this report.

Table 1 shows the distribution of the grades of renal vascular disease in these 500 patients. The percentage of cases of Grade 0 and Grade 1 was a

TABLE 1 *Distribution of Renal-Biopsy Grades*

GRADE	NO OF CASES	PERCENTAGE
0	21	4.2
1	96	19.2
2	111	22.2
3	218	43.6
4	54	10.8
Total	500	

little smaller than that in the first series of 100 patients—23.4 as compared with 28.0 per cent, and 45.6 per cent if one includes the Grade 2 cases, which really have very little arteriolar disease. Thus, 45 per cent of this series of 500 patients had so little anatomic change in their vascular systems that the blood flow through the kidneys could not conceivably have been reduced sufficiently to represent the sole factor in the production of the hypertension.

Added confirmatory evidence for the accuracy of our grading and for the adequacy of the biopsy is the fact that in 100 cases a biopsy was taken from each kidney and that in the large majority the grade of vascular disease was the same on both sides. In only 5 cases was there a difference of two grades, in 20, there was a difference of one grade, and in the rest (75 per cent), the grades were the same. These findings are in keeping with the known bilateral character of the renal changes when they occur, and also with split-clearance studies as carried out by Chasis and Redish.<sup>3</sup> These authors have

\*From the Departments of Pathology and Surgery, Massachusetts General Hospital.

†Presented in part at the Medical College of Virginia, Richmond, April 6, 1945.

The tables and charts were exhibited at the centennial meeting of the American Medical Association, June 1947.

‡Associate in pathology, Harvard Medical School, pathologist, Massachusetts General Hospital.

§Professor of surgery, Boston University School of Medicine, surgeon-in-chief, Massachusetts Memorial Hospitals.

## Old Way...

### CURING RICKETS in the CLEFT of an ASH TREE

FOR many centuries,—and apparently down to the present time, even in this country—ricketic children have been passed through a cleft ash tree to cure them of their rickets, and thenceforth a sympathetic relationship was supposed to exist between them and the tree.

Frazer\* states that the ordinary mode of effecting the cure is to split a young ash sapling longitudinally for a few feet and pass the child, naked, either three times or three times three through the fissure at sunrise. In the West of England, it is said the passage must be "against the sun." As soon as the ceremony is performed, the tree is bound tightly up and the fissure plastered over with mud or clay. The belief is that just as the cleft in the tree will be healed, so the child's body will be healed, but that if the rift in the tree remains open, the deformity in the child will remain, too, and if the tree were to die, the death of the child would surely follow.

\*Frazer J. G.: The Golden Bough, vol. 1, New York, Macmillan & Co., 1923



It is ironical that the practice of attempting to cure rickets by holding the child in the cleft of an ash tree was associated with the rising of the sun, the light of which we now know is in itself one of Nature's specifics.

## New Way...

### Preventing and Curing Rickets with OLEUM PERCOMORPHUM

NOWADAYS, the physician has at his command, Mead's Oleum Percomorphum, a Council-Accepted vitamin D product which actually prevents and cures rickets, when given in proper dosage.

Like other specifics for other diseases, larger dosage may be required for extreme cases. It is safe to say that when used in the indicated dosage, Mead's Oleum Percomorphum is a specific in almost all cases of rickets, regardless of

degree and duration. Mead's Oleum Percomorphum because of its high vitamins A and D content is also useful in deficiency conditions such as tetany, osteomalacia and xerophthalmia.

\* \* \*

#### COUNCIL-ACCEPTED

Oleum Percomorphum With Other Fish Liver Oils and Viosterol Contains 60,000 vitamin A units and 8,500 vitamin D units per gram and is supplied in 10 c.c. and 50 c.c. bottles; and in bottles containing 50 and 250 capsules.

MEAD JOHNSON & COMPANY, Evansville, Indiana, U S A.

Please enclose professional card when requesting samples of Mead Johnson products to co-operate in preventing their reaching unauthorized persons.

WELLESLE

group, those with Grade 2 and 3 eye-ground changes, all grades of renal vascular change were present

Is there any correlation between the age of the patient and the degree of renal vascular change? Table 4 shows the age distribution of the 500 patients. The great bulk, almost 75 per cent, of them were between thirty and fifty. There were, however, 61 patients under thirty (Table 5) and it is interesting to note that 38 per cent had Grade 0 or 1 biopsies and if the changes in Grade 2 are included, 62.5 per cent of the younger patients had minimal vascular disease. These figures are even more significant when they are compared with the cor-

adequate samples of their respective kidneys. The highlights of this evidence are as follows: First, approximately the same percentage of cases for each biopsy grade was present in a series of 500 cases as in the first series of 100 cases. Secondly, in 100 patients from whom biopsies were taken from both right and

TABLE 4 Age Distribution

AGE	NO OF PATIENTS
10-19	8
20-29	5
30-39	141
40-49	224
50-59	72
60-61	2
Total	500

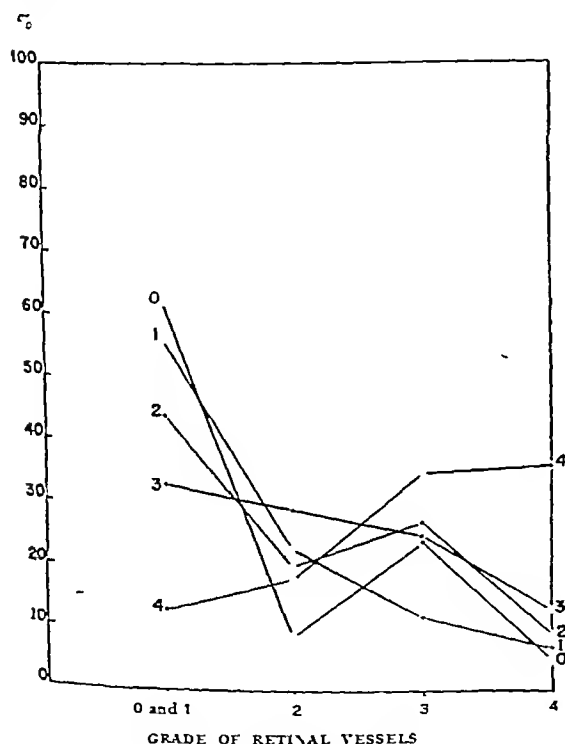


FIGURE 2. Correlation of Renal-Biopsy Grades with Retinal-Vessel Changes

responding percentage among all age groups—namely 23.4 and 45.6 per cent (Table 1). It is very difficult, if not impossible, to know when a patient develops hypertension. Many have had their disease for years before it is discovered. Thus a patient of forty-five may well have had hypertension for ten years or more before it was first discovered, but a patient in the twenties, by the mere limitation of his age, has probably had it for a relatively short period. Assuming that hypertension is primary and renal arteriosclerosis secondary, a much milder degree of vascular change is expected in the younger group, and this is what was found.

#### SUMMARY AND CONCLUSIONS

We believe that the material presented affords fairly conclusive evidence that the biopsies are

left kidneys the grade of vascular disease was the same in 75 per cent of cases, and in only 5 per cent was there a difference of two grades (thus, in 95 per cent, the degree of vascular disease for all practical purposes was identical on both sides). Thirdly, in this group of 100 double biopsies 40 patients had minimal or no arteriolar disease on each side. Fourthly, there was good correlation between the biopsy grades and renal function as measured by the phenolsulfonephthalein test in the entire series of 500 patients and in 20 patients when compared with renal plasma-flow values (previous study). Fifthly, there was fairly good correlation between the biopsy grades and the retinal-vessel changes when applied to the lowest and highest grades

TABLE 5 Distribution of Renal-Biopsy Grades among Patients Under Twenty-Nine Years of Age

GRADE	NO OF CASES	PERCENTAGE
0	5	8
1	18	30.0
2	18	29.5
3	15	24.5
4	5	8.0
Total	61	

Finally, of the 61 patients under thirty years of age 62.5 per cent had minimal or no renal vascular disease.

For these reasons we believe that the biopsy material provides an adequate basis for conclusions regarding the degree of arteriolar disease in hypertensive patients. To repeat, 23.4 per cent of the biopsies were placed in Grade 0 or 1 and 22.5 per cent in Grade 2. Thus, 45.6 per cent of a series of 500 cases had minimal or no vascular narrowing. Since no one had objected to the accuracy of the observations in the biopsies it must be concluded as in

shown that the decrease in the rate of glomerular filtration and effective renal blood flow in hypertensive patients is shared equally by the kidneys. "These results indicate that the destruction of renal parenchyma progresses equally in the two kidneys in hypertensive disease." Forty of the 100 patients with double biopsies had minimal or no vascular disease on each side. This large percentage of Grade 0 and 1 vascular disease is probably due to the fact that as the years have gone by we have gradually come to see hypertension in its earlier stages and in younger patients. It seems to us that this finding of minimal vascular change in 40 per cent of this series is quite significant because the chances of missing real vascular disease twice are very unlikely.

Although it is fairly well established that the majority of hypertensive patients do not have renal impairment as measured by the phenolsulfonephthalein test, the finding that those with the more severe vascular disease in their renal biopsies had a decreased renal function and those with minimal vascular disease good renal function would

TABLE 2 Correlation of Renal Biopsies with Renal Function

GRADE	NO OF CASES	RENAL FUNCTION		
		NORMAL	MODERATE REDUCTION	SHARP REDUCTION
0	21	84.6% {	20	0
1	96		1	1
2	111		16	4
3	218		31	28
4	54		25	28
Totals	500	316 (63.2%)	120 (24.0%)	64 (12.8%)

provide additional support for the adequacy and accuracy of these biopsies. Renal function was measured by the phenolsulfonephthalein test in this series (Table 2). Sixty-four patients, or 12.8 per cent, had poor renal function, and when these cases are divided into their respective renal-biopsy grades it is quite obvious that most of them represented definite vascular disease. Ninety-two per cent had either Grade 3 or Grade 4 biopsies. At the other end of the scale, those with Grade 0 or Grade 1 renal biopsies, there were 117 patients, 84 per cent of whom had excellent renal function. When this correlation is charted (Fig 1), the distribution of normal renal function among the renal biopsies in the first 100 cases was confirmed in the larger series of 500 cases.

Often, the severity of a patient's hypertension is based on the appearance of the eye-ground changes. We therefore believed that it would be interesting to compare the vascular changes in the retina with those in the renal biopsies. Table 3 shows that there is some correlation, especially in the very low and very high grades. For example,

in 48 of the 66 (about 70 per cent) of the patients with Grade 4 retinal changes — changes that most clinicians consider diagnostic of malignant hypertension — renal biopsy revealed Grade 3 or 4 vascular disease. Likewise, about two thirds of the patients with Grade 4 renal biopsies had Grade 3

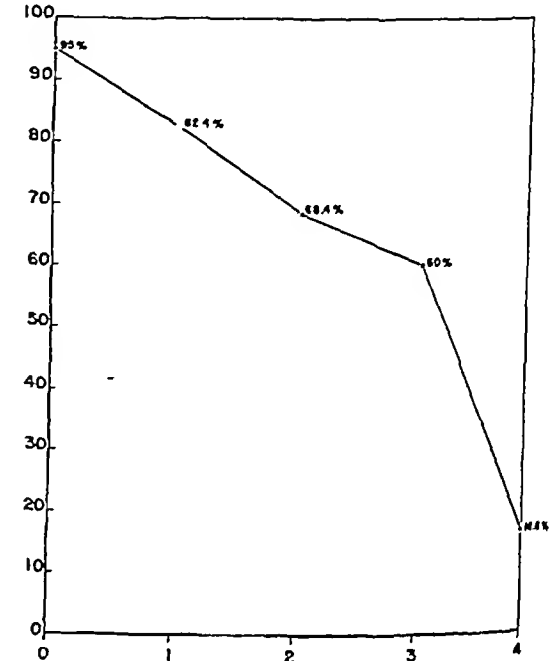


FIGURE 1 Distribution of Normal Renal Function among the Renal Biopsies

or 4 retinal change (37 out of 54). In the cases with Grade 0 or 1 renal biopsies, 78 per cent (91 out of 117) showed Grade 0, 1 or 2 retinal change. Although there were exceptions in all groups, in the Grade 2 and 3 renal biopsies all grades of retinal changes were rather well represented. This may

TABLE 3 Correlation of Renal Biopsies with Retinal Vessel Changes

GRADE	NO OF CASES	RETINAL VESSEL CHANGE				
		GRADE 0	GRADE 1	GRADE 2	GRADE 3	GRADE 4
0	21	2	11	2	5	1
1	96	11	43	22	13	7
2	111	13	36	22	30	10
3	218	10	62	65	54	29
4	54	0	7	10	18	19
Totals	500	36	159	119	120	66

be better visualized in Figure 2, in which the percentages of each of the retinal-vessel grades are calculated for each biopsy made. It is apparent that there is a definite correlation of the cases with Grade 0 and 1 eye grounds and those with Grade 4 eye grounds with the renal biopsies. In the middle

group, those with Grade 2 and 3 eye-ground changes, all grades of renal vascular change were present

Is there any correlation between the age of the patient and the degree of renal vascular change? Table 4 shows the age distribution of the 500 patients. The great bulk, almost 75 per cent, of them were between thirty and fifty. There were, however, 61 patients under thirty (Table 5), and it is interesting to note that 38 per cent had Grade 0 or 1 biopsies and if the changes in Grade 2 are included, 62.5 per cent of the younger patients had minimal vascular disease. These figures are even more significant when they are compared with the cor-

adequate samples of their respective kidneys. The highlights of this evidence are as follows: First, approximately the same percentage of cases for each biopsy grade was present in a series of 500 cases as in the first series of 100 cases. Secondly, in 100 patients from whom biopsies were taken from both right and

TABLE 4 Age Distribution

Age	No of Patients
10-19	8
20-29	53
30-39	141
40-49	224
50-59	72
60-61	2
Total	500

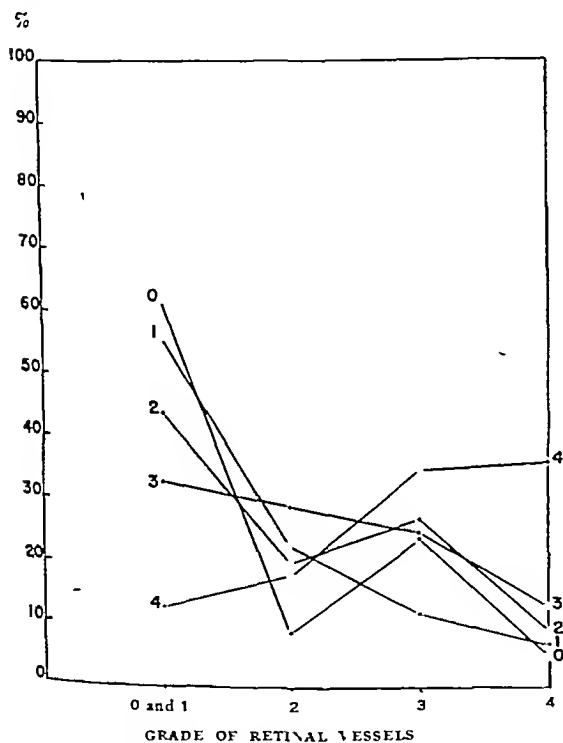


FIGURE 2 Correlation of Renal Biopsy Grades with Retinal Vessel Changes

responding percentage among all age groups — namely 23.4 and 45.6 per cent (Table 1). It is very difficult, if not impossible, to know when a patient develops hypertension. Many have had their disease for years before it is discovered. Thus a patient of forty-five may well have had hypertension for ten years or more before it was first discovered, but a patient in the twenties, by the mere limitation of his age, has probably had it for a relatively short period. Assuming that hypertension is primary and renal arteriosclerosis secondary, a much milder degree of vascular change is expected in the younger group, and this is what was found.

SUMMARY AND CONCLUSIONS

We believe that the material presented affords fairly conclusive evidence that the biopsies are

left kidneys the grade of vascular disease was the same in 75 per cent of cases, and in only 5 per cent was there a difference of two grades (thus, in 95 per cent, the degree of vascular disease for all practical purposes was identical on both sides). Thirdly, in this group of 100 double biopsies, 40 patients had minimal or no arteriolar disease on each side. Fourthly, there was good correlation between the biopsy grades and renal function as measured by the phenolsulfonephthalein test in the entire series of 500 patients and in 20 patients when compared with renal plasma-flow values (previous study). Fifthly, there was fairly good correlation between the biopsy grades and the retinal-vessel changes when applied to the lowest and highest grades.

TABLE 5 Distribution of Renal Biopsy Grades among Patients Ten to Twenty-Nine Years of Age

Grade	No of Cases	Percentage
0	5	8
1	18	30.0
2	15	24.5
3	15	24.5
4	8	13.0
Total	61	

Finally, of the 61 patients under thirty years of age 62.5 per cent had minimal or no renal vascular disease.

For these reasons we believe that the biopsy material provides an adequate basis for conclusions regarding the degree of arteriolar disease in hypertensive patients. To repeat, 23.4 per cent of the biopsies were placed in Grade 0 or 1, and 22.5 per cent in Grade 2. Thus, 45.6 per cent of a series of 500 cases had minimal or no vascular narrowing. Since no one had objected to the accuracy of the observations in the biopsies it must be concluded as in

our previous report, that hypertension frequently exists in man without evidence of renal vascular disease or with insufficient evidence to explain the elevated blood pressure. Therefore, some other functional factor or factors that are primarily responsible for the hypertensive state and precede the appearance of renal vascular disease must exist in many cases.

## REFERENCES

- 1 Castleman B and Smithwick R. H. Relation of vascular disease to hypertensive state based on study of renal biopsies from 100 hypertensive patients. *J A M A* 121 1256-1261 1943
- 2 Goldblatt H. Renal origin of hypertension. *Physiol Rev* 27 120-165, 1947
- 3 Chasis, H., and Redish J. Function of separate kidneys in hypertensive subjects. *Arch Int Med* 70 738-748 1942
- 4 Talbott, J. H. Castleman, B. Smithwick, R. H. and Melville R. S. Renal biopsy studies correlated with renal clearance observations in hypertensive patients treated by radical sympathectomy. *J Clin Investigation* 22 387-394 1943

## DOUBLE UTERUS WITH HORN MENSTRUATING INTO THE ABDOMEN

JOHN B. VERNAGLIA, M.D.\*

MEDFORD, MASSACHUSETTS

A review of the literature has disclosed no case similar to the one reported below, which is that of a completely separated double uterus, both halves well developed, in which one uterus did not communicate with the vagina and menstruated into the abdomen. The situation was recognized at operation at the time of the patient's third menstrual period, and a hemi-hysterectomy was done. Later, the patient became pregnant and was delivered of a living child by cesarean section.

Congenital anomalies of the uterus are interesting but potentially serious conditions that warrant the careful consideration of every surgeon, gynecologist and obstetrician. They can cause dysmenorrhea, sterility, inflamed appendages, miscarriage, abnormal presentations, difficult or impossible delivery, uterine rupture, puerperal sepsis, placenta previa, retained placenta, post-partum hemorrhage and subinvolution. When there is atresia in the vagina or cervix, one may find, in addition to dysmenorrhea, hematocolpos, hematometra and hematosalpinx.

Embryologically the uterus and vagina are formed by the fusion of the two müllerian ducts in their distal or caudal two thirds. The cephalic third of each duct remains unfused and forms the fallopian tube on each side. These ducts appear during the sixth week of embryonic life, close to the more developed wolffian ducts. Their caudal segments move medially and become fused from below upward during the twelfth to the fourteenth week and form one tube, the uterus, cervix and vagina. Lack of complete fusion and disappearance of the intervening septum, at any point from below upward or throughout the length of the two ducts, explains most of the anomalies observed, the rudimentary development of one duct or of the cervical canal of one side accounts for the remainder. Nonfusion occurs normally in lower mammals, so that Blair-Bell suggests the use of the term "atavism" in preference to "malformation,"

because an anomalous uterus conforms exactly with that of one of the lower orders. Marsupials or didelphys, like the kangaroo and the opossum, have double uteri and lateral vaginas with a central vaginal pouch. The rodents (rabbits, squirrels, rats, guinea pigs, porcupines and gophers) have double uteri with separate cervixes and vaginas in the lower forms, and double uteri with a single cervix and a single vagina in the higher forms. The carnivora (cats, dogs, bears, weasels, raccoons and seals) have uterine bodies that are fused in their lower parts to form a bicornuate uterus. In primates, such as monkeys, apes and man, the highest form of uterine development, the uterus simplex, is found.

Because of the close association of the müllerian ducts with the wolffian ducts, anomalies of the urinary tract are often found in conjunction with anomalies of the female genital tract, especially the absence of a kidney, more often the right, according to Findley<sup>1</sup> and most authorities. However, Eismayer<sup>2</sup> states that the left kidney is more frequently absent with double uterus. Also, double anus, double bladder, presence of a cloaca and incomplete rotation of the colon (Sweet<sup>3</sup> and Benjamin and Danforth<sup>4</sup>) have been reported.

The various types of uteri are illustrated in Figure 1. A simple classification of malformations of the uterus and the vagina is that of Jarcho,<sup>5</sup> which is a simplification of that of Kaufmann.<sup>6</sup> This classification identifies seven types: uterus didelphys, uterus duplex bicornis bicollis, uterus bicornis unicollis, uterus septus, uterus subseptus, uterus arcuatus or cordiformis, and uterus unicornis. The first can occur with double vulva and should not be called "uterus pseudodidelphys" but rather "uterus didelphys cum vulva duplici," according to Jarcho.<sup>5</sup> A double vagina is present almost always, in the first type and often in the second. An even simpler classification of uterine anomalies, which recognizes only four main types and is much like classifications used by Royster<sup>7</sup> and also by Sichel,<sup>8</sup> is as follows: uterus didelphys

\*Senior visiting surgeon, Cambridge City Hospital and Lawrence Memorial Hospital; consulting surgeon, Symmes Arlington Hospital.

—usually with septate (double) vagina, uterus bicornis including bicornis bicolis (often with septate [double] vagina) and bicornis unicollis, uterus septus, complete and incomplete, and uterus unicornis

The arcuate or cordiform uterus is merely a depression in the fundus of a normal uterus and is hardly worthy of a separate classification, though it may cause complications in pregnancy, labor and the puerperium. This classification is also essentially similar to that of Strassmann.<sup>9</sup>

The most serious complication of all these uterine malformations is the occurrence of pregnancy in a rudimentary or well developed horn that has no communication with, or a deficient cervical canal communicating with, the other uterus or the vagina. Pregnancy may occur in such a uterus by external migration of the spermatozoon or impregnated ovum. Rupture will occur at about four to six months with even more profuse hemorrhage than that from rupture in tubal pregnancy. Death usually occurs ten to fifteen minutes after rupture in about 90 per cent of cases (De Nicola and Petersen<sup>10</sup> — in 88 per cent of cases according to Mundell<sup>11</sup>). The case reported below was such a situation, discovered before pregnancy had occurred. Rarely, the fetus in such a pregnancy dies and becomes mummified. Scott and Forman<sup>12</sup> reported twin fetuses retained in a horn of a bicornuate uterus for twenty years. At operation, a pregnant uterine horn can be distinguished from a tubal pregnancy if the operator identifies the round ligament lateral to the mass. Also, the other uterine horn is found to have a tube and ovary on its lateral side only. In Mulsow's<sup>13</sup> case (1945) rupture of a pregnant rudimentary horn occurred at five months, with death in fifteen minutes. Mulsow, in a review of the literature since 1911, could find reports of only 9 cases of pregnancy in a rudimentary horn. De Nicola and Petersen<sup>10</sup> reported a pregnancy in a rudimentary horn in 1947 and cited a case from India by Waters (1944), which had not been mentioned by Mulsow. Fortunately, an incorrect diagnosis of a tubal pregnancy is usually made and the rudimentary horn is discovered at operation, otherwise the condition is discovered at autopsy. The first recorded case of such a pregnancy is credited to Moriceau and Vassel by Wardlaw and Smith.<sup>14</sup> Uteri with rudimentary horns are unsuspected because they do not have a vaginal septum. Injection of lipiodol followed by x-ray examination (uterosalpingography) will not reveal such a horn. In 1930 Grant and Rose<sup>15</sup> added a case to 6 recorded cases of bicornuate uteri with atresia and hematometra of one horn, the previous cases having been reported by Robinson<sup>16</sup> in 1910, Maclean<sup>17</sup> in 1911, Oliver<sup>18</sup> in 1912, Schwarz<sup>19</sup> in 1921, Nemes<sup>20</sup> in 1921 and Champel<sup>21</sup> in 1921. Several other cases have been reported without pregnancy in such

uteri, the horn having little or no connection with the other uterus or the vagina, and causing hematometra with or without hematosalpinx. No case is recorded in which a well developed horn menstruated into the abdomen under the peritoneum, forming a pseudocyst distended with menstrual blood, as in the case reported below. According to Puddicombe,<sup>22</sup> Kehrer, in 1900, collected 84 cases of pregnancy in rudimentary horns. In 1916 De Lee<sup>23</sup> reported about 100 cases of pregnancy in a rudimen-

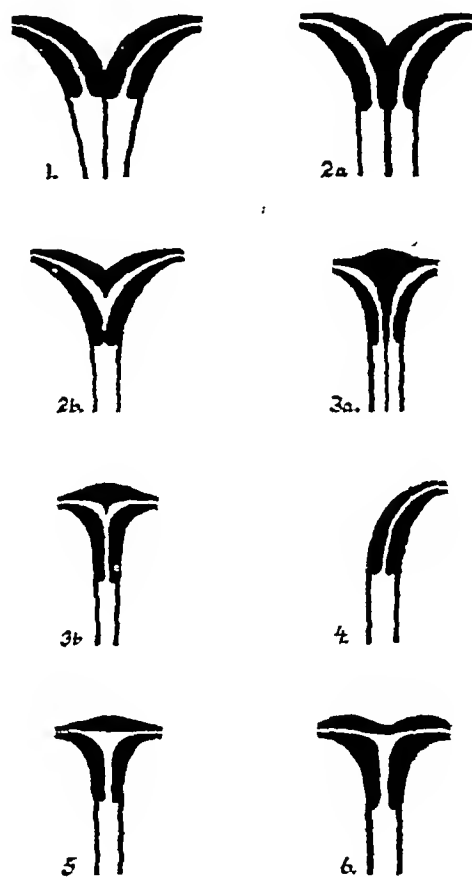


FIGURE 1 Various Types of Uterus

1=uterus didelphys 2a=uterus bicornis bicollis 2b=uterus bicornis unicollis 3a=uterus septus 3b=uterus subseptus 4=uterus unicornis 5=uterus simplex 6=uterus arcuatus or cordiformis

tary horn, indicating that the condition is not extremely rare.

In summary, therefore, the nonfused proximal thirds of the müllerian ducts normally form the two tubes, the fused middle thirds of the two ducts normally the single uterus and cervix, and the normal fusion of the distal thirds of the two ducts the single vagina. Various degrees of failure of fusion or of absorption of the intervening septum produce different types of doubling of the uterus, cervix and vagina. Uterus didelphys is caused by

our previous report, that hypertension frequently exists in man without evidence of renal vascular disease or with insufficient evidence to explain the elevated blood pressure. Therefore, some other functional factor or factors that are primarily responsible for the hypertensive state and precede the appearance of renal vascular disease must exist in many cases.

## REFERENCES

- 1 Castleman B and Smithwick R H. Relation of vascular disease to hypertensive state based on study of renal biopsies from 100 hypertensive patients. *J A M A* 121:1256-1261 1943
- 2 Goldblatt H. Renal origin of hypertension. *Physiol Rev* 27:120-165 1947
- 3 Chasis H and Redish J. Function of separate kidneys in hypertensive subjects. *Arch Int Med* 70:738-748 1942
- 4 Talbott J H, Castleman B, Smithwick R H and Melville R S. Renal biopsy studies correlated with renal clearance observations in hypertensive patients treated by radical sympathectomy. *J Clin Investigation* 22:387-394 1943

## DOUBLE UTERUS WITH HORN MENSTRUATING INTO THE ABDOMEN

JOHN B. VERNAGLIA, M.D.\*

MEDFORD, MASSACHUSETTS

A review of the literature has disclosed no case similar to the one reported below, which is that of a completely separated double uterus, both halves well developed, in which one uterus did not communicate with the vagina and menstruated into the abdomen. The situation was recognized at operation at the time of the patient's third menstrual period, and a hemi-hysterectomy was done. Later, the patient became pregnant and was delivered of a living child by cesarean section.

Congenital anomalies of the uterus are interesting but potentially serious conditions that warrant the careful consideration of every surgeon, gynecologist and obstetrician. They can cause dysmenorrhea, sterility, inflamed appendages, miscarriage, abnormal presentations, difficult or impossible delivery, uterine rupture, puerperal sepsis, placenta previa, retained placenta, post-partum hemorrhage and subinvolution. When there is atresia in the vagina or cervix, one may find, in addition to dysmenorrhea, hematocolpos, hemometra and hematosalpinx.

Embryologically the uterus and vagina are formed by the fusion of the two müllerian ducts in their distal or caudal two thirds. The cephalic third of each duct remains unfused and forms the fallopian tube on each side. These ducts appear during the sixth week of embryonic life, close to the more developed wolffian ducts. Their caudal segments move medially and become fused from below upward during the twelfth to the fourteenth week and form one tube, the uterus, cervix and vagina. Lack of complete fusion and disappearance of the intervening septum, at any point from below upward or throughout the length of the two ducts, explains most of the anomalies observed, the rudimentary development of one duct or of the cervical canal of one side accounts for the remainder. Nonfusion occurs normally in lower mammals, so that Blair-Bell suggests the use of the term "atavism" in preference to "malformation,"

because an anomalous uterus conforms exactly with that of one of the lower orders. Marsupials or didelphys, like the kangaroo and the opossum, have double uteri and lateral vaginas with a central vaginal pouch. The rodents (rabbits, squirrels, rats, guinea pigs, porcupines and gophers) have double uteri with separate cervixes and vaginas in the lower forms, and double uteri with a single cervix and a single vagina in the higher forms. The carnivora (cats, dogs, bears, weasels, raccoons and seals) have uterine bodies that are fused in their lower parts to form a bicornuate uterus. In primates, such as monkeys, apes and man, the highest form of uterine development, the uterus simplex, is found.

Because of the close association of the müllerian ducts with the wolffian ducts, anomalies of the urinary tract are often found in conjunction with anomalies of the female genital tract, especially the absence of a kidney, more often the right, according to Findley<sup>1</sup> and most authorities. However, Eismayer<sup>2</sup> states that the left kidney is more frequently absent with double uterus. Also, double anus, double bladder, presence of a cloaca and incomplete rotation of the colon (Sweet<sup>3</sup> and Benjamin and Danforth<sup>4</sup>) have been reported.

The various types of uteri are illustrated in Figure 1. A simple classification of malformations of the uterus and the vagina is that of Jarcho,<sup>5</sup> which is a simplification of that of Kaufmann.<sup>6</sup> This classification identifies seven types: uterus didelphys, uterus duplex bicornis bicollis, uterus bicornis unicollis, uterus septus, uterus subseptus, uterus arcuatus or cordiformis, and uterus unicornis. The first can occur with double vulva and should not be called "uterus pseudodidelphys" but rather "uterus didelphys cum vulva duplici," according to Jarcho.<sup>5</sup> A double vagina is present almost always, in the first type and often in the second. An even simpler classification of uterine anomalies, which recognizes only four main types and is much like classifications used by Royster<sup>7</sup> and also by Sichel,<sup>8</sup> is as follows: uterus didelphys

\*Senior visiting surgeon, Cambridge City Hospital and Lawrence Memorial Hospital; consulting surgeon, Symmes Arlington Hospital.

rudimentary horn is always advisable because of the danger of pregnancy. Whenever possible surgical intervention for uterine anomalies should be conservative. Surgical measures based solely on the presence of an anomaly are seldom justified (Jarcho,<sup>5</sup> Granberry and Faust,<sup>31</sup> Smith,<sup>32</sup> Schauffler,<sup>36</sup> Sweet<sup>2</sup> and Tyler<sup>37</sup>).

### CASE REPORT

E. L. (NH 59904) a 12½-year-old girl, was admitted to the hospital on March 24 1939 because of abdominal pain. The patient had had two normal periods each with moderate pain lasting 4 days. The present period, beginning 4 days before admission and on time, was accompanied by headache and decreased appetite. Three days previously she had complained of cramp-like pains all over the abdomen and had vomited once. There was an urgent desire to defecate, which was not relieved by enemas and a saline cathartic. The pain, the vomiting and the urgency to defecate became more marked. The pain was localized low in the abdomen and became severe and steady. Enemas produced little feces,—mostly thick gray mucus,—and the mother noticed that the enema tip could not be admitted satisfactorily more than 3.5 to 5.0 cm. On the day of admission the mucus contained some dark blood. There were no symptoms referable to the cardiorespiratory, genitourinary or neuromuscular system.

The past history was irrelevant. The patient had been born after a forceps delivery. Infancy and childhood had been normal. She had had measles, chicken pox and whooping cough but no serious illnesses, accidents or operations.

The mother and father were living and well. The patient was the oldest of a family of four children, all of whom were living and well. There were no familial diseases.

Physical examination disclosed a well developed and well nourished girl, who complained of severe pain in the lower abdomen, more marked on the right. The skin was pink, dry and warm. The head, heart and lungs were normal. The abdomen was not distended. No organs were felt, and there were no hernias. Marked tenderness was noted in the lower abdomen without muscle spasm and without rebound tenderness. Rectal examination revealed a tender mass in front of the rectum, 7.5 to 10.0 cm in diameter.

The temperature was 99°F, the pulse 80, and the respirations 22.

Examination of the blood showed a red-cell count of 4,050,000 with a hemoglobin of 82 per cent, and a white-cell count of 10,200, with 63 per cent neutrophils, 25 per cent small and 10 per cent large lymphocytes and 2 per cent eosinophils. Fluoroscopy with a barium enema demonstrated that the colon filled easily to the cecum, with normal regurgitation through the ileocecal valve. There was no tenderness over the cecum, which was movable and apparently not attached to the mass in the pelvis. There was a tender mass in the pelvis displacing the rectum to the left and apparently not attached to the cecum.

The patient was given intravenous saline solution, 50 mg of morphine, and 0.4 mg of atropine.

At operation, under ether anesthesia she was placed in the lithotomy position and catheterized after preparation and draping of the perineum. On specular examination, the cervix was found displaced to the left and forward by a cystic mass. Aspiration of the mass with a needle revealed black, dark blood. The patient was straightened out on the table, the abdomen was prepared and draped and a right lower paramedian incision was made. Exploration revealed no fluid or free blood. The appendix was normal. Behind the bladder rose two uteri separated about 2.5 cm at the lower ends and about 9 cm at the fundi. Each uterus had one round ligament, and one tube and ovary on its lateral side. The right tube was thick distended and congested. Retroperitoneally, anterior to the sacrum was an ovoid cystic bluish mass, 7.5 by 10.0 cm displacing the rectum to the left and the left uterus anteriorly and to the right. Obviously the cervix, found displaced to the left on specular examination, belonged to the left uterus. Pressure on the right uterus increased the tension in the mass confirming the suspicion that this uterus communicated with and not with the vagina. The mass was tapped and the thick bluish blood was obtained as from the tap of the

posterior cul-de-sac. There was no rectovesical ligament running from the bladder to the rectum and sigmoid as frequently occurs with double uterus. It was decided that the right uterus was menstruating under the peritoneum, forming a menstrual pseudocyst. The peritoneum was incised over the front of the lower end of the right uterus reflecting the bladder forward. A right hemi-hysterectomy and salpingectomy was done. The peritoneum was incised over the cystic mass, and it was easily dissected off the sacrum and rectum posteriorly and from the back of the lower part of the left uterus in front without rupturing. Its cavity communicated with the cervical end of the right uterus through a tract about 0.4 cm in diameter. The same thick bluish blood contained in the cyst distended the uterus and tube producing a moderate hematometra and hematosalpinx. The patient made an uneventful recovery and was discharged on the 12th day.

The gross specimen consisted of a thickened tube, 8.7 cm long, and a uterus about 6.2 cm long and 3.7 cm across its widest point. One side was perfectly smooth. The uterus tapered down to a cervix with a canal, 0.4 cm in diameter which communicated with a pear-shaped saccular structure 10.0 cm long and 6.2 cm wide. The uterus, the tube and the saccular structure contained thick old blood. The endometrium was markedly thickened and hemorrhagic.

Microscopical examination showed the tubal wall to be thickened and infiltrated with round cells. Sections of the uterus were not remarkable except that the endometrium was markedly thick and contained tortuous hyperplastic endometrial glands. Sections through the wall of the saccular structure showed it to be composed of fibrous tissue. The inner surface was covered with red cells. In one area the cyst was lined with tissue that had the appearance of endometrium. The adjacent tissue showed some old hemorrhage characterized by the deposit of hematoïdin and hemosiderin. Histologically the tissue was consistent with an endometrial implant. There was no evidence of cancer or tuberculosis.

The diagnoses were bicornuate uterus, hyperplastic endometritis, endometrial implant and chronic salpingitis.

After this episode the patient enjoyed good health except that she had painful periods, and in June, 1944, the right ovary was removed because it had become large, tender and cystic. At the same time the appendix was removed, and several cysts of the left ovary were resected. The left tube was found patent. The patient married in October 1946. She became pregnant and during the last month of pregnancy developed considerable lower abdominal pain with tenderness and tenseness of the uterus. On April 30 1948 3 weeks before term, she also developed some vaginal bleeding. Because of the danger of rupture of the uterus cesarean section was performed\*. At operation the uterus was tense and thin walled. On the front wall of the distended uterus ran five large veins each 0.6 cm in diameter, which converged low on the left side of the uterus. The lower two which lay in the line of the incision were tied off on either side to prevent unnecessary bleeding. A 4½-pound male baby was delivered, and the placenta showed some partial premature separation. Both mother and baby have done well.

### SUMMARY

The subject of uterine anomalies is reviewed with special reference to embryology, classification, etiology, complications and treatment.

A simplified classification is presented.

What is believed to be the first reported case of double uterus with one uterus not connected with a vagina and menstruating into the abdomen retroperitoneally is presented. Hemi-hysterectomy was done and this patient later bore a child.

Pregnancy in the rudimentary horn of a double uterus is stressed as even more dangerous than an ectopic pregnancy and the diagnosis is more difficult.

Conservative surgical treatment is emphasized.

\*The section was performed by Dr. Emilio D. Ermo, of Medford.

complete failure of fusion of the middle thirds of the ducts, resulting in a double uterus and a double cervix. If the intervening septum remains in the distal thirds, there is also a double vagina. Since obliteration of the septum usually occurs from below upward, a double vagina is almost always present with uterus didelphys and often with uterus bicornis bicollis. Uterus bicornis is due to partial failure of fusion of the ducts in the middle thirds. The region of the cervix may or may not fuse, causing a single or a double cervix. With double cervixes the vagina is often double, as stated above. Uterus septus is due to fusion of the middle thirds of the ducts with persistence of the intervening septum, and the vagina may or may not be double, depending upon what happens to the septum in the distal thirds of the ducts.

Theories to explain the factors responsible for failure of proper fusion of the müllerian ducts are variations in the germ plasma itself (von Winkle, quoted by Moench<sup>24</sup>), variations in biochemical environment during the time of development and fusion of the müllerian ducts — this is the likeliest theory in my opinion, errors in timing of arrival of ducts at midline — the left duct usually advances medially faster (Felix<sup>25</sup>) and interferes with development of the right duct (Anderson<sup>26</sup>), accounting for more variations on the right side, the presence of a rectovesical ligament or fold (Kussmaul, cited by Moench<sup>24</sup>), but this may be an associated anomaly rather than the cause, too short round ligaments (Newton<sup>27</sup> and Meyer<sup>28</sup>), too broad a pelvis, preventing union of ducts (Wardlaw and Smith<sup>14</sup> and Schwarz<sup>19</sup>) — this may be an associated condition and not a cause, fetal peritonitis (a very improbable and rare cause), associated disturbances of development of adjacent structures, such as the wolffian ducts and the urinary bladder or intestinal tract, or both (von Winkle, cited by Moench<sup>24</sup>), preventing normal union of the two ducts, distention of the bladder and uterus and fetal peritonitis are ruled out by Felix<sup>29</sup> because these factors must occur after the fusion that forms the uterovaginal canal, Thiersch<sup>30</sup> blamed the greater development and separation of the wolffian bodies as the most plausible cause, Pick<sup>31</sup> blamed tumors, or interference by stray cells of müllerian tissue keeping the ducts apart. Very probably, other causes are involved, and different factors may be responsible in different cases.

Patients with double uterus are more fertile, according to Findley,<sup>1</sup> but have more abortions. They have more transverse and breech presentations, and also have more prolonged labors. They have poorer uterine musculature and more rigid cervixes, and they run the danger of incarceration of the nonpregnant uterus in the pelvis, where it can act as an obstruction to delivery. The nonpregnant complications of double uterus are dysmenorrhea and the so-called retention complications (Sweet<sup>2</sup>),

hematocolpos, hematometra and hematosalpinx, depending upon the site of atresia. In 1926 Findley<sup>1</sup> collected 135 cases of double uterus and advised conservative management of pregnancy. Falls,<sup>32</sup> who stated that anomalies of the female genital tract occur in about 1 per cent of all women, stressed long labors, post-partum hemorrhage and placenta previa in these cases. He also emphasized an important fact, which bears repeating: the bladder is often carried back over the saddle of a bicornuate uterus in the rectovesical ligament, if present, where it can be damaged during cesarean section or hysterectomy. Strassmann,<sup>9</sup> of Berlin, who came to America to discuss Falls's paper in 1928, stressed the frequency of dysmenorrhea and inflamed appendages. He viewed pregnancy in a double uterus with the same apprehension as ectopic pregnancy, advocating emptying of the uterus and operation to form one cavity because of the frequency and danger of abnormal presentations, placenta previa, puerperal sepsis, retained placenta, post-partum hemorrhage, slow or obstructed labor and ruptured uterus. In 1896 Strassmann had first described his operation for conversion of uterus didelphys into a single uterus with a single cavity. At laparotomy, an incision is made running from fundus to fundus along the medial surfaces of the double uteri down into the internal os. Then the posterior cut edges are sutured to each other, as are the anterior edges up to and including the fundi. After closure of the abdomen, the vaginal septum and then the thick cervical septum are divided with a cautery.

In 1916 Rockey<sup>33</sup> reported a method of operation dividing the vaginal and the intrauterine septums, per vaginam, by leaving long clamps on the anterior and posterior margins of the septums for thirty-six hours, at the same time cutting between them with the cautery. He advised placing the patient in marked Trendelenburg position before the clamps are applied to the uterus in case the uteri are bicornuate because of the danger of clamping bowel between them.

Owing to the great variety of anomalies, each case is an individual problem, and no set rules regarding treatment can be formulated. The less the deformity, the less the danger. The average uterus didelphys will deliver quite normally from either side provided the other uterus does not drop down and get in the way, or does not contain a tumor or another pregnancy, as has not infrequently happened. Quite a few cases have been reported of a second pregnancy and subsequent delivery (involving the other uterus) several or more months after pregnancy in, and delivery from, the first uterus. These cases have been cited by some as proving the occurrence of true superfetation, or the presence of two fetuses of different ages, not twins, owing to impregnation of two ova from different periods of ovulation. The removal of a

admitted for the first time complaining of the attacks of abdominal pain. These attacks were aggravated by food and relieved by induced vomiting. At operation a chronically infected gall bladder filled with small stones was removed. The abdomen was explored, but no other disease was noted. Four years prior to admission she first experienced precordial pain and blurred vision during attacks. For the past 4 years she had been greatly incapacitated. The attacks had occurred as frequently as three or four times a day.

Physical examination disclosed a pale, thin woman, who appeared 20 years older than her stated age. There was no orthopnea or dyspnea. The fundi showed marked arteriovenous nicking and thickening of the arteriolar walls, but no papilledema, hemorrhages or exudate. The lungs were clear. The heart did not appear enlarged. Normal sinus rhythm, with occasional extrasystoles, was present. A coarse Grade II apical systolic murmur was heard. Examination

However, it was noted that there was a definite correlation between the daily hypertensive episodes and the symptoms. The paroxysmal attacks of hypertension accompanied by right-sided abdominal pain, precordial pain, headache and profuse diaphoresis seemed characteristic of an adrenalin-

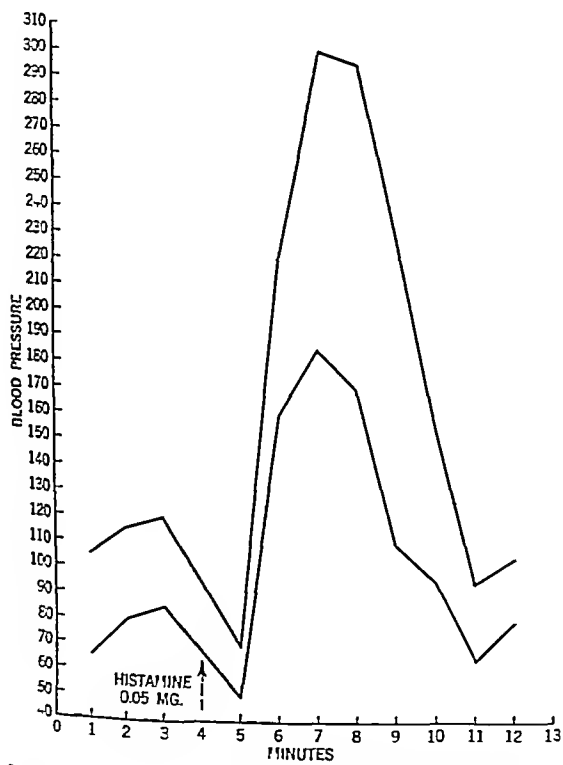


FIGURE 1 Histamine Test Using 0.05 mg of Histamine Base Intravenously

of the abdomen revealed only a well healed upper right rectus scar.

The temperature was 99°F, the pulse 96, and the respirations 18. The blood pressure was 130/100.

On admission and throughout the hospital course the urinalyses, blood counts, sedimentation rates and blood serologic findings were essentially normal. X-ray examination of the chest showed only moderate hypertrophy of the left ventricle of the heart. Repeated electrocardiograms including multiple chest leads, revealed left-axis deviation and inverted T waves in Leads 1, 2 and 4.

A tentative diagnosis of hypertensive cardiovascular disease with coronary insufficiency was made. The patient was placed on nitrites and a rice diet for approximately 3 weeks with no relief of symptoms. During the first 6 weeks it was observed to have a labile hypertension; the blood pressure varying from 250/150 to 130/80. Urine concentration and urea clearance tests were normal. Intravenous pyelograms were normal. Retrograde pyelograms were normal except that the right kidney appeared displaced somewhat laterally and inferiorly.

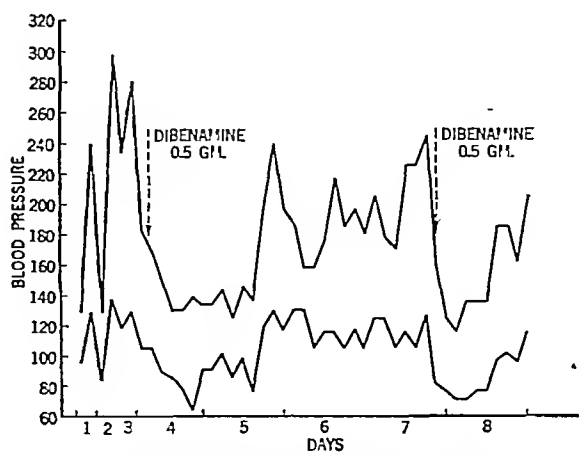


FIGURE 2 Blood-Pressure Recordings, Demonstrating the Effect of Dibenamine Hydrochloride

producing tumor the so-called pheochromocytoma. Accordingly, an intravenous histamine test, described by Roth and Kvale<sup>1</sup> as diagnostic of such a tumor, was performed. The results of this test, using 0.05 mg of histamine base intravenously, are shown in Figure 1. After an initial drop, the blood pressure rose precipitously, associated with precordial and abdominal pain, headache, nausea and diaphoresis.

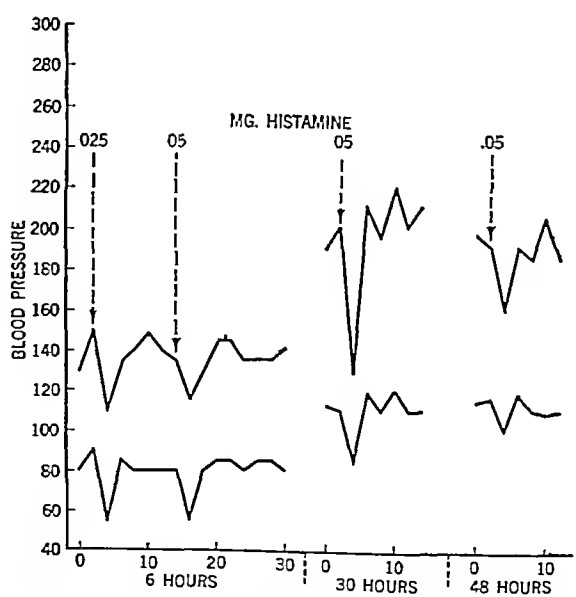


FIGURE 3 Histamine Tests Following the Administration of Dibenamine Hydrochloride

These symptoms cleared as the blood pressure fell. This test was repeated with similar results. A cold pressor test was done and a hyper-reactive blood-pressure response was elicited without the features of the attack previously described. Bilateral perirenal air insufflation with the con-

## REFERENCES

- Findley P F Pregnancy in uterus didelphys *Am J Obst & Gynec* 12 318-325 1926
- Eismayer G Über Uterusmissbildung bei kongenitalen Mangel einer Niere *Ztschr f urol Chir* 11 191-220 1923
- Sweet R H Uterus didelphys with report of case *New Eng J Med* 210 303-307 1934
- Benjamin E L and Danforth W C Bipartite uterus *Am J Obst & Gynec* 39 704-708 1940
- Jarboe J Malformations of uterus review of subject including embryology comparative anatomy diagnosis and report of cases *Am J Surg* 71 106-166 1946
- Kaufmann E *Lehrbuch der speziellen pathologischen Anatomie für Studierende und Ärzte* 2 vol Berlin Walter de Gruyter & Co 1922 Vol 2 Pp 1151 1155
- Royster H A Malformations of uterus with clinical reports *Am J Surg* 36 110 113 1922
- Sichel M S Some malformations of uterus with report of three cases *Minnesota Med* 11 474-477 1928
- Strassmann P Die operative Vereinigung einer doppelten Uterus nebst Bemerkungen über die Korrektur des sogenannten Verdoppelung des Genitalkanals *Zentralbl f Gynak* 31 1332 1335 1907
- De Nicola R R and Petersen M R Pregnancy in rudimentary horn of uterus *Am J Surg* 73 381-384 1947
- Mundell J J Case of pregnancy in double uterus (uterus didelphys) *Am J Obst & Gynec* 6 601 606 1923
- Scott E and Forman J Twin pregnancy in horn of bicornuate uterus with retention of fetuses for twenty years *Am J Obst* 73 470-474 1916
- Mulrow F W Pregnancy in rudimentary horn of uterus *Am J Obst & Gynec* 49 773 776 1945
- Wardlaw Y and Smith W P Uterus duplex bicornis *Surg Gynec & Obst* 38 497-500 1922
- Grant W H and Rose D Uterus bicornis unicolis with atresia and hematometra of one horn *Am J Obst & Gynec* 19 555 557 1930
- Robinson E M Supernumerary uterus in girl eighteen years old removal recovery *Alabama M J* 23 152-154 1910
- Maclean E Dysmenorrhea haematometra of one horn of uterus bicornis *J Obst & Gynaec Brit Emp* 20 18 1911
- Oliver J Accessory uterus distended with menstrual fluid enucleated from substance of right broad ligament. *Lancet* 1 1609 1912
- Schwarz, E. On case of uterus bicornis with rudimentary hemistern. horn *Am J Obst* 77 583 588 1918
- Nemes A Uterus duplex separatus cum haematometra. *Klin Wchnschr* 34 440 1921
- Champel Malformation genital (uterus biloculaire avec hematometrie unilaterale) chez une jeune fille *Lyon med.* 130 103 1036 1921
- Puddicombe J F Some uterine anomalies due to anomalous fusion of müllerian ducts partial review of literature with report of nineteen cases seen at Boston Lying in Hospital and Free Hospital for Women Brookline Massachusetts *Surg., Gynec & Obst* 49 799-803 1929
- De Lee J B *Principles and Practice of Obstetrics* Fourth edition 1123 pp Philadelphia W B Saunders Co 1914
- Moench G L Uterus duplex bicollis vagina simplex and septate fetusation *Am J Obst & Gynec* 13 60-64 1927
- Felix W Development of urogenital organs In *Manual of Human Embryology* Edited by F Keibel and F P Mall Vol 7 1032 pp Philadelphia J B Lippincott Co 1912 Pp 752 979
- Anderson C W Factors concerned in causation of uterine anomalies report of case uterus rudimentaris solidus duplex. *Californ Med* 28 449 453 1931
- Newton F C Uterus didelphys noted on its developmental etiology and clinical significance *Ann Surg* 79 102 112 1914
- Meyer R Zur Entstehung des doppelten Uterus *Ztschr f Geburt u Gynak* 38 16-25 1898
- Felix P 930
- Thersach C Bildungsfehler der Harn und Geschlechtswerkzeuge eines Kindes *Illustr med Zeitung* 17 14 1852
- Piel L Gebärmutterverdoppelung und Gebärmutterbildung unter Berücksichtigung ihres ätiologischen Zusammenhanges *Arch f Gynak* 52 389-407 1896 Zur Anatomie und Genese der doppelten Gebärmutter *Ibid* 57 596-634 1898
- Falls F H Study of pregnancy and parturition in primiparae with bicornuate uteri *Am J Obst & Gynec* 15 399-403 1928
- Rockey A E Ven bloodless operation for double uterus and double vagina *Ann Surg* 63 615-618 1916
- Granberry H B Jr and Faust F L Jr Duphcity of uterus and vagina *Am J Obst & Gynec* 35 1042 1046 1938
- Smith F R Significance of incomplete fusion of müllerian ducts in pregnancy and parturition with report on 35 cases *Am J Obst & Gynec* 22 714-728 1931
- Schanffler G C Double uterus with pregnancy *J A M A* 117 1516 1520 1941
- Tyler G T Jr Didelphys in sisters *Am J Surg* 45 357 1939

## THE USE OF DIBENAMINE IN PHEOCHROMOCYTOMA\*

## Report of a Case

HAROLD C SPEAR, M D,† AND DWIGHT GRISWOLD, M D‡

NEW YORK CITY

THE adrenolytic drug dibenamine hydrochloride (dibenzyl-beta-chlorethyl amine hydrochloride)§ is presented as a diagnostic aid when the presence of a pheochromocytoma is suspected and as a therapeutic agent once the diagnosis is confirmed.

The preoperative diagnosis of a pheochromocytoma is based on the clinical picture, retrograde pyelograms and perirenal air studies. But none of these criteria are specific. In the following case dibenamine apparently blocked the effects of a pheochromocytoma by its adrenolytic action. Thus, the drug affords a more specific test in the diagnosis of a pheochromocytoma.

## METHOD OF ADMINISTRATION

The patient was given an intravenous infusion of dibenamine hydrochloride. The dosage was

\*From the Department of Medicine, St. Luke's Hospital.

†Intern in surgery, Grace-New Haven Community Hospital, New Haven, Connecticut; formerly intern in surgery, St. Luke's Hospital.

‡Formerly, resident in medicine, St. Luke's Hospital.

§Supplied through the courtesy of Dr. W. Gump of Givaudan-Delawanna, Incorporated, New York City.

70 mg per kilogram of body weight. This was diluted in 300 cc of 5 per cent glucose in physiologic saline solution. For its administration a Y-infusion set was used. One arm was attached to the bottle containing the dibenamine, and the other to one containing 5 per cent glucose in physiologic saline solution. The infusion was started with the glucose in saline solution, and then was switched to the dibenamine, which was administered over a period of one hour to lessen the possibility of toxic reactions.

## CASE REPORT

On September 11, 1947, M P, a 51-year-old woman, was admitted to the hospital for the second time, complaining of attacks of precordial and abdominal pain, headaches, nausea, and diaphoresis.

The past and personal histories were noncontributory. The present illness had begun 21 years prior to admission, when the patient first experienced intermittent mild attacks of right-sided abdominal pain, headache, diaphoresis and nausea. They came on suddenly without any known precipitating factor, and even woke her at night. The pain spread from the abdomen superiorly to produce a severe, crushing headache. The duration of the attacks varied from a few minutes to days. Twelve years previously she had been

tolerance test was made to compare the results with the one performed preoperatively (Table 1). Preoperatively a hyperglycemic curve was noted whereas postoperatively the results showed a normal curve.

Postoperatively a histamine test was repeated (Fig. 7). This caused neither any rise in the blood pressure nor any untoward symptoms.

On December 21 the patient was discharged complaining only of residual discomfort in the right flank. When last

TABLE 1 Preoperative and Postoperative Glucose-Tolerance Curves

TIME OF DETERMINATION	GLUCOSE-TOLERANCE TEST				
	FASTING	AT 1/2 HR.	AT 1 HR.	AT 2 HR.	AT 5 HR.
	mg/100 cc	mg/100 cc	mg/100 cc	mg/100 cc	mg/100 cc
Preoperatively	119	144	20	161	61
Postoperatively	76	152	92	105	67

seen 5 months postoperatively she had remained well and the blood pressure had continued within normal limits.

### DISCUSSION

Once the paroxysmal attacks of precordial and abdominal pain, headache and diaphoresis had been correlated with the hypertensive levels of the blood pressure, the diagnosis was apparent, and yet unproved. Recent work on dibenamine hydrochloride<sup>2</sup> has shown that this compound is adrenolytic but not sympatholytic. This action seemed desirable from both the diagnostic and the therapeutic standpoint in the case presented above.

From the diagnostic standpoint the important finding was that the blood-pressure level remained within normal limits for twenty-four hours after the administration of dibenamine and furthermore that the symptoms were relieved for seventy-two hours. The blood-pressure level when the drug was administered was of no significance in affecting the success of the test. The histamine test was of definite value in proving the diagnosis but had the disadvantage of initiating an attack. This added strain was undesirable in a debilitated patient. For the most striking results the histamine test should be done while the blood pressure is within normal limits. Recently, benzodioxane<sup>3</sup> has been reported as an adrenolytic drug of value in the diagnosis of pheochromocytoma. This drug when used while the blood pressure is elevated will lower the pressure for a period of fifteen minutes.

From the therapeutic standpoint dibenamine relieved the patient of her symptoms. Her appetite returned and she gained 10 pounds in nine days. She slept well and appeared more rested. As

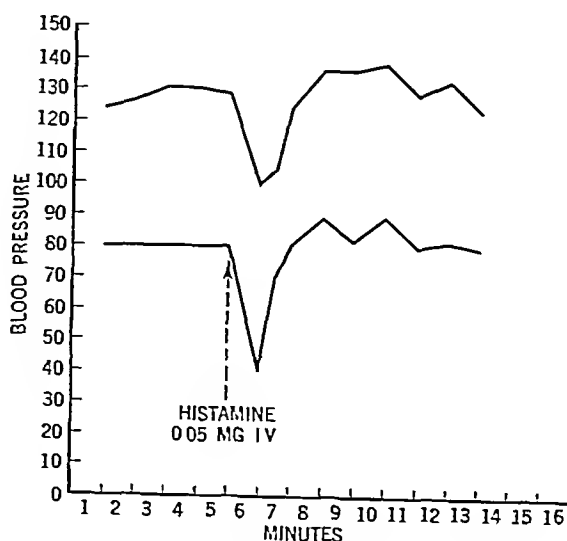


FIGURE 7 Histamine Test after Operation

a result she was prepared for operation more effectively.

### SUMMARY

The adrenolytic agent dibenamine hydrochloride was administered to a patient with a pheochromocytoma.

After the administration of dibenamine the paroxysmal elevations of blood pressure were eliminated for a period of twenty-four hours, and the patient was symptom free for seventy-two hours.

Dibenamine hydrochloride appears to be of value both in the diagnosis of a pheochromocytoma and in the therapy during preoperative preparation of the patient.

### REFERENCES

1. Roth G M and Kvale W F. Tentative test for pheochromocytoma. *J. M. Sc.* 210 65-660 1947.
2. Hecht, H H., and Anderson R B. Influence of dibenamine (N,N-dibenzyl-beta-chlorethyl amine) on certain functions of sympathetic nervous system in man. *J. Med.* 3:3-17 1947.
3. Goldenberg M, Snyder C H and Aranow H Jr. New test for hypertension due to circulating epinephrine. *J. A. M. A.* 135 971-976 1947.

comitant administration of dye intravenously revealed a normal-appearing left kidney and adrenal area. The right kidney was displaced anteriorly by a large mass in the region normally occupied by the adrenal gland. The mass appeared to be a large adrenal tumor.

The patient was given dibenamine as outlined above. She experienced only transitory nasal congestion while receiving the infusion. Figure 2 shows the effect of dibenamine on the blood pressure when administered on two occasions 3 days apart. On both occasions the pressure dropped to normal limits within 2 hours, with an associated clearing of the symptoms. Blood-pressure readings, taken hourly, remained within normal limits for roughly 24 hours on each occasion, after which paroxysmal hypertensive episodes were again noted. At the end of 72 hours the patient had a mild headache and was losing the sense of well-being she had experienced immediately after the administration of the drug. She was given a third dose of dibenamine with similar results. During this time she regained her appetite, slept

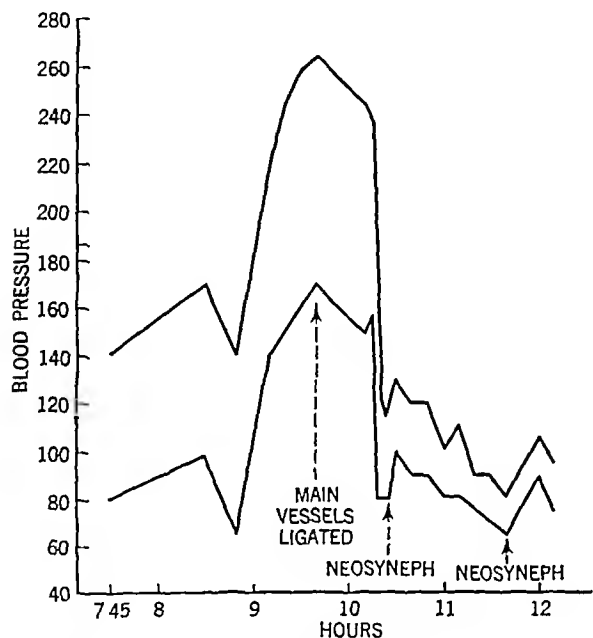


FIGURE 4 Blood-Pressure Recordings during Operation

well without interruption from an attack and regained strength as well as 10 pounds of weight.

The adrenolytic action of the dibenamine apparently had nullified the effects of the pheochromocytoma. To confirm this, histamine tests were repeated at intervals of 6, 30 and 48 hours after the administration of the drug (Fig. 3). At 6 hours there was no rise in blood pressure, and the patient felt no ill effects from the histamine. Although the tests at 30 and 48 hours were done when the blood pressure had returned to hypertensive levels, the administration of histamine did not cause a rise to levels seen in the test before the administration of the drug. Furthermore, she remained symptom free.

On the 76th hospital day, Dr. George F. Hoch, director of the Urological Service, operated on the patient. The right kidney was normal. Directly superior to the right kidney was a rounded, semi-fluctuant mass, approximately 8 cm in diameter. When the mass was dissected free, it ruptured, with the escape of tissue having the appearance and consistency of hyperplastic endometrium. The blood pressure dropped after the rupture (Fig. 4). Bleeding was controlled immediately by ligation of the pedicle of the mass. A drain was placed down to the ligated pedicle, and the wound closed. The patient was returned to her room in good condition.

On gross examination the tumor was found to be encapsulated and to contain soft, friable material, which was solid and without fibrous strands or stroma. Stained with potas-

sium bichromate, the tissue turned dark brown. Microscopically, it was composed entirely of small cells closely packed in a loose connective tissue carrying blood vessels.

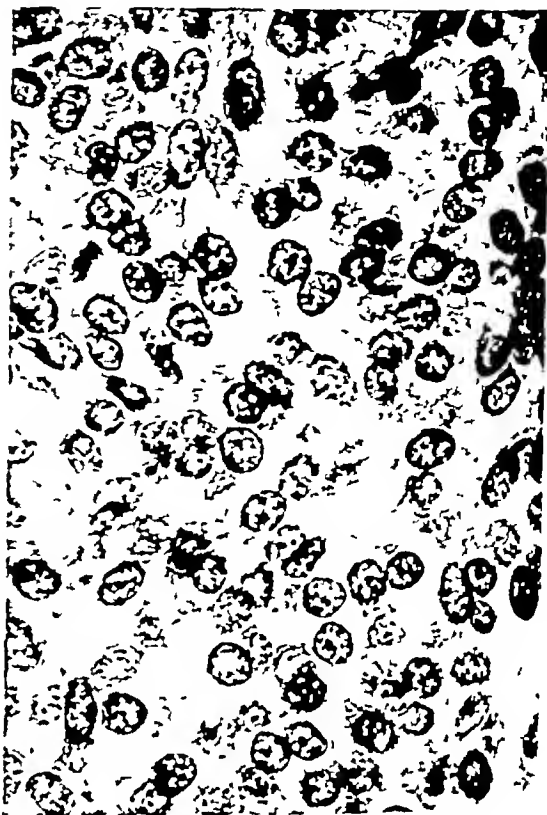


FIGURE 5 Section from Tissue Treated with Bichromate, Showing Granular Yellowish Material between the Cells (x900)

(Fig. 5) In the chromate-fixed tissue some cells contained granular, brown cytoplasm.

The postoperative course was uneventful except for a brief period of hypotension, which was controlled with neosynephrine.

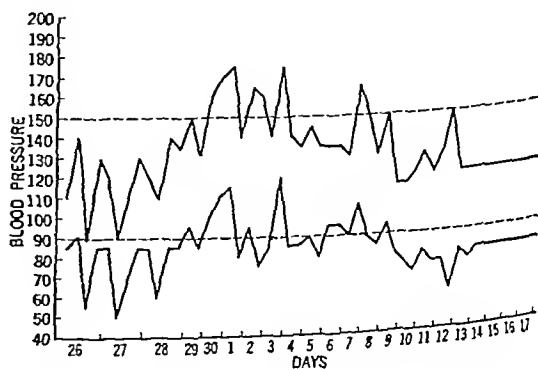


FIGURE 6 Blood-Pressure Recordings after Operation

sin. During the period of early ambulation, the blood pressure rose to levels as high as 175/120 (Fig. 6). Subsequently the level fell and stabilized at 120/80. A glucose

Museums that can afford it probably will use larger film, but unenlarged 35-mm slides of small lesions are large enough to view by magnifying glass. Cardboard mounts<sup>21</sup> are available that hold several slides, so that one mount can illustrate various signs or stages of a disease and be accompanied by explanatory text. These mounts can be clipped upon inexpensive standard lightboxes. Series of filled mounts can be stocked in reserve and, if space allows, left on display.

Enlarged transparencies in color make better displays than 35-mm film but necessitate especially constructed lightboxes. Lightboxes can be con-

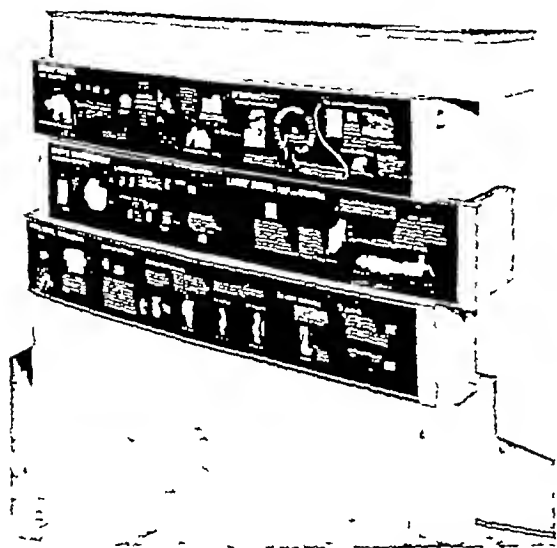


FIGURE 2 Sectional Take-Down Lightbox

structed like sectional bookcases<sup>22</sup> (Fig 2). Front panels windowed individually for each series of enlargements and screwed to such boxes are interchangeable so that extras can be held in store. If large pictures or charts are to be shown, a single front panel two or more units tall can be mounted on two or more back units.

Enlargements and viewboxes take as much space as gross specimens in jars and cost even more. But it is assumed that the photographic museum will use only a small proportion of permanent, and therefore semi-immobile, displays and that its backbone will be a store of slides for projection.

The 35-mm slide can be just as satisfactory—some,<sup>21</sup> including ourselves, prefer it in ordinary circumstances—as the 3¼-inch × 4-inch slide in projection. Small hooded screens make color projection practical in lighted rooms. Automatic projectors,\* operated by the visitor himself (Fig 3), can project sequences of 50 slides. Sequences can

be changed from week to week, and extra magazines kept loaded with those most in demand. The slide bank should be so cross-indexed that an attendant can project special sequences at request. For example, a visitor who inquires about lip lesions could be shown leukoplakia, mucous cyst, epitheliomas of varying grades of malignancy, hemangioma and chancre, preferably in conjunction with their microscopical sections, to which the film index can be keyed.

Comparative projection<sup>23</sup> has peculiar virtue: two or more projectors can demonstrate side by side the facies and the temperature chart, the gross and the microscopical appearances of a tumor, similar tumors of different grades of malignancy, contrasting graphs, a picture and a textual explanation, roentgenologic and operative appearances, and before-and-afters or, sometimes most useful of all, a normal with which deviation can be compared.

A contribution peculiar to the slide bank is the opportunity it offers of reaching beyond the walls



FIGURE 3 Photography of the Operative Field

of the museum into classroom, clinicopathological conference and staff or society meetings—that is, of bringing gross pathology to the man in practice. Clinicians are anxious to see gross disease, and color film is as logical a teaching tool in gross pathology as is the microtomic section in histopathology.

The contribution peculiar to color film is its ability to show *living* disease. Abnormal tissues, like normal, change with death, and the ordinary embalmed specimen bears no closer resemblance to living disease than does the embalmed body to the living man.

\* Available from Spindler and Sauppe, Los Angeles; and Bausch and Lomb, P. Peter, New York.

## THE PHOTOGRAPHIC MUSEUM\*

JOHN FALLON, M.D.,† AND JOHN MEYERS, M.D.‡

WORCESTER, MASSACHUSETTS

SINCE the times of Leonardo, Vesalius and John Hunter, visual teaching has been a preoccupation of medicine's greatest minds. Unfortunately it has also been, for the most part, the prerogative of that same group to indulge in it has required either artistic ability or unusual resources. Nowadays modern photography offers the privilege of visual teaching to the worker in the ranks.

Thus, 7 physicians in nonacademic group practice have assembled a pathological "museum" in a medium that is at once efficient and compatible with their funds and space. 35-mm color film. A few enlargements in viewboxes, viewing and projection paraphernalia and 7000 slides are contained in a space no larger than a good-sized closet (Fig. 1).

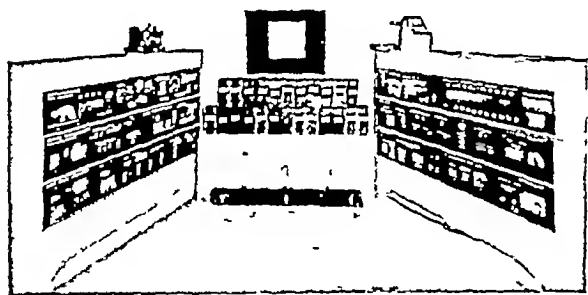


FIGURE 1 A Pocket Museum

The largest — and least important — constituents are the light-boxes for enlargements. All other items — the projector, automatic projector, rolled screen, hooded daylight screen, 7000 filed 35-mm color slides and (not illustrated) collapsible lightboxes for sheets of unenlarged slides — would fit into a large trunk.

The collection was built upon principles laid down some years ago and amplified here because of the growing interest in photographic museums<sup>4-11</sup> and because of the belief that some of the findings in a test case might be projected into more important endeavors.

The museum of gross specimens has two advantages over the photographic museum. Specimens offer third dimension and the possibility of microscopical restudy. However, color transparencies give fair third-dimensional illusion — better than that of black-and-white prints. Then, too, specimens after being photographed can be stored inexpensively in formaldehyde tanks for later study.

\*From the Surgical and the Medical Sections of the Fallon Clinic and the St. Vincent Hospital.

†Surgeon Fallon Clinic surgeon St. Vincent Hospital.

‡Physician Fallon Clinic assistant physician St. Vincent Hospital.

The photographic museum has advantages of its own. Thus, in the Buffalo Museum of Science

First — It has been found that transparencies and photographs hold the interest when original objects do not. Second — In some cases transparencies of a complete object make an original fragment intelligible. Third — In many instances they divert the attention back to the original.<sup>12</sup>

Photographic color is truer than the color of preserved gross tissue. Color usually disappears from the preserved specimen in a year or so.<sup>13</sup> Color slides last several years; how many we do not yet know. Specimens shrink and distort.<sup>14</sup> In an audience, specimens must pass slowly from hand to hand. Photographs are projected, or transilluminated, for all at the same time. If 35-mm film is used, 600 slides can be filed in the space required for 1 medium-sized specimen jar. Slide making is fast and efficient, while the preparation in color of actual tissue is time taking and puttery. Jars or watch glasses require frequent servicing, cleaning, refilling and resealing. The cost of preparing a gross specimen approximates three dollars, and that for taking and filing a slide nineteen cents. These are material expenses and include neither the cost of space and the salary for museum diener on the one hand nor the photographer's salary on the other. Without a biophotographer the photographic museum must remain, like ours, amateur.

The amateur — that is, the doctor — can with some study and effort take many of his own pictures.<sup>2, 3, 15-17</sup> He will meet a helpful welcome from the professionals of the Biological Photographic Association,<sup>18</sup> and he will find that composing pictures, like sketching, sharpens his eyes<sup>19</sup> and that his pictures will receive disproportionate praise from those whose photographic knowledge is a little scantier than his own. However, our kindest compliment, awarded some views of operative fields and recorded here with no pretense of modesty, was "Who does your surgery for you?" The fact that we were elated when the best of many amateur pictures thus were mistaken for routine professional results is a measure of the difference between amateur and professional. Professional photography is one of the few remaining bargains in medical care. Martinsen<sup>20</sup> reported in 1940 that the average of 110 full-time and part-time biologic photographic departments employed 1 1/4 persons, occupied 730 square feet of floor space, cost \$3146 yearly (of which 40 per cent went for materials) and used equipment valued at \$3109.

cases of sarcoidosis proved by biopsy with 18 different tuberculin, but noted no significant difference in reaction from 5 normal controls

### *Leprosy*

The occurrence of leprosy in a tuberculoid form that may be histologically indistinguishable from sarcoidosis<sup>248-249</sup> has suggested to a number of authors that the lepra bacillus or a closely related organism is an etiologic agent<sup>250-251</sup>. Further support has been lent to this view by the fact that in such tuberculoid forms, bacilli are so few as to be difficult or impossible to demonstrate by ordinary methods,<sup>248-252-253</sup> and that animal inoculations with lepra bacilli are invariably unsuccessful. Rabello<sup>250</sup> also notes that a torpid and discrete adenopathy analogous to that of sarcoidosis both clinically and histologically is frequently seen in such cases, and that characteristic pulmonary and osseous lesions may also occur, as well as tuberculin anergy. Cystic bone changes in the phalanges closely resembling those seen in sarcoidosis have also been described by others.<sup>5-134</sup>

There seems little doubt that leprosy is capable of mimicking at least part of the sarcoid picture, and it seems quite likely that some cases reported are, in fact, leprosy. Pardo-Castello<sup>248</sup> is of the opinion that sarcoid disease due to leprosy is indistinguishable from any other form of the disease, and Boeck himself is reported to have diagnosed a case of tuberculoid leprosy as a cutaneous sarcoid<sup>254</sup>. Whether leprosy can reproduce the entire clinical and pathological picture of sarcoidosis is another matter, however, and is considered by a number of authors as highly unlikely.<sup>255-256</sup> Furthermore, the tuberculoid forms of leprosy are almost invariably associated with the neural type of the disease<sup>248-257</sup>, in such cases the peripheral nerves show direct invasion,<sup>172</sup> something that must be exceedingly rare in sarcoidosis if it occurs at all.

Some efforts have been made to analyze this problem on the basis of immunologic reactions. Weeks and Smith<sup>255</sup> performed skin tests on 10 proved cases of sarcoidosis. They found 6 to be negative to both lepromin and tuberculin, whereas 2 were positive to both. Of 5 other cases similarly tested by Harrell and Horne,<sup>259</sup> 2 were negative to lepromin, and 3 gave a faintly positive reaction considered nonspecific, of the latter, 2 were tuberculin positive as well. Thus, in practically all 15 cases, the results with lepromin either were negative or could be explained on the basis of a cross reaction with tuberculin, which has been demonstrated to exist by a number of investigators.<sup>260-262</sup> This is in marked contrast with the fact that unlike the frequently weak or negative tuberculin reactions seen in sarcoid patients, the lepromin reactions in the tuberculoid (or sarcoid) forms of leprosy are strongly positive in 90 to 100 per cent of cases.<sup>248-252-263</sup> Fifteen

cases are admittedly a small sample on which to base conclusions, but in view of these findings it seems highly unlikely that, in this country at least, the tuberculoid form of leprosy masquerades as sarcoidosis in any appreciable number of patients. In such cases, the lepromin test might be expected to prove a useful aid in diagnosis.<sup>259</sup>

### *Other Infectious Diseases*

A number of granulomatous diseases known to be capable of wide dissemination have also come under suspicion, and several have been shown to exist in a sarcoid form. In all such cases organisms may be very difficult to find, and, as in tuberculosis and leprosy, both the prompt destruction of the organisms and the morphologic character of the lesions may be explainable by the same altered immunologic status of the host. Regardless of etiologic relation, however, the various disseminated granulomas frequently pose a difficult problem in differential diagnosis, and it is certain that they have been confused with sarcoidosis on more than one occasion.

**Brucellosis** In view of its ability to involve practically every organ in the body, its frequently low-grade chronic course, its association with non-caseating granulomas and its world-wide distribution, brucellosis has been considered a possible cause. It is quite possible that typical sarcoid lesions may be produced, though the usual lesions tend to be much less distinct with proliferation of cells of the reticuloendothelial system, and occasionally suppuration.<sup>264</sup> Pulmonary involvement may resemble that of sarcoidosis,<sup>265</sup> iridocyclitis may occur, and the bones may be involved as well, the characteristic bone changes of sarcoidosis have not been described, however. In the cases in which specific skin or agglutination tests have been performed they have all been negative, and Harrell<sup>42</sup> found that guinea pigs injected with tissue from sarcoid patients remained negative to brucellergin. These arguments do not, of course, constitute proof but simply indicate that brucellosis in its usual form is not sarcoidosis. It is well known that failure to culture the organism or to obtain positive skin or agglutination tests does not necessarily rule out the disease,<sup>264</sup> whereas, on the other hand, occasional positive findings might indicate little more than their coexistence.

**Syphilis** A number of cases reported as cutaneous sarcoidosis may have been due to syphilis.<sup>266-267</sup> As noted above, however, the serologic reactions are negative in the large majority of sarcoid patients so that it seems unlikely that syphilis can be the responsible agent in any appreciable number of cases.

**Mycoses** Some attempts have been made to implicate various yeasts and fungi as etiologic agents, usually on the basis of a similar pulmonary picture. Organisms such as aspergillus and

developed in an attempt to explain this peculiar immunologic situation

**Spontaneous desensitization** It has been known for a long time that skin sensitivity to tuberculin may be gradually lost—even to a degree whereby the subject may fail to react to large doses.<sup>232</sup> Tuberculin sensitivity induced by BCG vaccination may also be lost.<sup>233, 234</sup> Desensitization occurs spontaneously in animals<sup>235</sup> and has been produced experimentally by injections of tuberculin without impairment of immunity to reinfection.<sup>236, 237</sup> It has been postulated, therefore, that a similar effect may be produced by repeated hematogenous dissemination of tubercle bacilli as might be the case in sarcoidosis.<sup>120</sup>

If this theory is so, a reinfection with tubercle bacilli might be expected to cause a return of hypersensitivity as has been demonstrated experimentally.<sup>235, 238, 239</sup> As a matter of fact, it has occasionally been noted that a previously negative tuberculin test has become positive during or after a sanatorium stay or in the course of development of caseating tuberculosis in a sarcoid patient.<sup>7, 230</sup> In a number of cases the altered reactivity has preceded the clinical manifestations of active tuberculosis by several months.<sup>38</sup> On the other hand, vaccination of sarcoid patients with BCG, even in two or three times the usual dose, may fail to produce a positive tuberculin test,<sup>210, 211</sup> or may produce only a delayed or slightly positive reaction.<sup>226, 240</sup> Experimental reinfection of desensitized animals with very small numbers of attenuated or nonpathogenic acid-fast bacilli, however, has also resulted in marked delay or suppression of the development of hypersensitivity in comparison with controls,<sup>238, 239</sup> and repeated injection of attenuated bacilli into guinea pigs has caused some of them to lose their hypersensitivity while retaining their resistance.<sup>241</sup> These findings constitute no convincing proof but are at least sufficiently challenging to warrant further investigation.

**Anticutins** Substances capable of neutralizing the skin sensitivity to tuberculin (anticutins) or enhancing it (procutins) have been demonstrated in the blood serum of patients with sarcoid lesions associated with lack of tuberculin hypersensitivity.<sup>222, 228, 242</sup> Similar neutralizing substances have been demonstrated in the rat,<sup>228</sup> an animal that fails to develop tuberculin hypersensitivity after infection. The significance of the latter, however, has been questioned on the grounds that the rat is constitutionally resistant to hypersensitivity reactions in general.<sup>243</sup>

Pinner, Weiss and Cohen<sup>244</sup> have recently studied these substances in a small number of

normal, tuberculous and sarcoid persons. Anticutins were demonstrated in only 4 (36 per cent) of 11 patients with sarcoidosis; they were also demonstrable in 18 per cent of various groups of tuberculous patients—the highest percentage being in a group of 23 such patients with a low degree of hypersensitivity—and in 3 to 9 per cent of normal subjects. Procutins were found in another 36 per cent of the sarcoid patients. The authors were forced to conclude that anticutins played no significant immunologic role in sarcoidosis. Other authors have also failed to demonstrate them.<sup>44</sup>

**Local fixation of antibodies** This theory, supported by Leitner,<sup>55, 177</sup> suggests that in sarcoid patients the antigenic substances of the tubercle bacillus fix antibodies locally at their sites of origin (the reticuloendothelial system), and thus skin sensitization is prevented. Such a concept assumes the presence in tuberculosis of antibodies with secondary tissue-cell sensitization, but this has not yet been proved.

**Epidemiologic arguments** The majority of sarcoid patients give no history of unusual exposure to tuberculosis.<sup>10, 24</sup> although there is disagreement on this point.<sup>86</sup> In the various families and sibling pairs in which the disease has occurred, however, a significant incidence of tuberculosis has been recorded.<sup>49, 53, 56</sup> Such cases are interesting and possibly significant, but so far represent too small a proportion of the total cases reported to permit accurate evaluation. It is impossible at present to divorce the factors of infection, environment and constitution, or to establish for certain whether or not the incidence of tuberculosis in these groups differs in any way from that in other comparable groups.

In summary, the case for tuberculosis rests largely on negative, circumstantial or controversial evidence, a point freely admitted by at least one of its supporters.<sup>191</sup> The tubercle bacillus has not, however, been excluded as a possible etiologic factor. The validity of the few positive bacteriologic findings remains a crucial point, and here the issue has reached a stalemate. If, as is often the case, the identification of tubercle bacilli is accepted as *a priori* evidence that the case is one of tuberculosis and, therefore, not sarcoidosis, it is difficult to see how the point can be proved from a bacteriologic standpoint at least.

It has been suggested that other forms of tubercle bacilli, or related bacilli, are the responsible agents, but, in general, the arguments on both sides are the same as those already presented. Bacilli of the bovine<sup>7, 245</sup> and avian<sup>246</sup> strains have been reported in sarcoid lesions but, as in the human form, the majority of inoculations into susceptible animals has been negative. Immunologic studies have also provided little clue. Brooke and Day<sup>247</sup> tested 7

cases of sarcoidosis proved by biopsy with 18 different tuberculins, but noted no significant difference in reaction from 5 normal controls

### Leprosy

The occurrence of leprosy in a tuberculoid form that may be histologically indistinguishable from sarcoidosis<sup>248-249</sup> has suggested to a number of authors that the lepra bacillus or a closely related organism is an etiologic agent<sup>250-251</sup>. Further support has been lent to this view by the fact that in such tuberculoid forms, bacilli are so few as to be difficult or impossible to demonstrate by ordinary methods,<sup>248-252-253</sup> and that animal inoculations with lepra bacilli are invariably unsuccessful. Rabello<sup>250</sup> also notes that a torpid and discrete adenopathy analogous to that of sarcoidosis both clinically and histologically is frequently seen in such cases, and that characteristic pulmonary and osseous lesions may also occur, as well as tuberculin anergy. Cystic bone changes in the phalanges closely resembling those seen in sarcoidosis have also been described by others.<sup>8-184</sup>

There seems little doubt that leprosy is capable of mimicking at least part of the sarcoid picture, and it seems quite likely that some cases reported are in fact, leprosy. Pardo-Castello<sup>248</sup> is of the opinion that sarcoid disease due to leprosy is indistinguishable from any other form of the disease, and Boeck himself is reported to have diagnosed a case of tuberculoid leprosy as a cutaneous sarcoid<sup>254</sup>. Whether leprosy can reproduce the entire clinical and pathological picture of sarcoidosis is another matter, however, and is considered by a number of authors as highly unlikely.<sup>255-256</sup> Furthermore, the tuberculoid forms of leprosy are almost invariably associated with the neural type of the disease<sup>248-257</sup>, in such cases the peripheral nerves show direct invasion,<sup>172</sup> something that must be exceedingly rare in sarcoidosis if it occurs at all.

Some efforts have been made to analyze this problem on the basis of immunologic reactions. Weeks and Smith<sup>258</sup> performed skin tests on 10 proved cases of sarcoidosis. They found 6 to be negative to both lepromin and tuberculin, whereas 2 were positive to both. Of 5 other cases similarly tested by Harrell and Horne,<sup>259</sup> 2 were negative to lepromin, and 3 gave a faintly positive reaction considered nonspecific, of the latter, 2 were tuberculin positive as well. Thus, in practically all 15 cases, the results with lepromin either were negative or could be explained on the basis of a cross reaction with tuberculin, which has been demonstrated to exist by a number of investigators.<sup>260-262</sup> This is in marked contrast with the fact that, unlike the frequently weak or negative tuberculin reactions seen in sarcoid patients, the lepromin reactions in the tuberculoid (or sarcoid) forms of leprosy are strongly positive in 90 to 100 per cent of cases.<sup>248-252-253</sup> Fifteen

cases are admittedly a small sample on which to base conclusions, but in view of these findings it seems highly unlikely that, in this country at least, the tuberculoid form of leprosy masquerades as sarcoidosis in any appreciable number of patients. In such cases, the lepromin test might be expected to prove a useful aid in diagnosis.<sup>259</sup>

### Other Infectious Diseases

A number of granulomatous diseases known to be capable of wide dissemination have also come under suspicion, and several have been shown to exist in a sarcoid form. In all such cases organisms may be very difficult to find, and, as in tuberculosis and leprosy, both the prompt destruction of the organisms and the morphologic character of the lesions may be explainable by the same altered immunologic status of the host. Regardless of etiologic relation, however, the various disseminated granulomas frequently pose a difficult problem in differential diagnosis, and it is certain that they have been confused with sarcoidosis on more than one occasion.

**Brucellosis** In view of its ability to involve practically every organ in the body, its frequently low-grade chronic course, its association with non-caseating granulomas and its world-wide distribution, brucellosis has been considered a possible cause. It is quite possible that typical sarcoid lesions may be produced, though the usual lesions tend to be much less distinct with proliferation of cells of the reticuloendothelial system, and occasionally suppuration.<sup>264</sup> Pulmonary involvement may resemble that of sarcoidosis,<sup>265</sup> iridocyclitis may occur, and the bones may be involved as well, the characteristic bone changes of sarcoidosis have not been described, however. In the cases in which specific skin or agglutination tests have been performed they have all been negative, and Harrell<sup>42</sup> found that guinea pigs injected with tissue from sarcoid patients remained negative to brucellergin. These arguments do not, of course, constitute proof but simply indicate that brucellosis in its usual form is not sarcoidosis. It is well known that failure to culture the organism or to obtain positive skin or agglutination tests does not necessarily rule out the disease,<sup>264</sup> whereas, on the other hand, occasional positive findings might indicate little more than their coexistence.

**Syphilis** A number of cases reported as cutaneous sarcoidosis may have been due to syphilis.<sup>266-267</sup> As noted above, however, the serologic reactions are negative in the large majority of sarcoid patients so that it seems unlikely that syphilis can be the responsible agent in any appreciable number of cases.

**Mycoses** Some attempts have been made to implicate various yeasts and fungi as etiologic agents, usually on the basis of a similar pulmonary picture. Organisms such as aspergillus and

monilia have been found in the sputum of patients on occasion,<sup>30</sup> but these organisms are often saprophytic and do not necessarily possess etiologic significance. Cutaneous tests with blastomyces filtrates, monilia vaccine or coccidioidin, when done, have given negative or at best faintly positive results.<sup>42-47</sup>

Histoplasmosis occurs as a disseminated disease capable of involving most of the organs of the body and is now known to be world-wide in distribution.<sup>265</sup> It may also produce granulomatous lesions in which organisms are rare or absent.<sup>269</sup> The much higher incidence of histoplasmosis in infants and young children, the high male-sex incidence in the adult, the common presence of mouth and gastrointestinal lesions, the rarity of eye lesions and the high susceptibility of most laboratory animals<sup>265</sup> are findings at considerable variance with those of sarcoidosis, as in tuberculosis and brucellosis, however such data prove only that the usual form of histoplasmosis is not sarcoidosis.

Tornell<sup>270</sup> has pointed out the resemblance between the radiologic picture of the lung in sarcoidosis and that of "thresher's lung," a form of moniliasis, or possibly histoplasmosis, due to inhalation of burnt grain. This disease is acute, but he suggests that chronic exposure of susceptible persons to moldy dusts, as in cellars and attics, could produce a similar picture. Since the pulmonary picture of sarcoidosis is nonspecific, however, such arguments are unconvincing. The same thing may be said for such equally nonspecific manifestations as erythema nodosum, the occurrence of which in both sarcoidosis and coccidioidomycosis led Kerley<sup>168</sup> to suggest an etiologic relation.

**Leishmaniasis** Sarcoid forms of leishmaniasis have been described,<sup>271</sup> and certain clinical features such as hepatosplenomegaly and hyperproteinemia are suggestive. This seems an unlikely cause in most cases, however. Careful searches have been made for the organism in some cases without success,<sup>24</sup> but in some known cases of leishmaniasis, organisms may be very rare and difficult to find.<sup>272</sup>

**Virus diseases** The inability to identify organisms in the lesions of most cases has suggested a virus etiology to some authors. Attempts to implicate the virus of lymphogranuloma inguinale by means of the Frei test, at least, have usually been negative. The Kveim antigen, at first regarded as strong evidence for a virus etiology, has been shown to be nonspecific and highly thermostable.<sup>206-208</sup> If a virus is indeed the cause of sarcoidosis, it has yet to be demonstrated.

#### *Inorganic Agents*

The resemblance of the pulmonary forms of sarcoidosis to some of the pneumoconioses has suggested that they are related. The clinical course of silicosis, as well as the absence of silica in abnor-

mal amounts in the sarcoid lesions, seems to rule this out rather definitely. Sarcoidosis has been described in association with asbestosis on at least one occasion,<sup>273</sup> but the two types of lesions appeared distinct.

**Beryllium** The chronic form of a pulmonary disease occurring in workers exposed to compounds of beryllium bears sufficient resemblance to sarcoidosis to have suggested their identity to some authors.<sup>274</sup> The pulmonary picture may, in its later stages at least, closely simulate the roentgenologic findings of sarcoidosis, and some patients have also exhibited hilar and peripheral adenopathy, enlarged liver and spleen, and skin lesions. Moderate elevations in serum globulin and calcium have been observed, and in 1 case an elevated blood calcium was associated with renal stone.<sup>275</sup> Tuberculin tests have also been negative in a number of cases.<sup>276</sup> On histologic examination, granulomatous lesions composed of epithelioid and giant cells have been found in the lungs, lymph nodes, liver and skin, and deep-staining, concentrically laminated inclusion bodies of the type described by Schaumann in sarcoidosis have also been seen.<sup>72-73</sup>

Claims for identity of the two conditions, as with other suggested etiologic agents, stress individual similarities and ignore the clinical picture as a whole. Unlike the usual case of sarcoidosis, which tends to be asymptomatic or practically so, the so-called delayed chemical pneumonitis or pulmonary granulomatosis is characterized by severe dyspnea, anorexia, weight loss, gastrointestinal disturbances and often cough and cyanosis. The disease is frequently progressive to the point of incapacitation, and cor pulmonale with right-sided heart failure frequently supervenes. In 45 cases collected by Hardy,<sup>276</sup> at least 7 patients died, and only a few recoveries after prolonged illness have so far been reported. Bone lesions have not been seen. Even the roentgenographic picture of the lungs resembles sarcoidosis only in its later stages and, as such, is hardly pathognomonic, whereas the earlier "sand-storm" appearance has been considered by some to be entirely unique.<sup>77, 77</sup>

Histologic examination of the lungs of these patients reveals granulomatous lesions, but the general picture bears only a superficial resemblance to that of sarcoidosis. Similar granulomas have been seen in lymph nodes and other organs. Histologic lesions closely simulating those of sarcoidosis have been noted in the skin of 2 patients with the chronic pulmonary disease, and in 3 others who cut themselves on broken fluorescent lamps.<sup>77</sup> In most of these lesions, however, foci of necrosis of a type never seen in sarcoidosis have been present. The relatively limited exposure to beryllium compounds makes this an unlikely cause for any great number of sarcoid cases, particularly since sarcoidosis obviously antedates the wide-

spread industrial use of beryllium. Nevertheless it is possible that a few cases, particularly some with marked pulmonary fibrosis, dyspnea and cor pulmonale, have been so caused. The long delay in onset following exposure — up to five years in some cases — and the occurrence of the disease in persons who have lived close to, but never worked in, factories using beryllium<sup>276 278</sup> may account in part for failure to obtain a history of exposure in such patients.

#### *Nonspecific Agents*

Localized sarcoid lesions have been observed following a wide variety of nonspecific stimuli, including the introduction into the tissues of such substances as paraffin and various medicated oils<sup>279-281</sup> morphine, iron and arsenic preparations,<sup>282 283</sup> and glass and stone fragments<sup>75 76</sup>. Similar lesions have been noted at the sites of previous operations<sup>29</sup> or after trauma without known introduction of foreign substances into the tissue<sup>76</sup>. In many of these cases the histologic descriptions are inadequate, and some of them may simply represent foreign-body reaction, a few, however, have been of characteristic sarcoid structure. The granulomas are of the subcutaneous type, infiltrating connective tissue and muscle, and have in the past been grouped with the subcutaneous sarcoids of the so-called Darier-Roussy type. Giant cells may be numerous, and often contain asteroid or refractile inclusions. An interesting feature in most of these cases has been the long latent period between the traumatic episode and the onset of the lesion — varying from months to many years, a few have recurred after incomplete excision. It is possible that some of the isolated sarcoid lesions in the intestinal tract and other areas, as well as the local skin lesions produced by beryllium compounds, belong in this category.

Since the other features of sarcoidosis have not been associated, there is no justification for such a diagnosis in these cases. The wide variety of agents that seem capable of inducing such reactions — and the agent producing disseminated sarcoidosis appears to be only one — suggests some common underlying mechanism in their formation. Phospholipids, either introduced into the body or freed nonspecifically at the site of reaction, may represent such a common factor,<sup>22 176 284</sup> though in at least one study such substances have failed to cause characteristic reactions in patients with sarcoidosis<sup>287</sup>. It is possible, too, that foreign material capable of inducing a local histiocytic or reticuloendothelial response in some cases provides a site for localization of the etiologic agent of sarcoidosis during periods of dissemination such a phenomenon is suggested by the occurrence of positive Heim reactions only in patients with active disease. Whatever the responsible agent, however, an altered state of reactivity, either constitutional

or acquired — in effect, the *terrain sarcoidique* of the early French authors<sup>288</sup> — may well be a contributory factor in the genesis of the lesions.<sup>4 83 286</sup>

*Allergy.* Certain features of sarcoidosis, such as the so-called tuberculin anergy and the occasional occurrence of such allergic manifestations as eosinophilia and erythema nodosum, suggest that hypersensitivity plays a role in the disease. There is recent experimental evidence to indicate that granulomas of histiocytic and even epithelioid character are associated with anaphylactic response<sup>287</sup>. Teilum<sup>82</sup> has also postulated an allergic basis for the hyalinization of sarcoid lesions. According to this concept, such changes are related to the hyperglobulinemia, and have as their starting point a globulin precipitate, especially in the reticuloendothelial system, these precipitates are gradually transformed, either within or outside the granuloma, into a homogeneous substance resembling amyloid (paramyloidosis or hyalinosi). Similar changes are described in other disorders associated with hyperglobulinemia such as Letterer-Siwe's disease, lupus erythematosus and lymphogranuloma inguinale and are interpreted as the result of persistent and repeated stimulation of immune mechanisms.

\* \* \*

Progress in the understanding of sarcoidosis in recent years has largely been limited to clarification of the clinical picture and recognition of some of the pitfalls in diagnosis. It has been amply demonstrated that no single feature of the disease is sufficient for diagnosis, and many errors have been made through the too-frequent substitution of the part for the whole. The pulmonary roentgenographic picture may be simulated by erythema nodosum, the mycoses, beryllium granulomatosis and a host of other conditions, the bone lesions by leprosy, the histologic picture by many agents both specific and nonspecific.

Most of the features of the disease are consistent with those of a chronic infection having a special predilection for the tissues of the reticuloendothelial system. Even the electrophoretic patterns obtained in examination of the blood proteins have been similar to those seen in other chronic infections, and a differential diagnosis between sarcoidosis and other widely disseminated infections is often exceedingly difficult. It is these close resemblances in fact, that have given rise to most of the etiologic theories. Clinical diagnosis is further complicated by the fact that the disease progresses and regresses irregularly, with various localizations becoming evident or disappearing without definite temporal relation, or even stabilizing for long periods. It may therefore be necessary to follow some suspects for a considerable time before characteristic localizations make their appearance and definite diagnosis is possible. Obviously the

greater the number of such localizations, the more certain the diagnosis will be

Considerable confusion has also resulted in the past from the assumption that the morphologic appearance of the lesion is pathognomonic. When typical, the sarcoid lesion is highly characteristic, but many cases show sufficient departure from the generally accepted norm to make histologic differentiation from miliary tuberculosis, brucellosis or other granulomatous disease practically impossible. So little is actually known of the genesis of these lesions, particularly their early phases, that the extent of permissible variation is still largely a matter of conjecture, and pathologists disagree considerably among themselves regarding the morphologic criteria for diagnosis.

Even granting the presence of a typical sarcoid lesion, this alone cannot be construed to constitute diagnostic proof. A wide variety of agents, of which the unknown cause of sarcoidosis appears to be only one, seem capable of inducing the characteristic granuloma, and it has become increasingly clear that a careful distinction must be made between the "sarcoid lesion" and the disease "sarcoidosis." The evidence provided by biopsy is essential, but constitutes only one link in the chain of evidence required in making a reliable diagnosis.

The Kveim test, which has been found to be positive in a fair percentage of patients with active sarcoidosis, seems to be a significant recent development. The test in its present form is not especially practical as a means of diagnosis, but it may well shed some much needed light on the question of pathogenesis. In particular, the nonspecific character of the Kveim antigen raises again the question of altered tissue reactivity on the part of the host, a condition that may also account for the well known and puzzling tuberculin insensitivity of many patients. Preoccupation with tuberculin, unfortunately, has resulted in too little investigation of reactivity to other substances, and it is possible that sarcoid patients tested in appropriate endemic areas might show a refractiveness to coccidioidin, histoplasmin or lepromin of the same order as that to tuberculin. The sporadic tests so far performed with such substances have usually been negative but as a rule have been done in nonendemic areas. Any such group would, of course, require careful diagnostic screening since all these conditions can simulate sarcoidosis in one way or another.

The etiologic issue is still far from solution and has made little or no progress in more than twenty years. The tubercle bacillus and some unknown agent, perhaps a virus, remain the most favored possibilities but no real proof has yet been offered. An organism of the brucella group may also be involved. Whether further careful bacteriologic or viral studies, or study of inoculated animals for longer periods, will shed more light on this issue

remains to be seen, but this approach does not seem to be particularly hopeful at present.

## REFERENCES

- 228 Jadassohn W. L'origine tuberculeuse de la maladie de Boeck. *Bull. Soc. franç. de dermat. et syph.* 41 1344-1347 1934
- 229 Gardner L. U. Similarity of lesions produced by silica and by tubercle bacillus. *Am. J. Path.* 13 13-24 1937
- 230 Schaumann J. Observations cliniques bactériologiques et sérologiques pour servir à l'étude de la lymphogranulomatose bénigne. *Bull. Soc. franç. de dermat. et syph.* 41 1296-1322, 1934
- 231 Hollister W. F. and Harrell G. T. Generalized sarcoidosis of Boeck accompanied with tuberculosis and streptococcal bacteremia. Clinicopathologic study with autopsy and animal inoculations. *Arch. Path.* 31 178-188 1941
- 232 Rich <sup>ss</sup> P. 369
- 233 Calmette A. La vaccination préventive contre la tuberculose par le BCG 250 pp. Paris: Masson et Cie 1927
- 234 Courcoux A., Boulenger P. and Maclouf A. C. Durée de l'allergie cutanée conférée par le BCG. *Rev. de la tuberc.* 9 60 1944
- 235 Willis H. S. Studies on immunity to tuberculosis: waning of cutaneous hypersensitivity to tuberculin and relation of tuberculin immunity to tuberculoallergy. *Am. Rev. Tuberc.* 17 240-252 1928
- 236 Rothschild H., Friedenwald J. S. and Bernstein C. Relation of allergy to immunity in tuberculosis. *Bull. Johns Hopkins Hosp.* 54 232-276 1934
- 237 Birkhaug K. *Allergic Immunity in Experimental Tuberculosis* 61 pp. Bergen: A. S. John Griegs Boktrykkeri 1940
- 238 Schwabacher H. and Wilson G. S. Vaccination of guinea pigs with living BCG together with observations on tuberculous superinfection in rabbits. *J. Path. & Bact.* 46 533-547 1938
- 239 Wells A. Q. and Brooke W. S. Effect of vaccination of guinea pigs with vole acid fast bacillus on subsequent tuberculous infection. *Brit. J. Exper. Path.* 21 104-110 1940
- 240 Sohler R. and Gregoire J. Remarques sur le comportement après vaccination par le BCG SP de deux sujets atteints de maladie de Besnier-Boeck-Schaumann. *Bull. et mem. soc. méd. d'hop. de Paris* 61 315 1945
- 241 Duprez, C. Sur les relations entre l'allergie et l'immunité dans l'infection tuberculeuse. *Compt. rend. Soc. de biol.* 117 834-836 1934
- 242 Martenstein H. Sarkoid Boeck und Lupus pernio. *Arch. f. Dermat. u. Syph.* 147 70-99 1924
- 243 Rich <sup>ss</sup> P. 303
- 244 Pinner M., Weiss M. and Cohen A. C. "Procutis" and "antracosis." *Yale J. Biol. & Med.* 15 459-463 1943
- 245 Ramel E. D'un lupus pernio (type Schaumann) probablement déterminé par un bacille tuberculeux de type bovin. *Bull. Soc. franç. de dermat. et syph.* 41 1332-1344 1934
- 246 Danheft N. and Brandt, A. Sarkoidähnliche Hauttuberkulose durch Hühnertuberkelbacillen hervorgerufen. *Arch. f. Dermat. u. Syph.* 178 76-86 1938
- 247 Brooke W. S. and Day R. Skin sensitivity to mycobacterial tuberculin in sarcoidosis. *Bull. Johns Hopkins Hosp.* 72 101-107 1943
- 248 Pardo-Castello, V. and Tiant F. R. Leprosy: correlation of its clinical, pathologic, immunologic and bacteriologic aspects. *J. A. M. A.* 121 1264-1269 1943
- 249 Pautner L. M. Leprosy: a histologie of sarcoid dermique. *Bull. Soc. franç. de dermat. et syph.* 41 1284-1291 1934
- 250 Rabello Jr. Données nouvelles pour l'interprétation de l'affection de Besnier-Boeck: rôle de la lepre. *Ann. de dermat. et syph.* 7 571-597, 1936
- 251 Foreign Letters. Rio de Janeiro. Etiology of Besnier-Boeck's disease. *J. A. M. A.* 105 1205 1934
- 252 Rabello E. and Rabello Jr. Une classification clinico-épidémiologique des formes de la lepre. *Rev. bras. de leprol.* 6 229-233 1938
- 253 Balina, P. L. and Basombrio G. Classification des formes cliniques de lepre. *Rev. bras. de leprol.* 6 275-228 1938
- 254 Jadassohn <sup>ss</sup> P. 1293
- 255 Reensterna J. Possible role of leprosy in etiology of Besnier-Boeck's sarcoid and Schaumann's syndrome. *Internat. J. Leprosy* 5 433-436 1937
- 256 Wade H. W. Leprosy and sarcoid. *Internat. J. Leprosy* 5 503-507 1937
- 257 Fox, H. Discussion of Pardo-Castello and Tiant's.
- 258 Weeks K. D. and Smith D. T. Lepromin skin tests in Boeck's sarcoid. *Am. J. Trop. Med.* 25 519-521 1945
- 259 Harrell G. T. and Horne S. F. Reaction to lepromin of patients with sarcoid or tuberculosis compared with that of patients in general hospitals, with discussion of mechanism of reaction. *Am. J. Trop. Med.* 25 523-533 1945
- 260 Fernandez, J. M. M. Estudio comparativo de la reacción de Mitsuda con las reacciones tuberculínicas. *Rev. argent. dermatol.* 23 425-453 1939
- 261 Idem. Influencia del factor tuberculosis sobre la reacción a la lepromina. *Rev. argent. dermatol.* 1939 425-460 1943
- 262 Rotberg A. Estudios sobre as reações tuberculínicas na lepra. *Rev. bras. de leprol.* 6 245-272 1938
- 263 Fernandez, J. M. M. Early reaction induced by lepromin. *Internat. J. Leprosy* 8 1-14 1940
- 264 Harris H. J. *Brucellosis (Undulant Fever)*. Clinical and subclinical 286 pp. New York: Paul B. Hoeber Inc. 1941

25. Harvey W A Pulmonary brucellosis *Ann Int Med* 28 768-781 1948
26. Frazer C N and Hu C K. Isolation of *Treponema pallidum* from subcutaneous sarcoid *Proc Soc Exptl Biol & Med* 30 898-901 1935
27. Nicolas J, Massia G and Petouraud C. Les sarcoïdes syphilitiques *J de med de Lyon* 14 295-304 1953
28. Parsons R J., and Zarafonitis C. J. D. Histoplasmosis in man: report of 7 cases and review of 71 cases *Arch Int Med* 75 1-2 1944
29. Fickerton H. Histoplasmosis reticuloendothelial cytomycosis histoplasmosis of Darling cytomycosis of Darling. In *Oxfo Medicine* New York Oxford University Press Vol 5 Part 2 P 422 (7-18) 1944
30. Tetzell E. Is sarcoidosis fungoid disease? *Acta tuberc Scand* 20 212 255 1946
31. Dupont, A. Leishmaniose cutanee a structure histologique de sarcoïde de Boeck. *Bull Soc franç de dermat. et syph* 41 1291-1294 1944
32. Belin C. Leishmaniasis recidiva cutis leishmanid. *Arch. Dermat & Syph.* 41 874-886 1940
33. Skavlen J H., and Ritterhoff R. J. Coexistent pulmonary asbestosis and sarcoidosis. *Am J Path* 22 495-517 1946
34. Higgins H. L. Pulmonary sarcoidosis. *Connecticut M J* 11 350 359 1947
35. Hardy H. L. and Tabershaw I R. Delayed chemical pneumonitis occurring in workers exposed to beryllium compounds *J Indust Hyg & Toxicol* 28 197-211 1946
36. Hardy H. L. New clinical syndrome delayed chemical pneumonitis occurring in workers exposed to beryllium compounds *Bull New Eng M Center* 9 16-24 1947
37. Soiman M and Wilson S. Cited by Hardy and Tabershaw
38. Gelman I. Poisoning by vapors of beryllium oxyfluoride *J Indust Hyg & Toxicol* 18 371-379 1956
39. Gougerot H. Nombre de 'grossièmes' thérapeutiques sont des sarcoïdes tuberculeux. Deux cas de guérison par des vaccins antituberculeux. *Rev ger de der et d'orthop* 44 145-149 1950
40. Idem. Sarcoïdes par corps étrangers *Bull Soc franç de dermat et syph* 41 1370-1379 1954
41. Joltrain. Sarcoïdes sous-cutanées consécutives à injection huileuse *Bull Soc franç de dermat. et syph* 41 1384-1391 1954
42. Oppenheim, M. Riesenzellentumoren nach subkutanen Einspritzungen eines Arsen Eisenpräparates *Arch f Dermat u Syph* 116 459-446 1913
43. Idem. Knoten- und Strangbildungen nach Morphiuminjectionen (Pseudo-sarkoid) *Arch f Dermat u Syph* 137 86, 1921
44. Curtis A C. Discussion of Michelson
45. Dayer M J. Considerations sur la nature des sarcoïdes *Bull Soc franç de dermat et syph* 41 999-1002 1954
46. Levi-Luxardo I and Fegiz G. Malattia di Boeck, Besnier Schumann. *Arr Ist Carlo Forlaris* 10 201-220 1947
47. Goddard, I W. Granuloma characteristic 'qualitative change in focal anaphylactic inflammation' *Am J Path* 23 945 965 1947

## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

TRACY B MALLORY MD, Editor

BENJAMIN CASTLEMAN, MD, Associate Editor

EDITH E PARRIS, Assistant Editor

### CASE 34461

#### PRESENTATION OF CASE

**First admission.** A five-year-old girl was admitted to the hospital with a small nonpainful lump in the right axilla which had been present for a year and had increased in size over this period and spread up under the clavicle. Immediately before admission to this hospital the child had been taken to a clinic because of tonsillitis. Chest x-ray films were reported at this time to show an "intrathoracic tumor." An exploratory operation showed "a gravish, rosy, polycystic mass." The outer portion was attached to the fibers of the pectoralis major, and the inner portion extended deep to the pectoralis and disappeared under the clavicle. Following this the patient was admitted to this hospital.

Physical examination showed a moderately well nourished underdeveloped child. The right pupil was smaller than the left and eccentrically placed. There were numerous large pigmented areas over the entire body, with the exception of the lower extremities. The superficial veins of the right upper chest were prominent and the right arm appeared cyanotic. Masses were present immediately beneath the skin in the right axilla and in the right

supraclavicular fossa. The right upper chest was dull anteriorly and posteriorly, and the breath sounds were decreased. At the extreme apex there was an area of bronchial breathing. The pulse at the left wrist was greater than that on the right. The only positive neurologic finding was weakness of the right hand. Urine and blood examinations were negative. A chest x-ray examination was reported as follows: "Findings are those of a large mass in the upper mediastinum rising posteriorly, probably lobulated, a smaller lobe being on the left side, with soft-tissue masses in the right supraclavicular and right axillary region." An operation was performed through a paravertebral approach and portions of the second, third and fourth ribs on the right were resected. The tumor was found to be a neurofibroma of the invasive type, but a large portion was removed and the brachial plexus was freed. The patient did well postoperatively and was discharged on the twenty-fourth hospital day.

**Final admission** (twelve years later). In spite of the progressive character of the disease, resulting in increasing skeletal deformity, exertional dyspnea and also apparent hypogonadism, the patient completed school and was able to accept summer employment. In this interval she received some radiation treatment. One year before admission while being followed at another clinic the tumor in the right side of the neck began painlessly to increase in size. Four weeks before admission her voice weakened and became hoarse. Two weeks before admission she suddenly awakened with extreme shortness of breath. This was not associated with pain or cough or sputum and since then she had slept in a semi-squatting position with her legs tucked under her. Following this she noted swelling around the eyes, face and neck, most marked in the morning, and most severe on the left side. Difficulty in swallowing large mouthfuls was noted and severe supraorbital headaches, worse at night than

in the morning. There was no history of chills, fever or weight loss.

On physical examination the patient was poorly developed, orthopneic and markedly kyphoscoliotic. There were small plaques of pigmentation over the arms and trunk, with a marked area extending from the anterior axillary line at the level of the nipple extending along the medial surface of the right arm and involving the axilla. A firm, smooth fixed mass, 15 cm in its longest diameter, was present in the right supraclavicular area. There were small, shotty nodules in the right axilla and beneath the skin along the posterior axillary line. The superficial veins of the neck on both sides were distended, and the veins of the right hand failed to empty on full elevation. The blood pressure was 110 systolic, 80 diastolic, in both arms. The left border of the heart reached the left anterior axillary line. The temperature, pulse and respirations were normal. There was extreme weakness and areflexia in the right upper extremity. There was marked sexual underdevelopment. An electrocardiogram was normal. An x-ray examination of the chest was reported as follows: "There is marked, severe kyphoscoliosis of the dorsal lumbar spine so that the heart is on the right side of the thorax. Size and shape of the heart cannot be determined because of the severe deformity. There has been partial resection of the right upper ribs. A soft-tissue tumor is present over the dorsum of the right side of the chest." Urinalysis was negative. Blood examination showed a hemoglobin of 12.5 gm, and a white-cell count of 11,000, with a normal differential.

While in the hospital she developed rather severe precordial pain, which was pounding in character and located over the apex. There was very little that could be done for this girl except to supply sedation. On the eighth hospital day while she was sleeping at night it was noted by the nurse that respirations had stopped but the pulse was still present. Resuscitation measures were of no avail.

#### DIFFERENTIAL DIAGNOSIS

DR. EARLE M. CHAPMAN: May we see the x-ray films?

DR. JOSEPH HANELIN: There is an extremely severe spinal deformity, rather marked kyphoscoliosis or perhaps mostly scoliosis. The heart is just visible within the right thorax. There have been resections of the right upper ribs, and some rib regeneration has taken place. There is no obvious explanation for the scoliosis in the way of any structural or bony abnormality. There is evidence of a soft-tissue tumor in the right side of the thorax. There is a mass in the region of the right axilla. In the lateral view of the chest, which includes a large part of the patient, the abdomen appears to be somewhat protuberant. There is soft-tissue density present, with a lobulated appearance, which is observed to extend through the dorsal aspect of the

thoracic wall. I cannot be certain that this lesion is within the thoracic cavity although this is a general situation and cannot be interpreted particularly without stereoscopic films because of the marked deformity.

DR. CHAPMAN: May I ask if you see any area in the bony structure that suggests metastatic or destructive lesions?

DR. HANELIN: No, I do not.

DR. CHAPMAN: Do you see any lesions in the vertebral column?

DR. HANELIN: No, I see no lesions at all in the vertebrae.

DR. CHAPMAN: Is this a right dorsal kyphoscoliosis?

DR. HANELIN: It is to the left.

DR. JOSEPH AUB: May I add some information that Dr. Chapman ought to have? The patient had extreme cyanosis of the face and really had an enormous amount of dyspnea, which I do not think the record makes clear.

DR. CHAPMAN: From the evidence at hand it seems to me that this girl suffered from two diseases, either one of which alone would have brought about her death, and certainly both together have done so. The first is that she had multiple neurofibromatosis of the invasive type, diagnosed histologically here in this hospital twelve years before death. Then on top of these tumors that no doubt were multiple, she had an increasing deformity of the chest, which we are told was a left kyphoscoliosis compressing the lungs and the soft tissues within the chest to the point where the vital capacity was greatly diminished. Life was a battle. She was struggling to live in the face of great diminution of the pulmonary reserve, and she must have had what I once called pulmonocardiac failure.<sup>1</sup> The interference with breathing, the cyanosis and the description here indicate that there was also occlusion of venous return in the superior mediastinal region. One would think that the tumor produced a superior mediastinal syndrome more marked on the right than on the left according to the description. Beyond that I think any remarks are purely speculative as to what might be found at autopsy. I think, however, the description of the hypogonadism and the statement of the sexual underdevelopment warrant a few remarks. I would like to have information, for instance, whether or not the 17-ketosteroids were determined. I judge they were not done.

DR. JACOB LERMAN: No.

DR. CHAPMAN: There are perhaps androgen-producing tumors of the adrenal glands that could produce some of the signs present. One wonders if neurofibroma was present in the adrenal area or if one or both of the adrenal glands were involved in this type of tumor. One wonders if she had some other type of hormonal tumor of the adrenal cortex, producing the so-called adreno-

genital syndrome which comes on after puberty. At the age of seventeen her changes could go with a disordered pituitary function, and the signs are not classic of a type of adrenal tumor that comes on after puberty or before puberty. I see no way to include or exclude these possibilities. We have no index from the laboratory procedures recorded. I think this girl's death was due to progressive failure of the lungs, and it got to the point finally where she did not have enough respiratory exchange to survive.

Did she have some disease in the coronary arteries? You will recall that later in the history it says that she suffered from precordial pain which was pounding in character and located over the apex despite the previously normal electrocardiogram. I assume that the electrocardiogram was taken before that pain, although the record is not clear on that point. One wonders about coronary occlusion with myocardial infarction as a terminal episode. This form of accident in kyphoscoliotics is unusual, in fact, it is rare. The patients usually die and at autopsy the heart is found to be hypertrophied chiefly in the right ventricle and even in the right auricle, and yet seldom do they have signs of coronary-artery disease and likewise seldom, if ever hypertension, although a few have been described in which the hypertension is present in addition to a pulmonocardiac syndrome.

I can add very little to this discussion. Perhaps you can, Dr. Aub. You saw her on the wards, and I think I have covered the possibilities that I can see in this case.

DR CHESTER M. JONES: Probably she had been more or less anoxic and increasingly so for quite a few years. That condition was present during puberty. Might not that in itself have been sufficient to account for the sexual immaturity and incomplete growth?

DR CHAPMAN: I do not know how one could tell, but that is a fair statement. In general, kyphoscoliotic patients who begin the deformity early in life continue to be immature, without great sexual development. It would be a possibility just as a matter of general nutrition and general metabolic processes being lowered, and the hypogonadism being a part of it. On the other hand, we have seen these patients come through life and bear children and seem quite normal sexually, or they have no such stigmas of endocrine dysfunction as this patient had.

DR TRACY B. MALLORY: Have you anything to add, Dr. Aub?

DR AUB: No. I agree with Dr. Chapman. We thought that the hypogonadism might be due to prolonged anoxia and cyanosis, but the sexual immaturity we blamed on the pituitary body, otherwise we reasoned the way Dr. Chapman did.

DR LERMAN: When she came on the ward she was a malnourished, underdeveloped pathetic

creature, very orthopneic and dyspneic. The picture of kyphoscoliosis was complicated by the neurofibromatosis which involved the superior mediastinum and the right chest, and produced superior mediastinal syndrome — marked distention of the neck veins and facial edema. It was our impression that the underdevelopment of the sex activity was related to the combination of anoxia and malnutrition.

DR MALLORY: Have you anything to add from the surgical point of view, Dr. Scannell?

DR J. GORDON SCANNELL: She was seen in the Thoracic Clinic with the question of possible superior mediastinal syndrome. Obviously nothing could be done.

DR LERMAN: It was our impression that the kyphoscoliosis developed probably from progressive paralysis of the intercostal nerve as it grew. The kyphoscoliosis had been present for many years.

#### CLINICAL DIAGNOSES

Pulmonocardiac failure  
Neurofibromatosis  
Superior mediastinal syndrome

#### DR CHAPMAN'S DIAGNOSES

Multiple neurofibromatosis, invasive type  
Kyphoscoliosis, left-sided  
Pulmonocardiac failure  
Androgen-producing tumor of adrenal gland

#### ANATOMICAL DIAGNOSES

*Neurofibrosarcoma, with invasion of right innominate vein and superior vena cava*  
Superior-vena-cava obstruction  
Left dorsal scoliosis  
Pulmonary atelectasis  
Hypogonitalism  
Hyperplasia of adrenal glands

#### PATHOLOGICAL DISCUSSION

DR MALLORY: At post-mortem examination a very large tumor was found in the axilla and upper mediastinum on the right side. It was very difficult in the midst of the multiple lobules of the tumor to identify normal structures. We were unable to identify the vagus or the phrenic nerves. The carotid arteries passed through the tumor and were apparently uninvolved except perhaps by pressure. The internal jugular vein could not be identified, and the innominate vein appeared to be completely occluded by a mass of tumor tissue, which dangled down the superior vena cava to within about a centimeter of its mouth into the auricle. The brachial plexus was unrecognizable in the midst of the tumor, and there was enough tumor within the thoracic cage to have caused extensive collapse of the right lung. The heart was quite small, as were

in the morning. There was no history of chills, fever or weight loss.

On physical examination the patient was poorly developed, orthopedic and markedly kyphoscoliotic. There were small plaques of pigmentation over the arms and trunk, with a marked area extending from the anterior axillary line at the level of the nipple extending along the medial surface of the right arm and involving the axilla. A firm, smooth, fixed mass, 15 cm in its longest diameter, was present in the right supraclavicular area. There were small, shotty nodules in the right axilla and beneath the skin along the posterior axillary line. The superficial veins of the neck on both sides were distended, and the veins of the right hand failed to empty on full elevation. The blood pressure was 110 systolic, 80 diastolic, in both arms. The left border of the heart reached the left anterior axillary line. The temperature, pulse and respirations were normal. There was extreme weakness and areflexia in the right upper extremity. There was marked sexual underdevelopment. An electrocardiogram was normal. An x-ray examination of the chest was reported as follows: "There is marked, severe kyphoscoliosis of the dorsal lumbar spine so that the heart is on the right side of the thorax. Size and shape of the heart cannot be determined because of the severe deformity. There has been partial resection of the right upper ribs. A soft-tissue tumor is present over the dorsum of the right side of the chest." Urinalysis was negative. Blood examination showed a hemoglobin of 12.5 gm., and a white-cell count of 11,000, with a normal differential.

While in the hospital she developed rather severe precordial pain, which was pounding in character and located over the apex. There was very little that could be done for this girl except to supply sedation. On the eighth hospital day while she was sleeping at night it was noted by the nurse that respirations had stopped but the pulse was still present. Resuscitation measures were of no avail.

#### DIFFERENTIAL DIAGNOSIS

DR EARLE M. CHAPMAN: May we see the x-ray films?

DR JOSEPH HANELIN: There is an extremely severe spinal deformity, rather marked kyphoscoliosis or perhaps mostly scoliosis. The heart is just visible within the right thorax. There have been resections of the right upper ribs, and some rib regeneration has taken place. There is no obvious explanation for the scoliosis in the way of any structural or bony abnormality. There is evidence of a soft-tissue tumor in the right side of the thorax. There is a mass in the region of the right axilla. In the lateral view of the chest, which includes a large part of the patient, the abdomen appears to be somewhat protuberant. There is soft-tissue density present, with a lobulated appearance, which is observed to extend through the dorsal aspect of the

thoracic wall. I cannot be certain that this lesion is within the thoracic cavity, although this is a general situation and cannot be interpreted particularly without stereoscopic films because of the marked deformity.

DR CHAPMAN: May I ask if you see any area in the bony structure that suggests metastatic or destructive lesions?

DR HANELIN: No, I do not.

DR CHAPMAN: Do you see any lesions in the vertebral column?

DR HANELIN: No, I see no lesions at all in the vertebrae.

DR CHAPMAN: Is this a right dorsal kyphoscoliosis?

DR HANELIN: It is to the left.

DR JOSEPH AUB: May I add some information that Dr. Chapman ought to have? The patient had extreme cyanosis of the face and really had an enormous amount of dyspnea, which I do not think the record makes clear.

DR CHAPMAN: From the evidence at hand it seems to me that this girl suffered from two diseases, either one of which alone would have brought about her death, and certainly both together have done so. The first is that she had multiple neurofibromatosis of the invasive type, diagnosed histologically here in this hospital twelve years before death. Then on top of these tumors that no doubt were multiple, she had an increasing deformity of the chest, which we are told was a left kyphoscoliosis compressing the lungs and the soft tissues within the chest to the point where the vital capacity was greatly diminished. Life was a battle. She was struggling to live in the face of great diminution of the pulmonary reserve, and she must have had what I once called pulmonocardiac failure.<sup>1</sup> The interference with breathing, the cyanosis and the description here indicate that there was also occlusion of venous return in the superior mediastinal region. One would think that the tumor produced a superior mediastinal syndrome more marked on the right than on the left according to the description. Beyond that I think any remarks are purely speculative as to what might be found at autopsy. I think, however, the description of the hypogonadism and the statement of the sexual underdevelopment warrant a few remarks. I would like to have information, for instance, whether or not the 17-ketosteroids were determined. I judge they were not done.

DR JACOB LERMAN: No.

DR CHAPMAN: There are perhaps androgen-producing tumors of the adrenal glands that could produce some of the signs present. One wonders if neurofibroma was present in the adrenal area or if one or both of the adrenal glands were involved in this type of tumor. One wonders if she had some other type of hormonal tumor of the adrenal cortex, producing the so-called adreno-

intestinal tract for three or four months, with one massive hemorrhage

Physical examination helps me very little, and the laboratory studies add little, at least to my interpretation of the problem

We might look at the x-ray films. The barium enema was done to explain the symptoms of abdominal cramps and distention and is reported as negative. The chest films were reported negative also, although on looking at them I wondered if she had dilatation of the great vessels.

DR JAMES J. McCORT: It is difficult to say much about the esophageal lesion on the single outside film available and without being able to fluoroscope the patient. On the film available we find that the proximal esophagus is dilated. This terminates in a narrowed area 3 cm in length. Below this is a fairly large hiatus hernia within which the rugal folds have the appearance of gastric mucosa. There is a suggestion of a shelf defect on the upper posterior margin of the narrowed zone in the lower third of the esophagus. The edge of the narrowed area is slightly irregular, it may be slightly nodular, but this is hard to tell, since there may be mucous flecks mixed with the barium. The lower margin does not show a shelf defect. There is possibly a soft-tissue tumor of the narrowed segment, but this cannot definitely be determined on the one film available. The remainder of the stomach and the duodenum do not show any abnormality.

DR SCANNELL: I wondered about the area that you agree is suggestive of a shelf. I am interested that you agreed that the duodenum, without palpation I realize, was normal. The presence of a duodenal ulcer might be an additional red herring.

DR McCORT: We do not have sufficient films to determine whether it is a persistent shelf defect. The lungs are clear. The heart is not enlarged. There is slight tortuosity of the aorta.

DR ALLAN M. BUTLER: Why could they not do fluoroscopic studies?

DR SCANNELL: These are outside films, and that is all the evidence we have.

DR RICHARD H. SWEET: The patient had an adequate study before entry to this hospital, and we thought it would be redundant to repeat it here.

DR BUTLER: That is a very satisfactory explanation.

DR SCANNELL: In this case of course we know that she had a diaphragmatic hernia, and the question is whether or not that would explain all her symptoms. One might suppose that it was incarcerated, and incarceration is certainly associated with bleeding and it can explain the esophageal obstruction. One can assume that it was the diagnosis and sufficient indication to warrant surgery on the basis of bleeding and obstruction, which are disabling. However, we are suspicious because of the change in character of the symptoms and because of the x-ray picture, which on the films avail-

able, is not that of an entirely smooth narrowing of the lower end of the esophagus. It is certainly true that we do not have to make a diagnosis of cancer because hiatus hernia is frequently associated with a good deal of esophagitis and benign stricture of the lower end of the esophagus. I do not know the exact number of cases, but the latter are frequently associated with infradiaphragmatic disease in the nature of a duodenal ulcer, or possibly disease of the biliary tract and, therefore, it is a tenable diagnosis in this patient. A diagnosis of benign disease would be all right if we could agree that it was smooth narrowing and even better if we could demonstrate a small, benign-appearing ulcer. But in any event we would have to visualize this area to satisfy ourselves whether or not carcinoma were present. I think that the question of a dilated and tortuous aorta encroaching on the hiatus is a theoretical possibility but most inadequate to explain the symptoms. An unusual lesion in this region might be lymphoma, which I assume may occur here, although I have never seen one, and specific or nonspecific inflammation in the nature of syphilis, but there is no evidence to make that diagnosis.

Therefore, I come back to whether or not this patient had a carcinoma in the esophageal hiatus hernia, and I am inclined to think that she had, in spite of the fact that she had a little dilatation of the esophagus, which she may have had with her hiatus hernia over the years and which, therefore, certainly does not rule out carcinoma. I am basing it chiefly on the fact that she had changes in her symptoms in a lesion that she had had for many years—also, on the x-ray picture, which first of all, I gather, is suggestive of a soft-tissue mass, although that could be omentum or something in the hiatus hernia, and secondly, is suggestive of an irregular narrowing of the lower end of the esophagus. Therefore, on the eighth hospital day this was either visualized through an esophagoscope or, if the patient was a good risk, exploration carried out for sufficient indications even disregarding the suspicion of cancer. But I think we are justified in making a diagnosis of probable carcinoma of the lower end of the esophagus.

DR TRACY B. MALLORY: Dr Sweet, will you tell us your clinical impression?

DR SWEET: There are several very interesting aspects to this case from the standpoint of the history as well as the findings at operation, one of which is that in my experience with carcinoma of the esophagus massive hemorrhages are exceedingly rare. They occur in carcinoma of the stomach, but I do not recall any from carcinoma of the esophagus. I have encountered one case of lymphoma of the esophagus. Although lymphoma in other parts of the gastrointestinal tract may cause massive bleeding, that particular patient had none.

Another thing about the history that Dr Scannell did not have the benefit of is that she had improved

all the other organs, and there was no evidence of right-sided heart hypertrophy or dilatation of the right auricle. We found no passive congestion of the liver, spleen or kidneys, such as one might expect to find with kyphoscoliotic heart disease. I do not think we can give a dogmatic opinion in this regard. To what extent this tumor of the vena cava may have been responsible for the cardiac symptoms, I do not know. It came so close to the auricle that, with slight change in posture, it is not inconceivable that it could have dipped into the auricle at times. It was quite evident that death was sudden because the liver showed the marked glycogenation that one ordinarily sees in patients who die suddenly with an acute coronary attack or pulmonary embolism. The spine showed no disease of the bone or intervertebral disks, and the scoliosis, I am sure, was functional rather than structural. The uterus was quite small and almost infantile in dimensions. The ovaries were small and showed only slight activity. There were a few small ova and graafian follicles but almost no scars of corpora albicantia. The pituitary body was small and grossly normal. The adrenal glands, in contrast, were quite large, probably slightly larger than normal, but otherwise not remarkable. From their histologic appearance I would expect excess rather than decrease of the adrenal function.

DR AUB: How about the pituitary body?

DR MALLORY: It appeared small but otherwise normal.

DR CHAPMAN: I am intrigued by what you said about the size of the adrenal glands in proportion to the other endocrine glands, and you are not able to estimate of course the degree of function from observation histologically.

DR MALLORY: No.

DR CHAPMAN: It is of considerable interest that Cahill<sup>2</sup> in a recent article reports that the most frequent cause of changes from excess androgen is bilateral adrenal hypertrophy and that "with the exception of survival time there is often no difference between the symptoms of bilateral adrenal hypertrophy and unilateral tumor."

#### REFERENCES

- 1 Chapman, E. M., Dill, D. B. and Graybiel, A. Decrease in functional capacity of lungs and heart resulting from deformities of chest, pulmonocardiac failure. *Medicine* 18:167-202, 1939.
- 2 Cahill, G. F. Cancer of kidneys, adrenals and testes. *J. A. M. A.* 138:415-425, 1948.

#### CASE 34462

##### PRESENTATION OF CASE

A fifty-seven-year-old woman entered the hospital complaining of attacks of heartburn, distention, indigestion and abdominal cramps, which had been present for a number of years.

In the four-year period prior to admission these symptoms had all increased in severity. In addition

she recently had palpitation, regurgitation of food and a sensation of food sticking in her chest. Walking relieved the symptoms. The discomfort and heartburn always followed meals. X-ray studies done elsewhere four years previously revealed a diaphragmatic hernia. In the three or four months prior to admission she had felt much weaker than usual and had black stools. The hemoglobin had repeatedly been found to be low. There was one episode when she became pale and went into shock and the hemoglobin dropped rapidly. This was treated by transfusion. There had been no weight loss.

On physical examination the heart was not enlarged. The chest and abdomen were normal.

The temperature, pulse and respirations were normal. The blood pressure was 120 systolic, 65 diastolic.

Laboratory examination revealed a normal urine and a guaiac-positive stool. The hemoglobin was 11.8 gm., and the white-cell count 13,000, with a normal differential. There was moderate variation in size of the red cells, platelets appeared slightly increased, there was no achromia. A chest x-ray film and barium enema were reported negative. A gastric series was done just prior to admission here. These outside films were interpreted here, without a fluoroscopy being done at this hospital, as showing a hiatus hernia and a smooth narrowing in the distal esophagus over a distance of 3 cm., with dilatation proximal to this point.

On the seventh hospital day an operation was performed.

#### DIFFERENTIAL DIAGNOSIS

DR J. GORDON SCANNELL: The problem boils down to that of a fifty-seven-year-old woman who had symptoms pointing to the esophagus. They were symptoms of irritation, obstruction and bleeding. Looking first at the historical evidence, I would consider the following to be of significance. First of all, there was increase in symptoms over a relatively short period, four years. "Recently," which is not defined, there were palpitation, regurgitation and esophageal obstruction. So we wonder if she did not have the change in gastrointestinal symptoms, a change that raises the question of new growth in the gastrointestinal tract or any system of the body. She apparently had heartburn for a good many years, as well as distention and abdominal cramps. The latter are hard to explain on the same basis as heartburn, a symptom of esophageal irritation. Another bit of historical evidence is that four years before admission a diagnosis of diaphragmatic hernia was made, which apparently did not raise the suspicion of cancer. We assume, therefore, that some change had taken place in the x-ray picture. Furthermore, there was significant blood loss through the gastro-

# The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established 1828

Official Organ of

THE MASSACHUSETTS MEDICAL SOCIETY

and

THE NEW HAMPSHIRE MEDICAL SOCIETY

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND

PUBLISHED WEEKLY UNDER THE JURISDICTION OF THE

COMMITTEE ON PUBLICATIONS

James P. O'Hare, M.D. Richard M. Smith, M.D., *Chairman*  
Oliver Cope, M.D. Conrad Wesselhoeft, M.D.  
John Fallon, M.D.

Joseph Garland, M.D. *Editor*

ASSOCIATE EDITORS

Thomas H. Lanman, M.D. Donald Munro, M.D.

Henry Jackson, Jr., M.D.

Clara D. Davies, *EXECUTIVE EDITOR*

Robert O'Leary, *ASSISTANT EDITOR*

EDITORIAL BOARD

C. Guy Lane, M.D. Maxwell Fiola, M.D.  
Henry R. Vicks, M.D. James M. Faulkner, M.D.  
Robert M. Green, M.D. Carroll B. Larsoo, M.D.  
Dwight O'Hara, M.D. Francis D. Moore, M.D.  
Fletcher H. Colby, M.D. C. Stuart Welch, M.D.  
Robert L. Goodale, M.D. Vernon P. Williams, M.D.  
Cecilia M. Jones, M.D. Benjamin Castleman, M.D.  
Harvey R. Morrison, M.D. Hugh R. Leavell, M.D.

**SUBSCRIPTION TERMS** \$7.00 per year in advance, postage paid, for the United States (medical students \$4.00 per year) Canada, \$8.00 per year (Boston funds) \$9.50 per year for all foreign countries belonging to the Postal Union.

**MATERIAL** should be received not later than noon on Thursday three weeks before date of publication.

**THE JOURNAL** does not hold itself responsible for statements made by any contributor.

**COMMUNICATIONS** including those concerning classified advertising but without other advertising should be addressed to the New England Journal of Medicine, 8 Fenway, Boston 15, Massachusetts. Telephone EE 6-2024.

**NEW ENGLAND ADVERTISING REPRESENTATIVE** (except for classified advertising) Edwin B. Tyler, 89 State Street, Boston, Massachusetts. Telephone LA 3 5516.

## CONCERNING THE DOCTOR DRAFT

THERE is good reason to believe that early in 1949 Congress will debate an amendment of the Selective Service Act to remedy the shortage of physicians in the newly expanded armed forces. What the public reaction will be, both medical and lay, remains to be seen, but already cries of distress and charges of discriminatory legislation are being faintly heard in medical circles. Although it is too soon to pass judgment on legislation not yet born, it may be permissible to indulge in a little basic thinking on some of the issues underlying any draft of doctors.

For example, it is well to bear in mind Congress's purpose in undertaking this postwar expansion. Primarily it is to put teeth into its belated efforts

to prevent World War III, and failing that to give the kind of civilization in which we all believe a reasonable chance for survival in what would amount to a war of extermination—at least of ideologies. These would appear to be objectives to which only our enemies could take reasonable exception but as the country has already learned to its cost no objectives however greatly desired, are attained by wishful thinking.

The magnitude of the stake must never be forgotten. By now it should be clear to everyone over twelve years old that if another world war is not prevented there will be no question of seizing grandpa's musket from over the fireplace and hastening to Concord or Lexington. Nor will it be simply a matter of providing medical officers for the armed forces, by draft or otherwise. Every man, woman and child will be involved, and there will be no time for claiming constitutional rights, because the very existence of constitutional government will be in the balance.

But we have not come to such a pass yet, and, please God, with wisdom and resolution we shall not come to it. Congress's contemplated action will concern chiefly doctors who were trained under ASTP and V-12 at Government expense but were unable to complete their term of active duty owing to the sudden (and as it now seems, premature) demobilization of the country's military force. If they should be required to complete their contract by a few months of peace-time service, it would seem too reasonable a sacrifice to be fairly resented.

While one indulges in basic thinking, it may be well also to contemplate the alternative method of enrollment for service in time of public need. The volunteer system, if system it may be called, may have the advantage of avoiding compulsion, but it has also certain glaring faults. It is unfair. It rewards the shirker, the parasite and the self-seeker while it penalizes the willing, the conscientious and the ready. Most citizens are glad to do their share of the dirty work so long as everyone else is doing his, but they dislike being played for suckers. Its second obvious defect is inefficiency. There can be no assurance that the person who volunteers is qualified, or even needed, for the job. Finally the volunteer system has been and still

considerably in the past two months as manifested by the facts that she had stopped bleeding and she had less pain. The symptoms were not progressive the way they are almost invariably in carcinoma. In quite a large series of cases of carcinoma of the lower end of the esophagus and cardia that we have operated on here, I do not recall the exact figures, but approximately 13 per cent arose in this particular type of case in which there was a short-esophagus type of hiatus hernia in which there probably had been, or might have been, considerable esophagitis, ulceration and fibrotic stricture. We were, therefore, prepared in this patient to find either a carcinoma or an esophagitis.

#### CLINICAL DIAGNOSES

Peptic ulcer of esophagus in hiatus hernia  
Chronic lymphadenitis

#### DR. SCANNELL'S DIAGNOSES

Carcinoma of esophagus  
Diaphragmatic hernia

#### ANATOMICAL DIAGNOSES

*Peptic ulcer of esophagus*  
*Diaphragmatic hernia*

#### PATHOLOGICAL DISCUSSION

DR. SWEET: At operation the lesion was found to be quite characteristic of esophagitis. The peri-esophageal tissues in the mediastinum, as they usually are in that condition, were very much thickened. Dissection of the esophagus was difficult,—it is always more difficult in that lesion than it is in carcinoma,—and there was evidence of reaction all the way up the mediastinum as far as I pursued the esophagus. The area where one can see narrowing on the x-ray film was very firm but not so firm as carcinoma would be. It felt rather rubbery. The herniated portion of the stomach was not particularly unusual except that it was adherent, and the majority of these hernias are not unless there is some interference with the blood supply from an incarceration. I think she had had a lot of mediastinitis. After the esophagus

and stomach had been dissected free from the surrounding tissues it was possible to reduce the stomach below the diaphragm. In other words, this case was characteristic of the majority of cases of hiatus hernia. The shortness of the esophagus is more apparent than real. A true congenitally short esophagus is very unusual, but it does occur. Because of the lesion in the lower end of the esophagus, I chose to do a resection.

DR. BUTLER: Would a fluoroscopic examination have helped to make this diagnosis?

DR. SWEET: It was done at the time the films were made, but I do not believe it helped in this case.

DR. MALLORY: The resected segment consisted of the lower 3 or 4 cm. of esophagus and approximately equal portions of the cardia of the stomach. Just above the junction of the esophagus and stomach was an area of shallow ulceration from which the mucosa was completely denuded. Histologic examination of that area showed a fibrinoid membrane of the type that we characteristically see in active peptic ulcer. Peptic ulcers of the lower end of the esophagus are unusual but not extremely rare lesions. I believe that was the etiology of the ulcer in this case.

DR. SWEET: It looked to me on examining the gross specimen as we resected it as if the ulcer was completely annular. I could not see any normal mucosa whatever.

DR. MALLORY: There was no mucosa of any significance.

DR. SWEET: Do you think that these peptic ulcers in the lower end of the esophagus usually occur in the extension of gastric mucosa that we so often see in the lower end, or do you think they frequently occur in the mucosa, which is characteristic of the esophagus itself?

DR. MALLORY: Judging from the literature usually it is possible to show that there was extension of the gastric mucosa into the esophagus in the majority of these cases. This is not clearly evident here because of the complete denudation of the mucosa.

DR. SWEET: I have a distinct impression that the majority of these ulcers occur in upward extensions of the gastric mucosa, although they are actually in the esophagus.

not be necessary to maintain the blood and tissue concentrations continuously at effective levels to attain a cure. Nevertheless, the most rapidly effective method of treatment, except in certain special circumstances, is still to repeat injections at such frequency as to maintain the tissue levels continuously in excess of the concentration that kills organisms at the maximal possible rate.

If Eagle's thesis is correct, the therapeutic activity of a given dose of penicillin depends primarily on the total length of time for which it remains at bactericidal levels, with particular emphasis on the time for which it is present at the maximally effective concentration in addition to the time required for the organism to recover from the drug and effectively resume multiplication. The enormous differences observed in the curative penicillin doses when either the number of injections or the interval between them is varied should then rest primarily on the total period of effective penicillin action. Conversely, different schedules of treatment that have the same biologic effects should provide effective levels for the same total period, irrespective of the total curative dose used.

Eagle has carried out many experiments in support of his contention. In the meantime, a certain amount of evidence had accumulated from other sources to indicate that frequent doses may be unnecessary. Thus, it has been shown that the 100 per cent curative daily dose of penicillin for pneumococcal infections of mice is the same whether two injections are given daily every twelve hours or eight injections every three hours.<sup>2</sup> In streptococcal infections in mice, the daily penicillin dosage given in a series of small equally spaced amounts was no more effective than equivalent amounts given in one or two doses a day.<sup>3</sup>

In the treatment of human cases of pneumonia, likewise, small doses at rather long intervals were first used successfully in the earliest clinical trials by Tillet et al.<sup>4</sup> More recently, doses of 300,000 units in aqueous solution given every twelve to twenty-four hours have been used successfully at the New York Hospital,<sup>5</sup> and similar dosage schedules employing large individual doses of aqueous penicillin one to three times a day are being practiced in a number of other clinics. In one of the large Boston hospitals a dosage of 100,000 units

of aqueous penicillin every eight hours has been used for the treatment of most cases of pneumococcal and streptococcal infections for some time. In a series of cases of pneumococcal pneumonia recently reported by Price,<sup>6</sup> patients who received large doses of penicillin in aqueous solution twice daily responded as favorably as those who received the same total dosage at more frequent intervals. Of course larger and more frequent doses are required for infections with more resistant organisms, such as many staphylococcal infections and subacute bacterial endocarditis. No doubt the patient will appreciate the longer intervals between the injections, which should also serve to reduce somewhat the burden on the nursing staffs.

#### REFERENCES

- 1 Eagle H. Speculations as to therapeutic significance of penicillin blood level. *Am J Med* 28:260-278 1948
- 2 Gibson C D Jr. Comparative effectiveness of two penicillin treatment schedules in pneumococcal infections in mice. *Proc Soc Exper Biol & Med* 67:278-280 1948
- 3 White H J, Baker M J, and Jackson E R. Therapeutic effectiveness of single and divided doses of penicillin in streptococcal infection in mice. *Proc Soc Exper Biol & Med* 67:199-201 1948
- 4 Tillet W S, McCormack J E, and Cambier M J. Treatment of lobar pneumonia with penicillin. *J Clin Investigation* 24:589-594 1945
- 5 Conference on therapy treatment of pneumonia. *Am J Med* 4:423-435 1948
- 6 Price A H. Aqueous penicillin therapy for pneumococcal pneumonia: injections at twelve hour intervals. *JAMA* 138:292 1948

#### PUBLIC HEALTH IN INDIA

THE Government of India Information Services in an Independence Anniversary Review points out some of the difficulties India is encountering in her efforts to improve public health. The report also indicates the determination with which the new Government is attacking its problems, and augurs well for an eventual successful solution of them.

Many of the problems, of course, are of an emergency nature and are concerned with the unsettled condition of the country and the mass movements of population between India and Pakistan. Huge refugee camps have required medical relief, the camp at Kurukshetra having at one time accommodated 300,000 refugees under canvas for whom a thousand-bed hospital was established by the director-general of Health Services. Campaigns of inoculation and vaccination against cholera, smallpox and tuberculosis have been organized nearly 40,000 BCG vaccinations having been done up to the end of June, 1948. Periodic delousing operations have been carried out in this city of tents,

is being tried almost to the point of bribery, but without success

It need not be concluded on that account that the failure to meet military quotas by voluntary enrollment means a tendency on the part of the profession to shirk its duty. Rather, it may be considered a reflection of the ordinary man's desire for fair play and the thoughtful man's appreciation of the importance of meeting his country's vital undertakings with an equal efficiency of action. It is earnestly believed that any future legislation that is fair, efficient and necessary will be approved by the medical profession regardless of the personal sacrifices it may demand of individual physicians.

### PENICILLIN DOSAGE AND BLOOD LEVELS

THE problem of dosage of penicillin at present is considerably different from what it was when the antibiotic first became available and it was both scarce and expensive. The general tendency is to use amounts that are far greater than those that could be deemed necessary in most infections by any consideration of the sensitivity of the causative organisms and by the blood levels attainable. The purified crystalline preparations now available are relatively nonirritating, so that aqueous solutions in sterile water or physiologic saline solution in concentrations up to more than 100,000 units per cubic centimeter can be given with a minimum of discomfort. Doses of 100,000 units or more are often used every two or three hours in the treatment of acute bacterial infections due to such organisms as the pneumococcus and the hemolytic streptococcus, which in most cases are sensitive to between 0.01 and 0.08 units per cubic centimeter.

Considerable early experience has shown that doses of 10,000 to 15,000 units every three or four hours are quite adequate for most of these cases. Furthermore, recent observations by a number of experienced workers and some of the earlier results have indicated that cures may be effected in cases of lobar pneumonia even when intervals of eight to twelve hours are permitted each day during which no injections are given. This is true in spite of the fact that penicillin activity cannot be demonstrated in the blood during the greater part of this interval.

Eagle<sup>1</sup> very ably discussed the significance of the penicillin blood levels at last year's meeting of the American College of Physicians. A brief summary of his speculations, which are based on a considerable amount of experimental evidence, should be of interest.

Eagle argues that the penicillin blood level is of significance only so far as it provides a rough measure of the concentration in the tissues at the site of the infection. The curve of the tissue levels after an injection of penicillin is important and may be expressed in terms of three time periods: the length of time for which penicillin is present at maximally effective concentrations that kill the organism at the fastest possible rate, the time for which penicillin is present at somewhat lower concentrations that are more slowly bactericidal, and the period after the penicillin has fallen to concentrations lower than those that kill bacteria *in vitro* but during which the organisms continue to die in the body at a rate faster than they multiply. This continuing death of organisms may be due to penicillin that persists in the tissues longer than it does in the blood, or the organisms may be killed by lower concentrations of penicillin in the body than they are in the test tube, owing perhaps to the participation of the body's defenses, or the organisms that have been exposed to penicillin may recover from its deleterious effects slowly and during a temporary period of retarded multiplication they may be disposed of by the defense mechanisms of the host. Whichever the cause may be, the period of gradually disappearing penicillin activity provides a margin of safety in that the blood and tissue penicillin levels may be permitted to fall below those that are significantly bactericidal in the test tube without affecting the outcome of treatment.

Large injections of penicillin are more effective than small injections, according to Eagle, not because they provide higher absolute levels of penicillin, but because they provide the effective concentrations for longer periods of time. More organisms are thus killed by each injection, and fewer survive to remultiply in the interval between injections. That interval may then be prolonged because with fewer surviving organisms less harm is done by a penicillin-free interval during which the organisms multiply. In general, therefore, it should

Further attempt was made to provide for elasticity in the charges for certain operations or other services which seemed to evoke more than average contention by listing the minimum and maximum amounts considered equitable. These items bear the notation "AA," which indicates that the fee for the given service is to be determined by arbitration and agreement between the Veterans Administration and the Medical Society concerned.

May I reiterate that the Veterans Administration Fee Schedule Format is in no sense to be construed as an arbitrary or National Fee Schedule. Furthermore it is subject to periodic review and such modification as conditions may indicate.

If it meets with your approval I would appreciate it very much if you could possibly arrange to publish this as an open-letter in the *Journal of the American Medical Association*. I should like this to reach all the physicians throughout the country and I know of no better way to do it than through the *Journal*.

PAUL B MAGNISON, Chief Medical Director

Veterans Administration  
Washington 25, D C

## MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

### RICE DIET

The rice diet is at present in common use for the relief of hypertensive states. Patients upon diets prescribed for such therapeutic purposes not infrequently develop nutritional deficiencies as a result.

The Massachusetts Department of Public Health, therefore desires to call attention to deficiencies

not only in protein but also in many of the minerals and vitamins. Such a diet when calculated shows itself to be adequate in vitamin A only provided prunes, apricots or peaches are used daily, high in vitamin C when orange and grapefruit juices are used, and low in calcium, protein and components of the vitamin B complex, particularly riboflavin. Sufficient iron is not supplied unless apricots and prunes are consumed regularly. Some physicians include 8 ounces of prune juice daily to meet the need of iron. If pineapples, apples, grapes (or their juices) or pears and bananas are substituted, in whole or in part, for the above fruits the vitamin A, ascorbic acid and iron will fall below recommended levels.

The following menu is an example of a day's diet planned on Kempner's basic diet, and Table 1 shows how a day's rice diet, with these fruits, compares with the day's needs for a moderately active man.

#### BREAKFAST (7 A M)

1 cup orange juice  
2 cups boiled rice  
22 grapes

#### LUNCH (11 A M)

2 tablespoonsful honey on  
3 cups rice  
1 cup orange juice  
2 fresh peaches

#### SUPPER (4 P M)

Rice crown  
2 apricots  
(2 cups rice  
4 stewed apricot halves)  
1 cup prune juice  
1/2 cantaloupe

#### NIGHT (8 P M)

1 cup orange juice  
3 plums

TABLE 1 Daily Requirements of a Moderately Active Man Weighing 70 kg

DAILY INTAKE	CALORIES	PROTEIN	CALCIUM	PHOSPHORUS	IRON	VITAMIN A	THIAMINE CHLORIDE	ASCORBIC ACID	RIBOFLAVIN
		gm	gm	gm	mg	I U	mg	mg	mg
Ordinary diet	3000	70.0	0.8	0.88	12.0	5000	1.5	75	2.0
Diet with white rice	1874	51.6	0.337	0.587	11.5	15,870	1.13	368	0.54
Diet with brown rice	1909	28.8	0.421	1.175	24.1	13,870	1.78	368	0.64

of the unsupplemented rice diet. The rice diet frequently prescribed for hypertension may bring about nutritional deficiencies in certain patients with previously poor nutritional status if the diet is continued for more than a few weeks without added minerals and vitamins.

The basic rice diet outlined by Kempner in the *North Carolina Medical Journal* (February, 1945) consists of 400 gm of rice fruit, fruit juices and sugar. It furnishes about 2000 calories, 20 gm of protein, 0.2 gm of chloride and 0.15 gm of sodium. The following minimal doses are recommended: vitamin A, 500 units, vitamin D, 1000 units, thiamine chloride, 5 mg, riboflavin, 5 mg, niacinamide 25 mg, calcium pantothenate, 2 mg, and ferrous sulfate, 0.6 mg. Without this supplementation the meals of rice and fruit tend to be low

Both brown and white rice are recommended in rice diets. The above calculations do not take into account losses of thiamine, riboflavin and niacin that result from washing of rice. Such losses vary according to the rigor of the washing. They may be as high as 43 per cent of thiamine, 25 per cent of riboflavin and 23 per cent of niacin. Further losses result in cooking, but the most serious losses are due to washing. This will not be of importance if the diet is supplemented adequately, but may be of considerable consequence if the patient on the very restricted form of the diet makes a poor choice of fruits and overwashes the rice during preparation.

This particular day's diet includes both prunes and apricots and so provides a good amount of iron. The yellow foods, peaches, apricots, oranges

and fly and mosquito control measures have been developed and enforced

In addition plans for more permanent programs are being initiated. Health legislation has been passed and the reorganization of Delhi hospitals has been outlined. Steps are being taken for the establishment of health centers in Delhi Province and elsewhere. A program is under way for the improvement of medical schools and research institutes and for the development of postgraduate training.

The Health Ministry has moreover found the time and personnel to participate in various international conferences that have been held during the year. Delegations were sent to the International Cancer Research Conference in St. Louis in 1947, to the International Leprosy Congress in Cuba, to the International Congress on Tropical Medicine and Malaria in Washington last May, to the BCG Congress in Paris and to the first World Health Assembly at Geneva.

A tuberculosis institute is to be established in connection with the University of Delhi, and increased Government grants have been provided for the Tuberculosis Association of India. The activities of the Malaria Institute of India have resulted in further reduction in the incidence of malaria in Delhi.

Mother India, with her new-found freedom, is in fact fast becoming a modern mother. She has taken on the new look and has every intention of joining the other forward-looking mothers of the world.

### THE JAPANESE MEDICAL JOURNAL

WE WELCOME into the field of medical journalism *The Japanese Medical Journal*, of which the first two issues have come to hand, those of February and April, 1948. *The Japanese Medical Journal*, in English, is the official publication of the National Institute of Health of Japan, under the managing editorship of Hidetake Yaoi. Its contents, selected from papers submitted by all research institutions throughout Japan, may be considered, as the editor states, to be representative of the type of work being carried out in that country.

This journal, in a medical sense, is the first fruit of a reconstituted Japan. May it be representa-

tive of a new life and a new outlook, a step toward membership in a new society of nations that will look only in the direction of peace and the betterment of mankind!

### ROBERT N NYE MEMORIAL FUND

The Nye Memorial Fund has recently been increased by an additional gift of \$1000 from a previous donor.

### MASSACHUSETTS MEDICAL SOCIETY

#### VETERANS ADMINISTRATION FEE GUIDES

In order to give the subject of fee guidance schedules widespread publicity, the chief medical director of the Veterans Administration has requested that the following letter be reprinted in the various state journals. It first appeared in the *Journal of the American Medical Association*, May 22, 1948.

H. QUIMBY GALLUPE, *Secretary*

Dr. Morris Fishbein  
Editor, the *Journal of the American Medical Association*  
535 North Dearborn Street  
Chicago, Illinois

Dear Dr. Fishbein:

It has come to my attention that considerable misunderstanding has developed throughout the medical profession concerning the establishment of fees for medical services to be paid private physicians participating in the so-called "Home Town Medical Care Program for Veterans." It has been contended that the Veterans Administration has arbitrarily established a Fee Schedule which represents the maximum amount which may be paid for any given service and which is, in effect, a National Fee Schedule. It has also been contended that the various State Medical Societies and other interested groups were not consulted when this Fee Schedule was adopted.

In order to clear up any misunderstanding regarding this matter, it is desired to emphasize that my predecessor, Dr. Paul R. Hawley, had no intention at any time of establishing a National Schedule of Fees, nor do I contemplate doing so. However, the Fee Schedules originally submitted by the various State Medical Societies, when the "Home Town Medical Care Program" was inaugurated, varied so widely in format, terminology, and fees for similar or identical services, that it was deemed advisable to establish a uniform Fee Schedule Format and to set up tentative fees which could be used as a guide by the various State Medical Societies when submitting their proposals for the furnishing of medical care to veterans.

This uniform Fee Schedule Format was formulated by the Professional Group of National Consultants to the Chief Medical Director. This Group, representing the various specialties in medicine and surgery, is composed of eminent physicians from all parts of the country. Tentative fees were set up in the format after a careful analysis of Pre-Paid Medical Care Plan, Workmen's Compensation and Insurance Fee Schedules, and also the Fee Schedules in effect in the various States having agreements with the Veterans Administration. As was to be expected, considerable variation occurred in the Fee Schedules reviewed. The Professional Group of National Consultants made every effort to arrive at fees that were considered to be within reasonable limits and which would, as nearly as possible, allow a uniform provisional fee schedule for use as a guide in facilitating and expediting the preparation of agreements between State Medical Societies and the Veterans Administration.

ticks and so a vicious circle is formed, spreading and perpetuating the disease

In Massachusetts, ticks have been known to spread only tularemia and Rocky Mountain spotted fever. Tularemia made its first appearance in Massachusetts in 1937 in Falmouth, and a total of 17 cases had been reported to the Department of Public Health up to and including 1947. Ten of the 17 cases occurred in the tick-infested area and were attributed to tick bites. On the other hand, Rocky Mountain spotted fever first made its appearance in 1938 in Dennis, 10 cases have been reported, 2 being contracted outside Massachusetts and the remaining 8 in the tick area of the Cape. The problem of tularemia in Massachusetts has recently been discussed in detail in the *Journal*.<sup>2</sup>

Although it is important to attempt to control ticks in Massachusetts because of the possibility of their transmitting certain diseases, the most pressing reason for such control is the fact that they are a trying nuisance. In the southeastern portion of the Commonwealth, every spring and summer, residents and visitors in the area must perform the daily task of inspecting themselves and members of their families for the presence of ticks and must frequently perform the tedious chore of removing ticks from dogs and other pets.

The study was started too late this year to permit much information to be accumulated regarding the control of ticks by sprays. A few experiments have confirmed observations of others that the prevalence of ticks can be decreased by spraying of the grass and bushes in an infested area with DDT. Unfortunately, such a measure is only palliative and probably only affects in a minor way the eventual solution of the problem, because it is feasible to spray only restricted areas that are most frequented by residents and summer visitors and their dogs. Reproduction of ticks is continued because dogs wander into areas of lower prevalence and furnish the blood meals for ticks that will replenish the tick population.

If spraying operations could be supplemented by measures to keep ticks from obtaining their blood meals from dogs, a much more permanent effect could be obtained.

It is expected that the tick study will be continued for the next year or two so that some of these problems can be attacked. Dipping dogs is usually much more effective in getting rid of ticks, but the operation is messy and dog owners will not take advantage of this method of control. A thorough study of the usefulness of DDT, rotenone and other materials in powder form would be useful.

Any assistance that physicians can give to increase knowledge of the geographic distribution of the tick population will be useful in the study. In the August 26 issue of the *Journal*, a questionnaire, which is being used for accumulating information, was referred to. Any physicians who did not fill

out the form are asked to forward it with any information which is available.

## REFERENCES

1. Bequaert J. C. Ticks, or Ixodoidea of Northeastern United States and Eastern Canada. *Entomologica Americana* 25:73-232, 1946.
2. Ayres, J. C. and Feemster R. F. Epidemiology of tularemia in Massachusetts with review of literature. *New Eng J Med* 238:187-194, 1948.

## CORRESPONDENCE

### FURTHER DATA ON LOWER-NEPHRON AND MERCURIAL NEPHROSIS

To the Editor: It is believed that the following addendum to my paper on "Acute Renal Insufficiency Due to Lower-Nephron Nephrosis," which appeared in the November 4 issue of the *Journal*, will be of interest.

The pathologic lesion in mercurial nephrosis differs from that of lower-nephron nephrosis in that the proximal segment of the convoluted tubule is chiefly affected. The following case is of interest because, as pointed out by R. Batson and J. C. Peterson, in an article entitled "Acute Mercury Poisoning: Treatment with BAL in anuric states with continuous peritoneal lavage" (*Ann Int Med* 29:278-293, 1948), it is currently believed that "these patients who, not having received BAL therapy within the first few hours, will develop anuria secondary to tubular injury. These patients will ultimately die unless something can be done to provide a temporary means of controlling their uremia until renal function returns."

This case illustrates that the general principles originally put forth by J. P. Peters, A. J. Eisenman and D. M. Kidd, in an article entitled "Mercury Poisoning" (*Am J Med Sc* 185:149-171, 1933) remain sound.

A 48-year-old mechanical engineer (B. C. H. 1298442) accidentally ingested 0.5 to 1.0 gm. of mercuric bichloride on the morning of September 22, after which he had breakfast and then became nauseated, vomiting at first food and then bloody material. Shortly thereafter watery bloody diarrhea began. During the 8 hours prior to hospitalization he vomited five or six times, had at least ten watery, red stools and passed urine several times. On entry there was very mild evidence of shock. The hematocrit was 57 per cent, the hemoglobin 18 gm. per 100 cc., and the white-cell count 28,000. Shortly after admission he received an intravenous infusion of 500 cc. of physiologic saline solution followed by 500 cc. of citrated whole blood. Early the next morning the same quantity of blood and saline solution was administered. Since the hematocrit remained at 50 per cent in spite of this therapy, 1000 cc. of 10 per cent glucose in saline solution was given, after which the hematocrit declined to 44 per cent and the hemoglobin to 15 gm. Shortly after admission the patient voided 200 cc. urine, which gave a  $\pm$  test for albumin, with many casts and occasional white and red cells in the sediment. Nine days later 50 cc. of urine appeared. During the period of anuria the patient received approximately 750 cc. of 15 per cent of glucose in distilled water daily, as well as intravenous injections of an amount of physiologic saline solution or its equivalent as sodium bicarbonate or sodium lactate equal to the output in vomitus or stool.

Forty-eight hours after entry stool examinations were reported as positive for mercury (the patient up till this time had steadfastly denied the possibility of poisoning of any type). He therefore received 1575 mg. of BAL intramuscularly divided into nine equal doses during the next 48 hours. With the omission of all liquids and food by mouth, vomiting ceased promptly. Within a few days there was no further diarrhea. The temperature, pulse, respirations and blood pressure showed no essential change. The blood nonprotein nitrogen rose to a peak of 252 mg. per 100 cc. on the 15th day. The serum sodium remained at approximately 133 milliequiv. per liter. The serum potassium, which was 4.6 milliequiv. per liter on the 3rd day, never rose above 5 milliequiv. The

and the deeper-colored variety of cantaloupe make the diet more than adequate in vitamin A. However, calories, protein, calcium and riboflavin are very low, and wherever diets are low in calcium and protein they tend also to be low in phosphorus. The lowered calorie intake may need attention when an inactive patient returns to active work.

That protein restriction has a beneficial effect in hypertension has not yet been conclusively shown. This protein deficiency of the rice diet is being studied, and in some cases a form of low-sodium milk is in use to compensate for the deficiency of both protein and calcium.

## MASSACHUSETTS TICK SURVEY

JOHN C. AYRES, M.D.,\* AND

ROY F. FEEMSTER, M.D., DR. P.H.†

For many years, the wood tick, officially known as the American dog tick, has been an annual nuisance on Cape Cod and Martha's Vineyard and inland from the South Shore. In recent years, a few cases of such tick-borne diseases as Rocky Mountain spotted fever and tularemia have been occurring in the same area.

The Department was directed by Chapter 36 of the *Resolves* of 1948 to study the problem and seek to find ways by which the nuisance could be abated.

It is important, in connection with this study, to know the geographic distribution of this tick (*Dermacentor variabilis*) as well as any other important species of ticks with which it might be confused.

For the benefit of physicians who might like further information regarding the problem, a brief account of the ticks found in the State follows. Much of this information is taken from a voluminous compilation by Bequaert.<sup>1</sup>

### Varieties

Ticks are divided into two families: the *Argasidae* or soft ticks and the *Ixodidae* or hard ticks. The former are more primitive and less constantly parasitic, produce fewer offspring, feed frequently and at night, do not increase greatly in size when gorged on blood and seldom travel far; the latter are more specialized and more highly parasitic, produce more numerous offspring, and take only one blood meal in each stage but are capable of taking such great quantities that they increase many times in size and weight. The hard ticks possess a horny shield, which entirely covers the back in the male and partially covers it in the female.

### Prevalence

Of the four species of *Argasidae* found in the United States none is present in Massachusetts.

\*Epidemiologist, Massachusetts Department of Public Health.

†Director, Division of Communicable Diseases, Massachusetts Department of Public Health.

On the other hand, several species of the *Ixodidae* are present. These are the common wood or dog tick (*D. variabilis*), which attacks dog and man and which feeds to a large extent in the immature stages on small rodents such as meadow mice, the rabbit ticks (*Haemaphysalis leporis palustris* and *Ixodes dentatus*), which do not attack man but which are often present in large numbers on rabbits and may also be found on meadow larks, quail and other birds, the mouse ticks (*Ixodes scapularis*, *Ixodes muris*), which are rather common on meadow mice, other small rodents and more rarely on rabbits, and other ticks (*Ixodes bruneus*, *I. cookei*, *I. marxi* and *Haemaphysalis chordeilis*), which infest small animals and birds primarily.

*D. variabilis* is the most important one of this group since it is found regularly on dogs and frequently on human beings. It is a three-host tick. The fertilized female drops 2000 to 8000 eggs on the ground. In one or two months the eggs hatch, and the larvae attach themselves to small mammals and engorge for two to eight days. Then they drop to the ground, digest their meal and molt to nymphs. The first winter they usually spend as unfed nymphs. The following spring the nymphs attach themselves to rodents, engorge, drop to the ground, digest their meal and molt to adults. The unfed adults attach themselves to larger mammals, including man, mate, engorge and drop off.

The distribution of ticks in areas depends upon the presence of hosts. The meadow mouse is the principal host of the young forms, and the best "mouse country" is uncut, ungrazed grassland dotted with variable amounts of thickets and shrubs. Beach grass, grassy patches in woodland, and areas denuded in lumbering are also favorable, but ticks are seldom found in forests.

### Ticks As Transmitters of Disease

Ticks have been recognized as transmitters of disease in man and animals since 1893. Many species not only carry disease-producing organisms through several stages of change in form but also transmit them through the eggs to the next generation. They transmit five groups of disease: rickettsial, viral, bacterial, spirochetal and protozoan. In America, ticks have been proved to be transmitters of Rocky Mountain spotted fever, tularemia, Q fever and Colorado tick fever and to cause tick paralysis by a poisonous substance that they produce. Furthermore, in the laboratory they have been shown to be capable of transmitting other diseases, such as encephalitis.

Ticks obtain micro-organisms from their various hosts. These organisms in turn develop within the tick, invading all tissues and passing through all stages finally to the egg. Once the tick is infected it can transmit the disease to other animals, birds, rodents and even man. The newly infected hosts then act as new reservoirs for other uninfected

## NOTICES (Concluded from page 762)

## SOCIETY MEETINGS AND CONFERENCES

## CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, NOVEMBER 18

## THURSDAY NOVEMBER 18

8:15 p.m. Boston Society of Psychiatry and Neurology Boston Medical Library 8 Fenway

## FRIDAY NOVEMBER 19

9:00 a.m.-12:00 p.m. Combined Medical and Surgical Staff Rounds Peter Bent Brigham Hospital  
12:00 p.m. Lunch Conference Margaret Jewett Hall Mt. Auburn Hospital Cambridge

## MONDAY NOVEMBER 22

12:15-1:15 p.m. Clinicopathological Conference Main Amphitheater Peter Bent Brigham Hospital

## TUESDAY NOVEMBER 23

12:15-1:15 p.m. Clinicoröntgenological Conference Peter Bent Brigham Hospital  
1:30-2:30 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children Massachusetts General Hospital  
5:00 p.m. Anesthesia Study Committee New England Society of Anesthesiologists Auditorium of Building A Boston University School of Medicine

## WEDNESDAY NOVEMBER 24

11:00 a.m.-12:00 p.m. Medical Rounds Amphitheater Children's Hospital  
12:00 p.m.-1:00 p.m. Clinicopathological Conference (Children's Hospital) Amphitheater Peter Bent Brigham Hospital  
2:00-3:00 p.m. Combined Clinic by the Medical Surgical and Orthopedic Services Amphitheater Children's Hospital

\*Open to the medical profession.

OCTOBER 1-MAY 20 Metropolitan State Hospital Page 41b issue of September 9

NOVEMBER 15 South Boston Medical Society Page 762

NOVEMBER 16 Greater Boston Medical Society Page 762

NOVEMBER 16 South End Medical Club Page 762

NOVEMBER 16 23 and 30 Boston City Hospital House Officers Association Page 762

NOVEMBER 17 Middlesex East District Medical Society Page 644 issue of October 21

NOVEMBER 17-JANUARY 26 Boston State Hospital Psychiatric Seminar Schedule Page 762

NOVEMBER 18 Boston Society of Psychiatry and Neurology Page 762

NOVEMBER 20-23 American Academy of Pediatrics Annual Meeting Chalfonte-Haddon Hall Hotel Atlantic City New Jersey

NOVEMBER 23 New England Society of Anesthesiologists Page 762

NOVEMBER 30 Hampden District Medical Society Page 492 issue of September 23

DECEMBER 2 Suffolk Censors Meeting Page 492 issue of September 23

DECEMBER 4 American Federation for Clinical Research Page 644 issue of October 21

DECEMBER 4-9 American Academy of Dermatology and Syphilology Page 728 issue of November 4

DECEMBER 6-8 American Academy of Allergy Fifth Annual Meeting Chalfonte-Haddon Hall Hotel Atlantic City New Jersey

DECEMBER 7-9 Southern Surgical Association Annual Meeting Page 543 issue of April 8

DECEMBER 9 Recent Advances in Thoracic Surgery Dr. Joseph P. Lynch, Pentucket Association of Physicians 8:30 p.m. Haverhill

DECEMBER 9 and 10 New York State Society of Anesthesiologists Page 34 issue of July 1

FEBRUARY 4 1949 American Board of Obstetrics and Gynecology Inc. Page 244 issue of August 5

MARCH 7-9 1949 American Academy of General Practice Page 728 issue of November 4

MARCH 28-APRIL 1 1949 American College of Physicians. Page 158, issue of July 22

MAY 16-19 1949 American Urological Association Biltmore Hotel Los Angeles California

MAY 26-28 1949 American Gout Association Hotel Lorraine Madison, Wisconsin

NOVEMBER 11 17 1949 Third Inter American Congress of Radiology Page 158 issue of July 22

## DISTRICT MEDICAL SOCIETIES

## HAMPDEN

NOVEMBER 30 8:30 p.m. Academy of Medicine Springfield Caroma of the Breast Dr. Grantley W. Taylor

## MIDDLESEX EAST

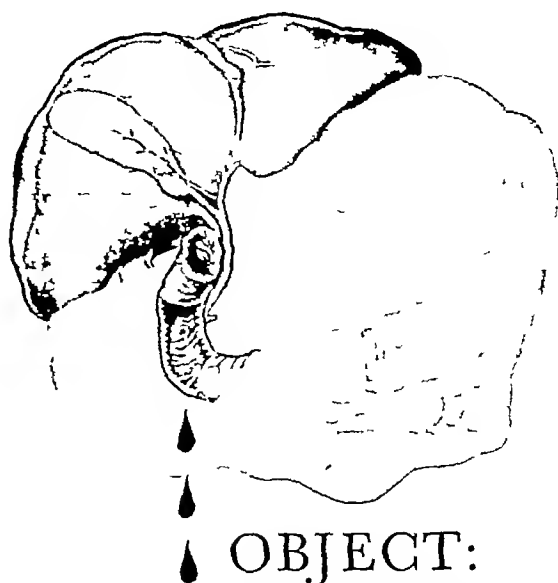
NOVEMBER 17  
JANUARY 19  
MARCH 23  
MAY 11

## SUFFOLK

DECEMBER 2 Suffolk Censors Meeting

## WORCESTER NORTH

DECEMBER 15 Leominster Hospital Leominster  
FEBRUARY 23 Burbank Hospital Fitchburg  
APRIL 27 Annual Meeting

OBJECT:  
DRAINAGE

In discussing the management of chronic cholecystitis without stones, Albrecht states

"The object of the medical procedure is to assist in draining an infected organ" \*

The specific hydrocholeretic action of Decholin (chemically pure dehydrocholic acid) accomplishes this purpose

Decholin induces bile secretion which is thin and copious, flushing the passages from the liver to the sphincter of Oddi, and carrying away infectious and other accumulated material

HOW SUPPLIED Decholin in 33 1/4 gr tablets Packages of 25, 100, 500 and 1000

\*Albrecht, F. K. Modern Management in Clinical Medicine, Baltimore, The Williams and Wilkins Co., 1946 p 170



**Decholin**  
BRAND REG U S PAT OFF

**AMES COMPANY, INC.**  
ELKHART, INDIANA

serum chloride declined to a low of 68 millicquiv, and the carbon dioxide to 9.9 millicquiv per liter. On the 9th day 50 cc of urine was passed, followed on successive days by 100, 260, 500, 1000, 2000 and 3300 cc. This urinary output was associated with a falling nonprotein nitrogen and a rise in serum chloride and carbon dioxide. With the urine output at 2000 cc the patient was allowed fluids and food freely by mouth and made an uneventful recovery. He returned to work 24 days after the onset of illness.

Since my manuscript was submitted for publication, gastric and intestinal lavage has been successfully employed in the treatment of 7 patients with uremia associated with prostatism, by V. Vermooten and D. M. Hare reported in an article entitled "The Use of Continuous Gastric Lavage in the Treatment of Uremia Associated with Prostatism" (*J Urol* 59:907-919, 1948), and in a patient with anuria and uremia secondary to the ingestion of cleaning fluid by H. H. Marquis and F. P. Schnell as noted in a report entitled "The Treatment of Anuria by Intestinal Perfusion" (*Am J M Sc* 215:686-693, 1948). In this case, no attempt was made to follow the level of serum potassium until cardiac arrhythmia appeared, when it was found to be 1.2 millicquiv per liter, or approximately a fourth normal. Death appeared to have been caused by this extreme hypokalemia.

MAURICE B. STRAUSS, M.D.  
Chief of Medical Service

Cushing Veterans Administration Hospital  
Framingham, Massachusetts

## NOTICES

### ANNOUNCEMENT

Dr. Carl V. Lendgren announces the removal of his office to 8195 California Avenue, South Gate, California.

### SOUTH BOSTON MEDICAL SOCIETY

A meeting of the South Boston Medical Society will be held on Monday, November 15, at 9 p.m., at the Carney Hospital. Dr. Grantley W. Taylor will speak on the subject "Oral Carcinoma."

### GREATER BOSTON MEDICAL SOCIETY

A meeting of the Greater Boston Medical Society will be held at the Boston Medical Library on Tuesday, November 16, at 8:15 p.m. A symposium entitled "Recent Advances in the Diagnosis and Treatment of Psychiatric Disorders" will be presented, with Dr. Harry C. Solomon as chairman.

#### PROGRAM

Lobotomy Dr. James Poppen  
Current Somatic Therapies in Psychiatry Dr. Milton Greenblatt.  
Psychotherapy Illustrated by dermatologic cases Dr. Lester L. Hasenbush

### SOUTH END MEDICAL CLUB

The next regular meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on Tuesday, November 16, at 12 noon. The speaker will be Dr. William J. Mulligan, who will discuss the subject, "Disorders of Menstruation."

Physicians are cordially invited to attend.

### BOSTON STATE HOSPITAL PSYCHIATRIC SEMINAR SCHEDULE

Psychiatric seminars will be held in the Reception Auditorium of the Boston State Hospital during 1948-1949 on Wednesdays at 12 noon, followed by a staff luncheon at 1 p.m.

#### SCHEDULE

1948

November 17 The Electroencephalogram in Psychiatric Research Dr. Robert S. Schwab  
November 24 The Work of the Psychologist in Relation to Psychiatry Dr. Herbert I. Harris  
December 1 Psychotherapy for Psychosomatic Disorders Dr. Grete L. Bibring  
December 8 Care of the Disturbed Psychotic Patient (To be announced)  
December 15 Teaching Psychotherapy in an Outpatient Department Dr. Bernard Bandler  
December 22 A Theory of Personality Dr. Andras Angyal  
December 29 Mongolian Idiocy Dr. Clemens Banda.

1949

January 5 What Society Should Do for the Alcoholic (To be announced)  
January 12 The Neurological Basis of the Emotions Dr. Stanley Cobb  
January 19 (To be announced)  
January 26 Recent Developments in the Treatment of Epilepsy Dr. Harry Kozol

### BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

A meeting of the Boston Society of Psychiatry and Neurology will be held at the Boston Medical Library, 8 Fenway, on Thursday, November 18, at 8:15 p.m.

#### PROGRAM

Acoustic Tumors Intracapsular removal versus total resection Gilbert Horrax, M.D. Lantern slides (thirty minutes)  
Psychometric Changes after Lobotomy Charles A. Atwell, M.A. (fifteen minutes)  
Sexual Behavior after Lobotomy Julius Levine, M.D., and Harold Albert, M.D. (fifteen minutes)

### NEW ENGLAND SOCIETY OF ANESTHESIOLOGISTS

A meeting of the Anesthesia Study Committee of the New England Society of Anesthesiologists will be held in the Auditorium of Building A, Boston University School of Medicine, on Tuesday, November 23, at 8 p.m. The chairman will be Dr. Meyer Saklad. There will be a presentation of case reports on morbidity and mortality, followed by a discussion from the floor.

Physicians and medical students are invited to attend.

### BOSTON CITY HOSPITAL HOUSE OFFICERS' ASSOCIATION

The Boston City Hospital House Officers' Association announces the following programs in its evening lecture series.

November 16 Practice Inside and Outside the Hospital Dr. Samuel A. Levine  
November 23 Hypertension as a Disease of Adaptation Dr. Hans Selye, professor and director of the Institute of Experimental Medicine and Surgery, University of Montreal Faculty of Medicine  
November 30 Physiology of the Liver, and Liver-Function Tests Dr. Franklin M. Hanger, Jr., associate professor of medicine, Columbia University College of Physicians and Surgeons and associate attending physician, Presbyterian Hospital, New York City  
These programs are held at 7 p.m. in the New Cheever Amphitheater of the Dowling Building, Boston City Hospital.

All interested persons are invited to attend.

(Notices concluded on page xviii)

# The New England Journal of Medicine

Copyright 1948 by the Massachusetts Medical Society

Volume 239

NOVEMBER 18, 1948

Number 21

## MEDICAL ASPECTS OF ATOMIC ENERGY\*

SHIELDS WARREN, M.D.†

BOSTON

THE Atomic Energy Commission has been charged by you and your fellow citizens with the responsibility of ensuring that the best use will be made of this new source of energy consistent with the national security as well as with maintaining the secret of the atomic bomb and making it available as a weapon. In such a program medicine naturally has a significant role. There is first the problem of maintaining health of the workers in the varied processes incident to the activities of the atomic-energy program. These hazards range from those of radioactive substances in amounts undreamed of a few years ago to the drab and prosaic fall from a stepladder or the almost routine automobile accident. It speaks well for the foresight, the skill and the industry of those charged with medical responsibility in the Manhattan project days that only two people have been killed by radiation hazards. When we remember that many thousands were exposed for several years to potential but adequately controlled hazards this is a remarkable showing, from the fact that among a handful of people exposed more than twenty years ago to the radium watch-dial paint in New Jersey many times this number of radiation deaths occurred, one can see the progress that has been made.

This progress, like the iceberg, showed but little above the stream of contemporary knowledge in the pre-war days. The patient work of the early radiologists, the biophysicists and the experimental biologists gradually and unobtrusively built up a mass of knowledge on which standards of permissible dosage could be safely built. Today there is less hazard in going into plants of the Commission than there is in crossing downtown streets. The knowledge and patient devotion to duty of the health physicists now maintain safety not only for those within the plants but also for those who might be injured by some accident in the environs of the plant.

Secondly, we have the task of developing ourselves and making it possible for others to develop those forays into intellectual darkness by which new continents of knowledge may be mapped out and developed. To give you some idea of the extent to which work in the field of basic medical and biologic research is being carried on, in addition to millions being spent in the Commission's own establishments, over \$1,300,000 has been allocated in the last six months for fundamental medical and biologic research in medical schools and hospitals.

Thirdly, no program can be better than the personnel by whom it is conceived and executed. This country is faced today with the scarcity of trained scientists that harks back to the waste of manpower that occurred in the last war. War is always wasteful but no country in World War II was as careless as ours of its trained personnel or as shortsighted regarding the scientific needs of the future. To help repair this loss—a loss that in the world of today is more serious than that of many army divisions or battles—the Atomic Energy Commission has established a fellowship program reaching through all the sciences, but because of our particular interests I shall discuss only those having to do with medicine, biology and biophysics. The National Research Council, at the request of the Commission, has established a fellowship program with Commission funds that is available not only for the doctor of medicine and for the doctor of philosophy in biology or basic medical sciences but also for the college graduate. The postdoctoral fellowships are for two years, the predoctoral are for one year but may be renewed. It is hoped that a considerable number of predoctorate fellows will continue on to obtain their M.D. or Ph.D. degree by means of aid afforded them through this fellowship program. This program envisages the training of 100 predoctoral fellows and 75 postdoctoral fellows each year.

Fourthly, the Atomic Energy Commission is providing radioactive isotopes for experimental and therapeutic purposes.

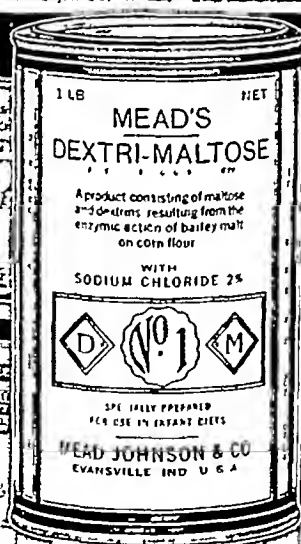
\*Presented at the annual meeting of the Massachusetts Medical Society, May 2, 1948.

†Professor of pathology, Harvard Medical School, pathologist, New England Deaconess Hospital, director, Division of Biology and Medicine, Atomic Energy Commission.

# BACKGROUND

The use of cow's milk, water and carbohydrate mixtures represents the one system of

infant feeding that consistently, for over three decades, has received universal pediatric



recognition. No carbohydrate employed in this system of infant feeding enjoys so rich and enduring a background of authoritative clinical experience as Dextri Maltose.

## THE CLINICAL CHARACTERISTICS OF EARLY DIABETES MELLITUS

SAMUEL B. BEASER, M.D.\*

BOSTON

CURRENT descriptions of diabetes mellitus vary markedly—as much as 300 per cent—regarding the symptoms of the disease.<sup>1,2</sup> Likewise, there is little exact information about its early course. The present survey of the population of a large diabetic clinic was undertaken to clarify these points.

## METHODS

The records of 500 consecutive patients were examined and 182 with adequate descriptions of the onset of the disease were accepted for study.

TABLE 1 Clinical Features at the Time of Diagnosis

PRESENTING COMPLAINT*	TOTAL NUMBER	PERCENTAGE OF GROUP	PERCENTAGE OF TOTAL
<b>Diabetic group</b>			
Polydipsia	32	49.0	16.8
Polyuria	50	46.0	15.8
Weight loss	50	46.0	15.6
Weakness	35	38.0	15.1
Fruity odor	23	32.0	12.1
Nocturia	9	14.0	7.4
Polyphagia	7	11.0	5.7
Refractive changes	4	6.0	2.1
Headache	2	3.0	1.0
Acroemia	1	1.5	0.5
Drowsiness	1	1.5	0.5
Patients with onsets with one or more of above	65	100	34.0
<b>(Diabetic) complication group</b>			
Pain or definite neuritis†	22	62	11.5
Ulceration	12	35	6.5
Charact.	2	5	1.1
Patients with onsets with one or more of above	36	100	19.0
<b>Casual group</b>			
Onset	15	16.9	7.9
Cardiac condition‡	15	14.6	6.5
Chronic headache	5	5.1	2.6
Intermittent claudication	2	2.5	1.1
Halt examination	2	2.5	1.1
Cerebral retinal thrombosis	1	1.0	0.5
Myelolysis	61	69.0	32.0
Patients with onsets with one or more of above	89	100	47.0

\*Since many patients had more than one presenting complaint the total of both types of onset (150) and presenting complaints exceed that of patients.

†Chief of vulva—scrotal or other skin areas.

‡Symptoms either proved to be due to definite neuritis or carefully investigated to rule out other diseases and subsiding promptly (usually in weeks) after institution of diabetic care.

§Due to bacterial or mycotic organisms and including skin, genitourinary, and feet.

¶Includes angina pectoris, myocardial infarction and congestive failure, arrhythmia, or both.

They had all been followed on the wards or in other clinics and had been referred to the diabetic clinic because of diabetic symptoms or glycosuria. In most cases a complete medical history had been

taken, but an additional diabetic history was elicited. Of these 182 patients, 113 who were found to have had one or more urinalyses prior to diagnosis (usually on morning post-prandial specimens) were investigated in greater detail. Patients with renal glycosuria were excluded from this study.

## RESULTS

Classified according to the types of chief complaint, the patients fell into three groups: "diabetic onset," with diabetic symptoms, "complication onset," with diabetic complications, and "casual onset," with glycosuria alone. It can be seen that the incidence of symptoms can vary significantly, depending on the method of analysis (Tables 1 and 2). However, no one complaint occurred in more than 50 per cent of the patients and fully 23 per cent had no diabetic symptoms (Table 3). The chief complaints comprised only a minority of elicitable diabetic symptoms, individual symp-

TABLE 2 Total Diabetic Symptoms Present, Including Both Presenting Complaints and Those Elicited by Further Questioning of All Patients, Regardless of the Type of Onset

SYMPTOM	TOTAL NUMBER	PERCENTAGE OF TOTAL ONSETS
Weight loss	94	49.5
Polydipsia	72	38.0
Polyuria	69	37.0
Fruity odor	49	26.0
Weakness	46	24.0
Nocturia	44	23.0
Polyphagia	17	9.0
Refractive changes	4	2.0
Headache	2	1.0
Anorexia	1	0.5
Vertigo	1	0.5
Drowsiness	1	0.5

toms being overlooked, as follows: weight loss 64 cases (70 per cent of the total), polydipsia, 40 (58 per cent), and polyuria, 39 (57 per cent).

Table 4 confirms statistically the validity of classifying the complications separately from the symptoms of diabetes. This is further substantiated by the variation of their incidence among the different types of onset (Table 3).

Decompensation of carbohydrate metabolism can be defined quantitatively. Thus, the patients with the diabetic type of onset are in advanced and the others in partial metabolic failure. There is a definite correlation between insulin need and the degree of metabolic decompensation (Fig. 1).

†Partial or advanced decompensation of the diabetes state is defined as simply the possession of any diabetic symptoms or of the progression of such symptoms to the status of chief complaints.

\*Assistant in Medicine, Harvard Medical School; assistant in medicine, Beth Israel Hospital.

†This group 97 per cent of the patients were over forty years of age at time of diagnosis, as contrasted with 51 and 65 per cent in other groups.

‡In this study the term "onset" refers to the date of clinical diagnosis and institution of treatment.

To the biologist this has brought unparalleled opportunity for study of metabolic processes and for providing continuous temporal orientation of vital processes that never before could be achieved. To him it has also brought a means of study of chemical relations almost hopelessly snarled.

To the physician it has brought a means of following in detail the action of drugs and distribution of hormones, and has cast new light on problems of metabolism and structure. It has hinted, but only hinted, at new therapeutic methods. As yet there is little hope that we shall find among the radioactive isotopes a control of infection or a cure of cancer. We have found with radioactive phosphorus palliation of certain types of leukemia, palliation of polycythemia vera and some retardation of plasma-cell myeloma. We have found that radioactive isotopic iodine may be taken up by an occasional cancer of the thyroid gland and its metastases and that some of the isotopes in colloidal form may be taken up by the reticuloendothelial system and thus irradiate tumor cells. There are other isotopes that might be useful but for one reason or another—the inherent toxic quality of the element, its long half-life or the specific localization—are unsuitable for use.

The practicing physician needs at present to be concerned with the problem of the atomic bomb. As one of the best educated persons in his community, and the only one technically qualified to evaluate the biologic effects of an atomic explosion, it is his responsibility to orient the members of his community regarding the problems raised by the hazard of such an explosion—problems that are in part psychologic, in part medical and in part organizational.

The air burst of an atomic bomb has many points in common with that of the more usual types of high explosive bombs, but at much higher intensity. An explosion of either type of bomb produces local heat and an air-pressure wave. The explosion of an atomic bomb also causes liberation of radiant energy ranging the whole electromagnetic spectrum from infrared rays to very short gamma rays, as well as producing a flux of neutrons. In an air burst of an atomic bomb the bulk of the fission products are carried to the stratosphere by the rapidly rising superheated air and gases, and are there so widely disseminated as to exert no dangerous effect under ordinary conditions. Hence,

there was little or no residual radioactivity to be reckoned with in the Japanese cities.

In an underwater burst, on the other hand, heat and blast are minor factors, but the bulk of the fission products are trapped in the water and spray deluged over the area, a wide zone thus being contaminated with radioactive materials.

It was this type of contamination that made radioactive the ships at Bikini, some of which are too "hot" radiologically to be of any use even up to the present time. In addition, in an underwater burst there may be activity of fairly short half-life as a result of neutron-produced radioactivity. Outside the immediate zone of the explosion the extent of the radioactive contamination will hinge on the speed and direction of the wind prior to the final settling out of the droplets of the radioactive water.

In the United States, as a result of the fairly high level of education, the ready means of disseminating information and what might even be denominated a national tendency to sensationalism the atomic bomb has been endowed with almost supernatural attributes. It is highly probable that in any threat of use of atomic weapons we ourselves should be more vulnerable than anyone else.

It is in this regard that the doctor can be of particular help in enabling those with less information than he to attain the proper perspectives in this new and startling field. Because the doctor is peculiarly fitted to deal with emergency situations, it is natural that much of the planning for atomic defense will fall upon his shoulders. The details of these plans are yet to be worked out because facts are being constantly added to our store of pertinent knowledge. However, sufficient data are available to enable the broad framework of meeting such a disaster to be sketched out.

This is now being done by the Office of Civilian Defense Planning with the aid and co-operation of the Atomic Energy Commission. For the present, the medical profession can best serve by reviewing its knowledge of the effects of ionizing radiation and the therapy of injuries produced by it as well as placing atomic weapons in their proper perspective not as virtually a supernatural force but rather a means of mass destruction cheap and irresistible but nonetheless subject to definite limitations.

195 Pilgrim Road

## THE CLINICAL CHARACTERISTICS OF EARLY DIABETES MELLITUS

SAMUEL B BEASER, M D \*

BOSTON

CURRENT descriptions of diabetes mellitus vary markedly — as much as 300 per cent — regarding the symptoms of the disease<sup>1 2</sup> Likewise, there is little exact information about its early course. The present survey of the population of a large diabetic clinic† was undertaken to clarify these points.

## METHODS

The records of 500 consecutive patients were examined, and 182 with adequate descriptions of the onset‡ of the disease were accepted for study.

TABLE 1 Clinical Features at the Time of Diagnosis

PRESENTING COMPLAINT*	TOTAL NUMBER	PERCENTAGE OF GROUP	PERCENTAGE OF TOTAL
Diabetic group			
Polydipsia	32	49.0	16.8
Polyuria	30	46.0	15.8
Weight loss	30	46.0	15.8
Weakness	25	38.0	13.1
Pruritus†	23	32.0	12.1
Nocturia	9	14.0	7.4
Polyphagia	7	11.0	3.7
Refractive changes	4	6.0	2.1
Headache	2	3.0	1.0
Anorexia	1	1.5	0.5
Drowsiness	1	1.5	0.5
Patients with onsets with one or more of above	65	100	34.0
(Diabetic) complication group			
Pain or definite neuritis‡	22	62	11.5
Infection	12	33	6.3
Cataract	2	5	1.1
Patients with onsets with one or more of above	36	100	19.0
Casual group			
Operations	15	16.9	7.9
Cardiac condition*	13	14.6	6.5
Chronic headache	5	5.1	2.6
Intermittent claudication	2	2.3	1.1
Health examination	2	2.3	1.1
Central retinal thrombosis	1	1.0	0.5
Miscellaneous	61	69.0	32.0
Patients with onsets with one or more of above	89	100	47.0

\*Since many patients had more than one presenting complaint the totals of both types of onset (150) and presenting complaints exceed that of patients.

†Itching of vulvar, scrotal or other skin areas.

‡Symptoms either proved to be due to definite neuritis or carefully investigated to rule out other diseases and subsiding promptly (usually in several weeks) after institution of diabetic care.

§Due to bacterial or mycotic organisms and including skin, genitourinary tract and feet.

¶Including angina pectoris, myocardial infarction and congestive failure or arrhythmia or both.

They had all been followed on the wards or in other clinics and had been referred to the diabetic clinic because of diabetic symptoms or glycosuria. In most cases a complete medical history had been

taken, but an additional diabetic history was elicited. Of these 182 patients, 113 who were found to have had one or more urinalyses prior to diagnosis (usually on morning post-prandial specimens) were investigated in greater detail. Patients with renal glycosuria were excluded from this study.

## RESULTS

Classified according to the types of chief complaint, the patients fell into three groups: "diabetic onset," with diabetic symptoms, "complication onset," with diabetic complications, and "casual onset," with glycosuria alone. It can be seen that the incidence of symptoms can vary significantly, depending on the method of analysis (Tables 1 and 2). However, no one complaint occurred in more than 50 per cent of the patients, and fully 23 per cent had no diabetic symptoms (Table 3). The chief complaints comprised only a minority of elicitable diabetic symptoms, individual symp-

TABLE 2 Total Diabetic Symptoms Present, Including Both Presenting Complaints and Those Elicited by Further Questioning of All Patients, Regardless of the Type of Onset

SYMPTOM	TOTAL NUMBER	PERCENTAGE OF TOTAL ONSETS
Weight loss	94	49.5
Polydipsia	72	38.0
Polyuria	69	37.0
Pruritus	49	26.0
Weakness	46	24.0
Nocturia	44	23.0
Polyphagia	17	9.0
Refractive changes	4	2.0
Headache	2	1.0
Anorexia	1	0.5
Vertigo	1	0.5
Drowsiness	1	0.5

toms being overlooked, as follows: weight loss, 64 cases (70 per cent of the total), polydipsia, 40 (58 per cent), and polyuria, 39 (57 per cent).

Table 4 confirms statistically the validity of classifying the complications separately from the symptoms of diabetes. This is further substantiated by the variation of their incidence among the different types of onset (Table 3).

Decompensation of carbohydrate metabolism can be defined quantitatively§. Thus, the patients with the diabetic type of onset are in advanced and the others in partial metabolic failure. There is a definite correlation between insulin need and the degree of metabolic decompensation (Fig. 1).

§Partial or advanced decompensation of the diabetic state is defined as simply the possession of any diabetic symptoms or of the progression of such symptoms to the status of chief complaints.

\*Assistant in medicine, Harvard Medical School; assistant in medicine, Tufts College Medical School; head, Diabetic Clinic, Beth Israel Hospital.

†In this group 97 per cent of the patients were over forty years of age; ‡At the time of diagnosis, as contrasted with 51 and 65 per cent in other groups.

§In this study the term "onset" refers to the date of clinical diagnosis and ‡ institution of treatment.

Insulin need is further shown to be greater in youth (Fig 2), but advanced metabolic decompensation raises the insulin requirement to a maximum level regardless of age (Fig 2B). The lesser insulin requirements of the older patients may be partly explained by the greater proportion of only partially decompensated patients in that group.

TABLE 3 Differential Characteristics of Types of Onset

TYPE OF ONSET	TOTAL ONSETS	PERCENTAGE OF TOTAL ONSETS	INCIDENCE OF PREVIOUS GLYCOSURIA	INCIDENCE OF DIABETIC SYMPTOMS	INCIDENCE OF DIABETIC COMPLICATIONS	AVERAGE AGE
			%	%	no / patient	
Diabetic	65	34	60	100	3 2	57
(Diabetic) complication	36	19	36	47	1 3	53
Casual	89	47	60	73	1 7	59
Totals	190	100				57
Averages			56	77	—	56

earlier date. Table 5 indicates the progressive increase in incidence of such glycosuria with increasing numbers of haphazard urinalyses performed.

TABLE 4 Coincidence of Other Diabetic Symptoms with Selected Single Diabetic Symptoms or Complications

SYMPTOM OR COMPLICATION	NO OF PATIENTS	PATIENTS WITH OTHER DIABETIC SYMPTOMS
		%
Weakness	49	92
Pruritus	44	88
Neuritis	30	66
Infection	15	40

(Fig 3). However, there is an independent ameliorating effect of age, as illustrated by the paradox that the older patient with symptoms actually

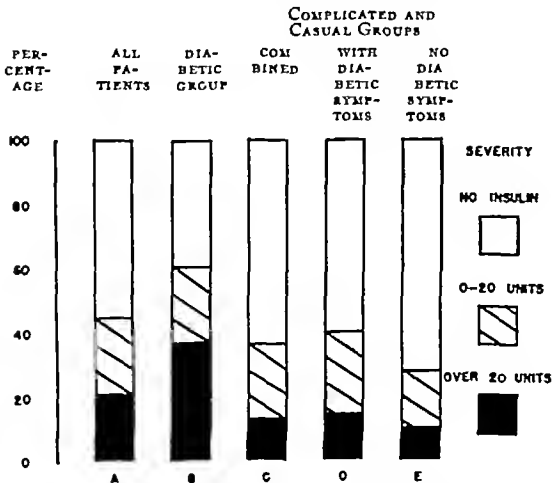


FIGURE 1 Relation between Degree of Metabolic Decompensation and Severity (Insulin Requirement). The insulin requirement was that on a diet of 175 to 200 gm of carbohydrate and 80 to 100 gm of protein and fat per day, with minimal glycosuria.

needs less insulin than the younger patient without symptoms (Fig 2). The 113 patients with a record of prior urinalyses were clinically similar to the original group of 182

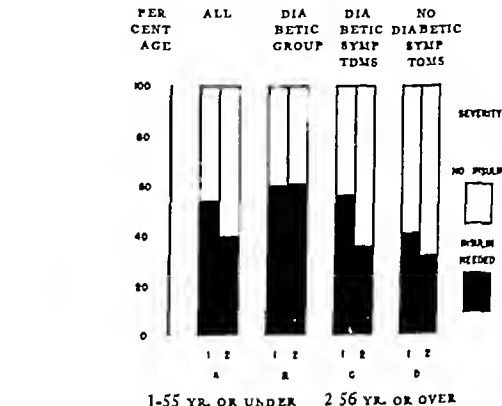


FIGURE 2 Relation between Age, Metabolic Decompensation and Severity (Insulin Requirement). Columns C and D are composed of all patients, including all types of onset, subdivided by symptoms.

and the probable diagnostic uselessness of single negative determinations. Accordingly, 13 such cases were eliminated from this study.

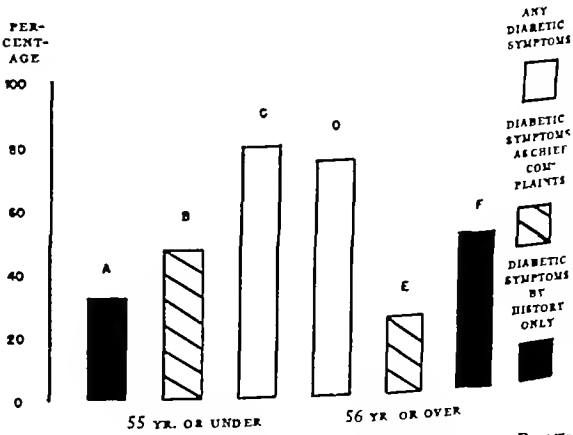


FIGURE 3 Relation between Age and Metabolic Decompensation.

Of the remaining 100 patients with previous urinalyses, 56 per cent had had glycosuria. The

other 44 per cent had had none in spite of similar distribution of urinalyses through the years. As an estimate of the duration of the glycosuric stage of the disease, 79 per cent of all the patients with positive determinations had had glycosuria for

TABLE 5 *Relation between the Number of Urinalyses Performed and the Incidence of Glycosuria*

TOTAL NO OF URINALYSES BEFORE ONSET	TOTAL NO OF PATIENTS	PATIENTS WITH GLYCOSURIA	
		NO	PERCENTAGE
1	13	0	0
2-5	48	23	48
6-10	26	13	50
11+	26	20	77

two or more years, and 36 per cent for over six years. Glycosuria preceded symptoms in all cases by two to eleven years (in 33 per cent by over six years)

TABLE 6 *Relation between the Duration of Glycosuria and the Type of Onset*

INTERVAL BEFORE ONSET OF EARLIEST GLYCOSURIA	PATIENTS WITH DIABETIC TYPE OF ONSET	PATIENTS WITH COMPLICATION AND CASUAL TYPE OF ONSET
	%	%
yr		
1	32	19
2-5	37	46
6-10	26	27
11+	5	8
Totals	100	100

The diabetic patients had the greatest incidence but the shortest duration of both glycosuria and symptoms (Table 6 and 7)

TABLE 7 *Relation between Duration of Diabetic Symptoms, Glycosuria and Type of Onset*

TYPE OF ONSET	TOTAL NO OF PATIENTS	PERCENTAGE WITH DIABETIC SYMPTOMS*	PERCENTAGE WITH GLYCOSURIA*
Diabetic	14	100	29
Complication and casual	17	65	18
Total	31		
Averages		73	23

\*Duration of one year or less

The records of the patients with untreated glycosuria showed progressive increase of the glycosuria through the years as well as the acquisition

TABLE 8 *Distribution of Types and Symptoms of Onset*

EXAMINATION OF URINE BEFORE ONSET	DIABETIC ONSET	INCIDENCE OF ANY DIABETIC SYMPTOMS AT ONSET	AVERAGE NO OF DIABETIC SYMPTOMS PER PATIENT	COMPLICATION ONSET	CASUAL ONSET
	%	%		%	%
Glycosuria	32	74	2.0	8	60
No urine	30	74	2.2	20	50

of symptoms. Clinically, the patients with negative determinations seem to have arrived at essentially the same end result (Table 8). However,

neglect of diabetes in the glycosuric stage resulted in higher insulin requirements (Fig 4). The incidence of decompensation among patients with both negative and positive determinations was equal (Table 8), so that this factor played no part in the variation of the insulin needs. Actually, prior glycosuria acted synergistically with both advanced and partial metabolic decompensation

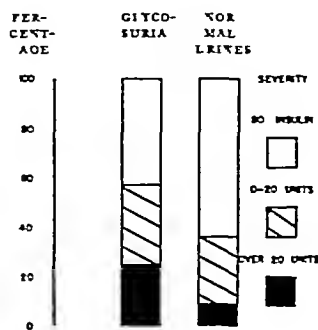


FIGURE 4 *Relation between Prior Glycosuria and Severity (Insulin Requirement)*

in increasing the insulin requirement (Fig 5 and 6). Yet prior glycosuria seemed to be a more potent factor in this direction than partial decompensation (as shown by comparison of the second and third columns of Figure 6).

To summarize, the factors that are correlated with enhanced insulin requirement, in order of effect, are a positive history of untreated glyco-



FIGURE 5 *Relation between Prior Glycosuria and Severity (Insulin Requirement) in Advanced Metabolic Decompensation (Diabetic Group)*

suria, advanced metabolic decompensation, youth, and partial decompensation.

The patients with diabetic complications as their presenting complaint were oldest, had less prior glycosuria and required least insulin. Paradoxically, 53 per cent had no diabetic symptoms even though they had complications of the disease (Table 3).

Insulin need is further shown to be greater in youth (Fig 2), but advanced metabolic decompensation raises the insulin requirement to a maxi-

patients It is assumed that any previous glycosuria in a diabetic patient with a normal renal threshold suggests the existence of diabetes at the

TABLE 3 Differential Characteristics of Types of Onset

TYPE OF ONSET	TOTAL ONSETS	PERCENTAGE OF TOTAL ONSETS	INCIDENCE OF PREVIOUS GLYCOSURIA	INCIDENCE OF DIABETIC SYMPTOMS	INCIDENCE OF DIABETIC COMPLICATIONS	AVERAGE AGE
Diabetic	65	34	%	%	%	yr
(Diabetic) complication	36	19	60	100	17 0	53
Casual	89	47	36	47	100 0	59
			60	73	14 5	57
Totals	190	100				
Averages			56	77	—	56

imum level regardless of age (Fig 2B) The lesser insulin requirements of the older patients may be partly explained by the greater proportion of only partially decompensated patients in that group

TABLE 4 Coincidence of Other Diabetic Symptoms with Selected Single Diabetic Symptoms or Complications

SYMPTOM OR COMPLICATION	No. OF PATIENTS	WITH OTHER DIABETIC SYMPTOMS
Weakness	49	92
Pruritus	44	88
Neuritis	30	66
Infection	15	40

(Fig 3) However, there is an independent ameliorating effect of age, as illustrated by the paradox that the older patient with symptoms actually

earlier date Table 5 indicates the progressive increase in incidence of such glycosuria with increasing numbers of haphazard urinalyses performed

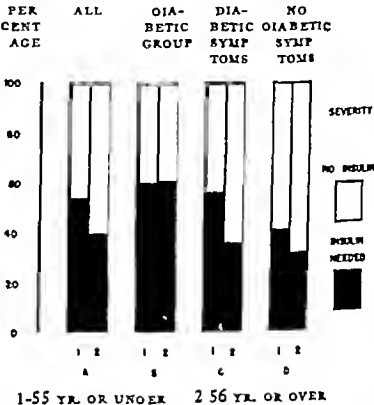


FIGURE 2 Relation between Age, Metabolic Decompensation and Severity (Insulin Requirement) Columns C and D are composed of all patients, including all types of onset, subdivided by symptoms

and the probable diagnostic uselessness of single negative determinations Accordingly, 13 such cases were eliminated from this study

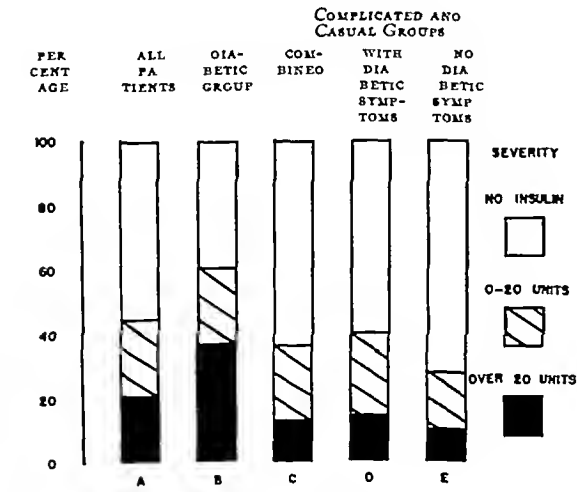


FIGURE 1 Relation between Degree of Metabolic Decompensation and Severity (Insulin Requirement) The insulin requirement was that on a diet of 175 to 200 gm of carbohydrate and 80 to 100 gm of protein and fat per day, with minimal glycosuria

needs less insulin than the younger patient without symptoms (Fig 2) The 113 patients with a record of prior urinalyses were clinically similar to the original group of 182

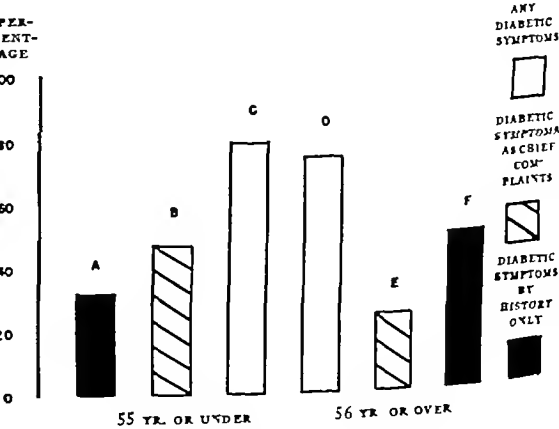


FIGURE 3 Relation between Age and Metabolic Decompensation Of the remaining 100 patients with previous urinalyses, 56 per cent had had glycosuria The

other 44 per cent had had none in spite of similar distribution of urinalyses through the years. As an estimate of the duration of the glycosuric stage of the disease, 79 per cent of all the patients with positive determinations had had glycosuria for

TABLE 5 *Relation between the Number of Urinalyses Performed and the Incidence of Glycosuria*

TOTAL NO OF URINALYSES BEFORE ONSET	TOTAL NO OF PATIENTS	PATIENTS WITH GLYCOSURIA	
		NO	PERCENTAGE
1	13	0	0
2-5	48	23	48
6-10	26	13	50
11-	26	20	77

two or more years, and 36 per cent for over six years. Glycosuria preceded symptoms in all cases by two to eleven years (in 33 per cent by over six years).

TABLE 6 *Relation between the Duration of Glycosuria and the Type of Onset*

INTERVAL BEFORE ONSET OF EARLIEST GLYCOSURIA	PATIENTS WITH DIABETIC TYPE OF ONSET	PATIENTS WITH COMPLICATION AND CASUAL TYPE OF ONSET
	%	%
3+	32	19
1	37	46
2-5	26	27
6-10	5	8
11+		
Totals	100	100

The diabetic patients had the greatest incidence but the shortest duration of both glycosuria and symptoms (Table 6 and 7).

TABLE 7 *Relation between Duration of Diabetic Symptoms, Glycosuria and Type of Onset*

TYPE OF ONSET	TOTAL NO OF PATIENTS	PERCENTAGE WITH DIABETIC SYMPTOMS*	PERCENTAGE WITH GLYCOSURIA*
		%	%
Diabetic	14	100	29
Complication and casual	17	65	18
Total	31		
Averages		73	23

\*Duration of one year or less

The records of the patients with untreated glycosuria showed progressive increase of the glycosuria through the years as well as the acquisition

TABLE 8 *Distribution of Types and Symptoms of Onset*

EXAMINATION OF URINE BEFORE ONSET	DIABETIC ONSET	INCIDENCE OF ANY DIABETIC SYMPTOMS AT ONSET	AVERAGE NO OF DIABETIC SYMPTOMS PER PATIENT	COMPLICATION ONSET	CASUAL ONSET
	%	%		%	%
Glycosuria	32	74	2.0	8	60
real urine	30	74	2.2	20	50

of symptoms. Clinically, the patients with negative determinations seem to have arrived at essentially the same end result (Table 8). However,

neglect of diabetes in the glycosuric stage resulted in higher insulin requirements (Fig 4). The incidence of decompensation among patients with both negative and positive determinations was equal (Table 8), so that this factor played no part in the variation of the insulin needs. Actually, prior glycosuria acted synergistically with both advanced and partial metabolic decompensation

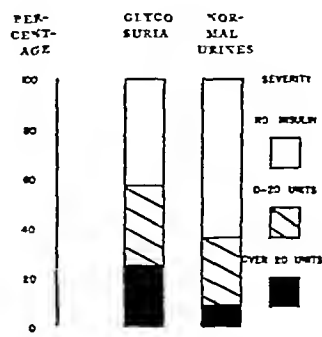


FIGURE 4 *Relation between Prior Glycosuria and Severity (Insulin Requirement)*

in increasing the insulin requirement (Fig 5 and 6). Yet prior glycosuria seemed to be a more potent factor in this direction than partial decompensation (as shown by comparison of the second and third columns of Figure 6).

To summarize, the factors that are correlated with enhanced insulin requirement, in order of effect, are a positive history of untreated glyco-

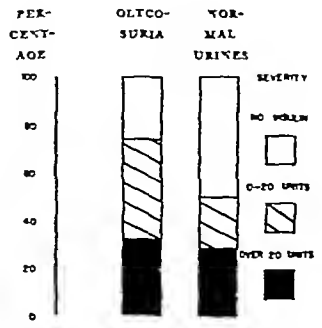


FIGURE 5 *Relation between Prior Glycosuria and Severity (Insulin Requirement) in Advanced Metabolic Decompensation (Diabetic Group)*

suria, advanced metabolic decompensation, youth, and partial decompensation.

The patients with diabetic complications as their presenting complaint were oldest, had less prior glycosuria and required least insulin. Paradoxically, 53 per cent had no diabetic symptoms even though they had complications of the disease (Table 3).

Blood sugar tests had been performed in a few cases in the years prior to diagnosis, and were usually negative because they had been performed in the fasting state. However, 9 fasting blood sugar and 3 sugar tolerance tests had been positive five

greater eventual insulin requirement than those with negative determinations.

It is conceivable that, if treatment had been started earlier in the course of the glycosuric phase, less insulin would have been required. This may also apply to the prevention of metabolic decompensation, since all 56 of these patients had been seen prior to symptoms.

The patients with negative determinations seem to be heterogeneous. There is one group with a long course, little hyperglycemia and greater tendency to develop complications and a second group with a tendency to rapid development of decompensation once hyperglycemia had appeared (Table 8). In the first, only a glucose tolerance test would have sufficed for diagnosis, in the second, time for diagnosis by any test was probably short. Even though the patients without glycosuria were in the earlier, hyperglycemic phase of diabetes, lack of treatment carried the same poor prognosis (Table 8).

Dolger<sup>7</sup> has raised the somber question whether diabetic complications are inevitable regardless of control, since they eventually occurred in all patients with well controlled diabetes. If the arteriosclerotic complications are included under this heading, this is more than an academic question in an aging population. However, the degree of hyperglycemia in the insulin-treated patient with best controlled disease is probably greater than that in the worst of the untreated patients with complications described above. Yet this group, given time, developed one or more of the diabetic complications. It is highly possible that a patient with diabetes controlled so as to enable him to enjoy normoglycemia at all times will never develop complications, but the disease probably can be so well controlled only in patients detected and treated in the early stage.

Accordingly, from the point of view of preventing metabolic decompensation or of minimizing insulin requirements and diabetic complications, a vigorous attempt to find and arrest diabetes at this early stage is highly important. Although by the age of forty (the youngest of the present group) only 1 out of 6 potential diabetic patients have already been detected,<sup>8</sup> the foregoing analysis indicates that this is none too early to begin the search for the asymptomatic stage of the remainder.

This study shows that in early diabetes single negative urinalyses for sugar do not rule out the disease. More important, even a single slightly positive test obtained under routine conditions, even though apparently overshadowed by one or more previous, simultaneous or succeeding negative tests, should be taken to mean diabetes unless a glucose tolerance test proves otherwise. A fasting blood sugar test is totally inadequate for this purpose.

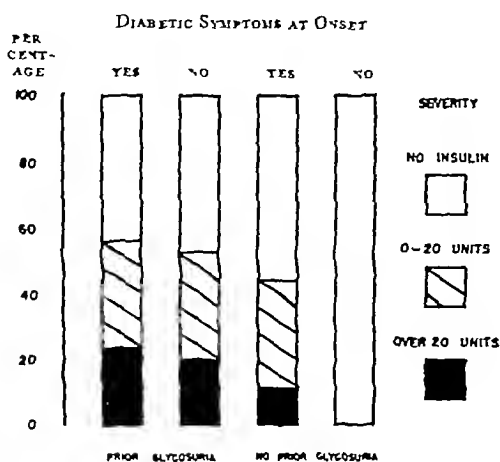


FIGURE 6 Relation between Prior Glycosuria and Partial Metabolic Decompensation (Complication and Casual Groups Combined) in Their Effect upon Severity (Insulin Requirement)

to fourteen years before final diagnosis and treatment.

### DISCUSSION

It is apparent that more exact classification of the symptoms of diabetes mellitus will help clarify concepts of this disease. Only 34 per cent of cases of advanced metabolic failure corresponded to the textbook description of the disease. A more complete history increased the incidence of symptoms to 77 per cent. However, almost a quarter of the cases remained to be discovered only by means of a glycosuria that was often only mild and intermittent.

True onset must be sharply separated from the clinical onset of diabetes. On the hypothesis of an earlier silent hyperglycemic in addition to a glycosuric stage of the disease (one to eleven years), prediagnosis diabetes would occupy a large portion of the adult life of a majority of diabetic patients. Both these periods may vary markedly in duration. In the purely hyperglycemic period, the individual patients, subjected to the stress of increasing hyperglycemia, react by developing metabolic decompensation or complications, or both. Those with more slowly developing decompensation have time to develop the complications. This explains the paradox of the appearance of a complication of this disease simultaneously with or even before symptoms.<sup>4-6</sup>

The patients with glycosuria showed both increase of their glycosuria through the years and

## SUMMARY

Only 34 per cent of a group of adult diabetics had classic diabetic symptoms as presenting complaints at the time of diagnosis. Diabetic symptoms of any type could be elicited from only 77 per cent of all the patients under consideration.

Diabetic complications were shown to be in a different category from the symptoms and were the presenting complaints of only 19 per cent.

There was a lower incidence of severe diabetic symptoms with increasing age.

Severity, as measured by insulin requirement, seemed to be correlated with the following factors: untreated prior glycosuria, metabolic decompensation and age (in order of decreasing importance).

Single, negative urinalyses are of practically no value for the exclusion of diabetes mellitus. Isolated asymptomatic glycosuria, regardless of a negative, fasting blood sugar test, should be considered diabetic unless a glucose tolerance test proves the contrary.

In 56 per cent of a group of adult patients, glycosuria had been noted up to sixteen years (80 per cent over two years) prior to definitive diagnosis. Glycosuria preceded symptoms by two to eleven years.

Detection and treatment in the earliest stage of the disease (hyperglycemic or glycosuric) is urged to prevent progression of severity or complications.

## REFERENCES

- 1 Joslin E P, Root H F, White P, Marble A and Bailey C C. *The Treatment of Diabetes Mellitus*. Eighth edition. 861 pp. Philadelphia: Lea & Febiger, 1946. P. 315.
- 2 Christian H A. *The Principles and Practice of Medicine Designed for the use of practitioners and students of medicine*. 15th edition. 1498 pp. New York: D Appleton-Century Company Inc., 1944. P. 588.
- 3 Smith B and Grishaw W H. Survey of diabetes: statistical data and control comparisons with various insulins. *Arch Int Med*, 66:46-47, 1940.
- 4 Langdon H M. Blood chemistry of patients with primary cataract. *Tr. Optic Soc. U Kingdom* 45:204-207, 1925.
- 5 O'Brien C S. Hyperglycemia in persons with advanced senile cataract. *J A M A* 98:284-291, 1932.
- 6 Sherrill J W. Diagnosis of latent or incipient diabetes. *J A M A* 77:1779-1785, 1921.
- 7 Dolger H. Clinical evaluation of vascular damage in diabetes mellitus. *J A M A* 134:1289-1291, 1947.
- 8 Joslin et al.: P. 132.

## FATAL TOXIC NEPHROSIS FOLLOWING THE ADMINISTRATION OF MERCURIAL DIURETICS\*

MICHAEL S. BRUNO, M.D.†

NEW YORK CITY

FATAL toxic nephrosis resulting from the administration of mercurial diuretics is undoubtedly a rare condition. When one considers the extent to which these drugs are used, as well as the failure to find lesions at autopsy that suggest that they have caused ill effects, it becomes evident that morbidity and mortality resulting from their use is infinitesimal.

Friedenson<sup>1</sup> has reported a case in which a total of 1250 cc of mercupurin (mercuzanthin) was administered over a period of several years to a young rheumatic patient. Autopsy failed to reveal demonstrable abnormalities in the kidneys after careful microscopical study. Gold et al.<sup>2</sup> observed the administration of mercurial diuretics in doses given two or three times weekly for periods of six months to three years and followed 3 patients who had received daily doses for periods of two to three years, without evidence of renal damage. Numerous other reports indicate that mercurials may be used frequently and over long periods without producing renal damage.

The first reported case of fatal toxic nephrosis following mercurial diuretics occurred after the administration of salyrgan.<sup>3</sup> Since then 2 additional

cases have been reported,<sup>4, 5</sup> but the diagnosis is not conclusive in either of these cases.

The history of mercurial diuretics since their introduction has been essentially a search for means of reducing their toxicity. Despite all efforts to render the organic mercurials innocuous, however, toxic reactions continue to occur.

### TYPES OF TOXIC REACTIONS

Toxic reactions following the administration of mercurial diuretics may be classified in five groups: local reactions, allergic reactions, sudden death, reactions due to the diuretic response, and mercurialism.

**Local reactions.** Burning, smarting, erythema, local histamine-like reactions and an occasional sterile abscess have occurred after intramuscular administration.

**Allergic reactions.** Allergic reactions varying from mild to severe episodes have been reported. Fox, Gold and Leon<sup>6</sup> described a case in which the patient reacted severely to the injection of both salyrgan and mercupurin. Apparently sensitivity to the drug is related to its molecular structure as a whole inasmuch as these reactions can frequently be avoided by employing another preparation. Changing the mode of administration, however, failed to alter both the occurrence and severity of reactions in patients who had previously demon-

\*From the Fourth (New York University) Medical Division, Bellevue Hospital.

†Assistant resident in pathology, Fourth (New York University) Division, Bellevue Hospital.

strated hypersensitivity. The occurrence of an allergic reaction should give the physician pause, lest further administration of the offending drug result in more severe reactions and even in death.<sup>7</sup>

**Sudden death.** This reaction has occurred only after administration by the intravenous route. In 1942 DeGraff and Nadler<sup>8</sup> collected 26 such cases. A number of cases have been reported since that time.<sup>9-10</sup> In some cases the initial dose was the fatal one, whereas in others, patients had received many previous injections without untoward reaction. Barker, Lindberg and Thomas<sup>11</sup> thought the deaths to be on a cardiac basis, and, after considerable animal experimentation, it was concluded that sudden death was the result of ventricular fibrillation. The opinion was expressed that mercurial diuretics acted primarily on the heart through the mechanism of vagal stimulation, and on the respiratory center if the vagal effect was removed.

Volini, Levitt and Martin<sup>10</sup> reported 3 cases of sudden death following an intravenous injection of a mercurial diuretic, and in 2 of these the electrocardiogram taken just prior to death demonstrated the presence of ventricular fibrillation.

**Reactions due to the diuretic response.** The diuretic property of mercurial compounds, first described by Saxl and Heilig<sup>12</sup> in 1920, has proved to be a most valuable tool in the treatment of cardiac failure. Mercurial diuretics are the most potent and effective diuretic drugs available to the physician. The urine excreted in response to the drug has a chloride ion concentration much greater than that usually present. Concomitantly, there is a decrease in the serum chloride concentration. This decline in serum chlorides is related to the fact that the kidney under the influence of a mercurial diuretic fails to reabsorb chloride ions in normal amounts, and thus the concentration in the urine is greater than that present in an equivalent volume of body fluid.<sup>13</sup> Occasionally, when there is a profuse diuresis, symptoms related to electrolyte depletion may appear. These symptoms of dehydration may occur despite the presence of peripheral edema. This is probably related to the removal of a large amount of edema fluid containing disproportionately greater concentrations of chloride ions, leaving behind extracellular fluid containing solutes in lower than normal concentration.

Another reaction that has been described is that of digitalis toxicity due to its mobilization from extracellular fluid by the mercurial diuretic. This reaction is probably not nearly so common as is thought, and concern over its occurrence may be obviated by the initiation of mercurial diuretic therapy with smaller doses in fully digitalized patients.

**Mercurialism.** Poisoning due to the mercury ion per se after the parenteral use of organic mercurial diuretics is rare. Mercurialism is seen most frequently after the administration of inorganic mer-

cury compounds, such as bichloride of mercury. The signs and symptoms of such toxicity are referable to the gastrointestinal tract and the kidney. In the kidney the effect of mercury is to produce a toxic nephrosis in which the damage is localized in the tubules. Although, as mentioned above, organic mercurial diuretics rarely cause mercurialism, probably because the mercury is in a nonionizable organic combination, when it does occur, the signs and symptoms are in no way different from those following the administration of inorganic mercury compounds. Kidney damage after the administration of organic mercurials is exceedingly uncommon, and damage sufficient to cause anuria, uremia and death is rare. For this reason the following case is reported.

### CASE REPORT

H. N., a 49-year-old woman, was admitted to Bellevue Hospital for the first time on September 15, 1947, with the chief complaints of generalized edema and severe dyspnea of 1 month's duration.

About 15 years previously, the patient was told that she had diabetes mellitus. The diabetes was well controlled for about 13 years by diet alone, but a symptomatic relapse 2 years before admission necessitated a daily injection of 35 units of protamine zinc insulin. The patient's diabetes remained well controlled thereafter. In December, 1946, the patient had begun to have exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea and ankle edema. The severity of these symptoms progressed rapidly, and she was referred to the cardiac clinic of another hospital. She was followed at weekly intervals for 3 months and was digitalized and maintained on 0.1 mg of digitoxin daily. In addition, she was placed on a low-salt and limited-fluid intake and given weekly injections of mercupurin intramuscularly. Despite all therapy the symptoms progressed and in April she was admitted to the other hospital.

Physical examination showed a blood pressure of 210/84 and evidence of hypertensive arteriosclerotic changes in both retinas and distention of the neck veins. The thyroid gland was enlarged to three times its normal size, and there were several hard nodules in the left lobe. A few crackling rales were heard at both bases, and there was evidence of free fluid in the lower half of the right side of the chest. A harsh systolic murmur was heard over the entire precordium and was loudest at the base and extended into the neck. There was also a high-pitched diminuendo diastolic murmur at the base, which was transmitted downward along the sternum to the apex. The liver edge was palpable 2 cm below the right costal margin. There was no ascites, but there was marked pitting edema of both legs and thighs and moderate sacral edema.

Examination of the urine revealed a +++ test for albumin. The fasting blood sugar was 165 mg, the total protein 6.0 gm (with an albumin-globulin ratio of 3:4:2:6), the cholesterol 278 mg, the calcium 9.4 mg, and the phosphorus 4.4 mg per 100 cc. Two phenolsulphonphthalein tests disclosed 70 and 65 per cent excretion of the dye in 30 minutes. Two urea clearance tests were reported as 35.0 and 35.7 per cent of average normal.

The patient was put on complete bed rest and a low salt and limited-fluid diet. She was continued on 0.1 mg of digitoxin daily without improvement. On the 14th hospital day, the patient was started on 2 cc of mercupurin intramuscularly and 6 gm of ammonium chloride daily. This regimen was discontinued after 3 days because the diuretic response was poor. The patient developed signs of increased fluid at both bases, and the daily dose of digitoxin was raised to 0.2 mg. In the next few days she began to lose weight. Thoracenteses on three separate occasions yielded 500, 550 and 400 cc of clear fluid. A daily dose of 6 gm of ammonium chloride and 2 cc of mercupurin intramuscularly every other day was reinstituted, with marked improvement. Between the 37th and the 39th hospital day, the blood urea

nitrogen rose to 60 mg per 100 cc, whereas it had previously ranged around 25 mg, and mercurhydrin was discontinued. The patient was discharged to the cardiac clinic asymptomatic, but at the time it was believed that she was entering a terminal phase of uremia.

The patient was seen at the clinic at weekly intervals and was given 2 cc. of mercurhydrin intramuscularly at each visit. Digtoxin, 0.1 mg daily, was continued in addition to a low-salt diet. Despite all therapy and a marked curtailment of activity, the original cardiac complaints returned within 2 months, and she was readmitted to the hospital. While there she had numerous thoracenteses, 2 cc. of mercurhydrin was administered intramuscularly three times a week, and 0.2 mg of digtoxin was given each day. She improved somewhat and was discharged to the clinic, where she was followed on the same regimen. In the next 4 weeks the patient developed severe dyspnea, orthopnea, paroxysmal nocturnal dyspnea and anasarca, and was referred for admission to Bellevue Hospital.

Physical examination revealed a poorly developed, well nourished woman in acute respiratory distress and with anasarca. The pertinent physical findings were evidence of hypertensive arteriosclerotic changes in both retinas, a markedly enlarged left lobe of the thyroid gland and distention of the neck veins. There were bubbling rales and rhonchi in both lungs and signs of fluid at the right base. The heart sounds were obscured by the respirations. The cardiac rhythm was regular. The abdomen was tense and distended, and a fluid wave was present. The liver and spleen were moderately enlarged. There was very marked edema of the lower extremities, with moderate edema of the remainder of the body.

The temperature was 98.6°F, the pulse 88 and the respirations 32. The blood pressure was 170/70.

Urinalysis revealed a +++ test for albumin, a trace of sugar, no acetone and a few hyaline and granular casts in the sediment. Examination of the blood disclosed a red-cell count of 4,090,000, with a hemoglobin of 13.4 gm, and a white-cell count of 9400, with 79 per cent neutrophils, 14 per cent lymphocytes, 6 per cent monocytes and 1 per cent basophils. The Mazzini serologic test for syphilis was negative.

It was evident that the patient's condition was grave. She was put on absolute bed rest and a low-salt diet but was given as much fluid as she desired. A daily maintenance dose of 0.2 mg of digtoxin was ordered. The patient was weighed and given 2 cc. of mercurhydrin intramuscularly and 6 gm of ammonium chloride. On the 2nd hospital day she weighed 165 pounds. A paracentesis was performed, and 3000 cc. of fluid was removed. This reduced the patient's weight to 155 pounds. Since she had had a good diuretic response the day before, another 2 cc. of mercurhydrin was administered intramuscularly. The nonprotein nitrogen was 50 mg, the chloride 401 mg, the cholesterol 172 mg, and the cholesterol esters 46 mg per 100 cc, and the carbon dioxide combining power was 29 vol per cent. On the 4th hospital day the patient weighed 152 pounds but was clinically unimproved. She developed nausea and vomiting, and the digtoxin was discontinued. On the 5th hospital day a slight icterus developed, nausea and vomiting persisted, and a bigeminal pulse was present. The nonprotein nitrogen was 60 mg, the creatinine 1.76 mg, and the total protein 7.2 gm per 100 cc, the albumin-globulin ratio was 3:1.4:1. The serum sodium was 306 mg per 100 cc, and the icteric index was 50.

X-ray films revealed engorgement of both lungs with thickened pleura and evidence of free fluid in the lower half of the right pleural space. On the 6th hospital day a third 2-cc. dose of mercurhydrin was given intramuscularly. The patient continued to excrete urine in large amounts and lost 4 pounds, the weight dropping to 153 pounds. However, the weakness progressed to the point where she could not get out of bed for her daily weighing, and it was decided that her urine output would be checked instead. On the 8th hospital day a thoracentesis was performed, and 740 cc of fluid was removed.

It was then decided that a more vigorous dehydration regimen was necessary as the clinical course was progressing rapidly downhill. Since mercurhydrin had produced excellent diuretic responses up to this point, it was decided to administer 2 cc. of mercurhydrin intramuscularly every 12 hours. Therapy was continued for 5 days. During this period the patient voided adequate amounts of urine but she became

incontinent and exact measurement of the output soon became impossible. On the 12th hospital day, mercurhydrin was discontinued since the nonprotein nitrogen had risen from 100 to 160 mg per 100 cc. in a period of 4 days. The carbon dioxide combining power dropped from 36 to 28 vol per cent. By the 14th hospital day, the patient became incontinent and disoriented. She lapsed into coma and died on the 16th hospital day.

Post-mortem examination 8 hours after death showed moderate icterus and anasarca. The trachea was shifted to the right, and a stony-hard, freely movable mass was palpable in the substance of the left lobe of the thyroid gland. The left pleural cavity was partially obliterated by dense fibrous adhesions, the right pleural cavity contained approximately 1000 cc of clear, yellow fluid. The abdominal cavity contained 4000 cc. of similar fluid.

The heart was moderately enlarged, weighing 500 gm. There was sclerosis of the leaflets of the mitral and aortic valves and some thickening and shortening of the mitral chordae tendineae. There was some hypertrophy of the left ventricle, moderate sclerosis with narrowing of the coronary arteries and focal myocardial fibrosis. The lungs were congested but were otherwise normal. The liver weighed 1320 gm, and its surface was covered by dense fibrous adhesions.

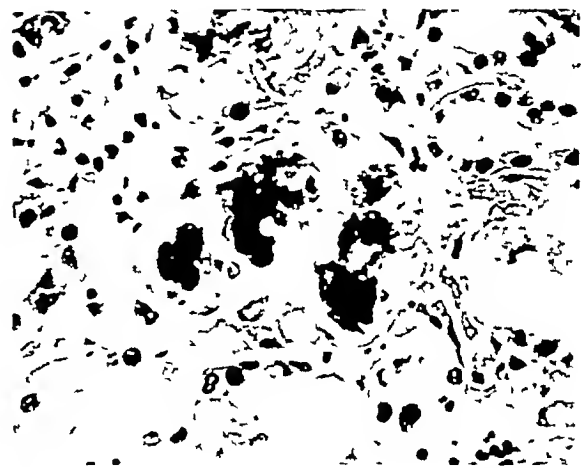


FIGURE 1 Photomicrograph of the Kidney, Showing Recent Calcium Deposition in the Necrotic Tubular Epithelium (X258)

About the efferent veins a narrow, red zone was seen. The spleen, pancreas, adrenal glands and biliary tree were normal.

The left kidney weighed 220 gm, and the right 210 gm. There was a deep U-shaped scar in the cortex of the lower pole of the right kidney. Both capsules stripped with ease, revealing a surface that was finely granular. The parenchyma was moderately congested, the cortex was thin, the pyramids were of average size and color and the corticomedullary junction was well demarcated. The pelvic organs and gastrointestinal tract were not unusual.

The thyroid gland weighed 160 gm. The left lobe was almost completely replaced by a single nodule, which was calcified and well encapsulated. The remainder of the gross anatomic findings were not remarkable.

Histologic examination showed that in the kidney many of the glomeruli had been transformed into compact masses of hyalin. In other glomeruli small rounded masses of hyalin were found at the periphery of the tuft. The basement membrane of the capsule of Bowman was frequently thickened and the space of Bowman filled with a granular precipitate. Epithelial cells of the proximal convoluted tubules were occasionally seen that were swollen, the cytoplasm being dense and the nucleus pyknotic. Some of these necrotic cells were still in their normal position, others were free in the lumens. Masses of calcium were found in the lumens of these tubules.

in others calcium clumps were present in tubules so altered that it was impossible to identify them. In places the calcium clearly lay in necrotic desquamated epithelial cells and appeared to have been recently deposited (Fig 1). More frequently the calcium deposits appeared to have been present for a longer time (Fig 2). Tubules that were lined with flattened cells having a large elongated nucleus and much chromatin were often seen. Occasional mitotic figures were



FIGURE 2 Photomicrograph, Showing Old and Recent Calcification of a Number of Kidney Tubules (X72)

noted in the epithelial cells. The interstitial tissue was moderately increased. Calcium was found to be deposited in the media of a large artery near the tip of a pyramid, and the intima of the vessel was markedly sclerotic.

The Reinsch test for mercury was performed on 10 gm of kidney tissue, and mercury was found to be present in large quantities. It was estimated that approximately 0.3 to 0.5 mg of mercury was contained in the 10 gm of kidney tissue examined.

The anatomic diagnosis of toxic nephrosis due to mercury, with extensive calcification of the kidney tubules, intercapillary glomerulosclerosis and Mönckeberg's sclerosis, was made. Other incidental lesions were those of tuberculous endometritis, biliary cirrhosis, chronic passive congestion of the spleen and lung, focal accumulation of fat in the myocardium, adenoma of the thyroid gland with calcification and hyperplasia of the parathyroid gland.

### DISCUSSION

Why fatal toxic nephrosis following the administration of mercurial diuretics should occur remains a puzzling problem. The fact that many patients receive these drugs in large doses for prolonged periods without clinical or autopsy evidence of renal damage indicates that there were unknown factors in the case presented above. Whether pre-existing kidney damage contributes to a toxic nephrosis is a much debated point, although much evidence is accumulating that patients with renal impairment respond satisfactorily to the administration of mercurial diuretics.<sup>14</sup> Indeed, as Goldring<sup>15</sup> has indicated, there is no reason for believing that a diseased kidney is more vulnerable than a normal kidney to the nephrotoxic action of mercury. "In fact, it might be supposed that the functionally im-

paired kidney is less likely to injury, since its inability to concentrate would result in a more dilute solution of mercury in its tubular fluid than in the normal kidney."

What part the large dosage of mercury played in the outcome in this case is also questionable, since such large doses have been given to other patients with renal impairment without ill effect. Although some of the calcification seen in the kidney sections appears to have been of recent origin, much of it seems to have been present for a longer time. This indicates that considerable calcification occurred while the patient was being given smaller doses of the drug as well as when she was on the larger, more recent dosage.

The mercurial diuretics are indispensable in the treatment of many cardiac conditions. The dramatic conversion of a bedridden patient in congestive heart failure to a useful social and economic position in society would often be impossible without these drugs.

In a recent study<sup>16</sup> their importance was emphasized by comparison with digitalis in the control of heart failure, and it was suggested that "in patients with chronic advanced failure who require mercurial diuretics, the mercurial is often the drug of greater importance but that in such cases with auricular fibrillation, digitalis may continue to serve a useful purpose which is not as apparent in those with a normal rhythm." Gold et al<sup>2</sup> believe "that the sequence employed in the most common practice of trying digitalis first and then adding a diuretic, if necessary, is in need of revision." The basis of their system of therapy rests upon an effective technic for dehydration, with salt restriction, free supply of water and the use of a potent diuretic. The excellent results obtained by this group in the treatment of congestive heart failure, in comparison with routine methods employed by others, testifies to the increasing importance of the mercurial diuretics.

It would be extremely unwise to discard or in any way to limit the therapeutic application of mercurial diuretics because of an occasional toxic reaction. Deaths following the administration of these drugs are extremely rare, and sudden death has occurred only after intravenous administration. There probably exist no contraindications to the use of the drugs other than severe allergic reactions and oliguria or anuria, as in acute glomerulonephritis, lower-nephron nephrosis and other conditions.

Dilution of an individual dose or slowing of the injection time has not reduced the incidence of toxic symptoms.<sup>17, 18</sup> Previous medication with other drugs, such as digitoxin, aminophylline, ammonium chloride and the barbiturates, has not lowered the animal lethal dose.<sup>8</sup>

Probably the surest way to avoid severe toxic reactions would be to avoid administering mercurial diuretics intravenously, except in the few cases of severe congestive failure with acute pulmonary edema in which time is of the greatest importance, to administer a small test dose when the drug is given for the first time, and to change the mercurial diuretic to another drug of this group when an allergic reaction has occurred

### SUMMARY

A case of fatal toxic nephrosis following the administration of multiple intramuscular doses of a mercurial diuretic is reported. Other toxic reactions are discussed.

### REFERENCES

1. Fredenston M. Prolonged use of mercury diuretics in heart failure: report of patient who received 627 injections. *Ann Int Med* 20: 306-310 1944
2. Gold H. et al. System for routine treatment of failing heart. *Am J Med* 3: 565-592 1947
3. Roseenthal M. Anatomical lesions of fatal mercurial intoxication from salyrgan. *Arch Path* 15: 352-356 1935
4. Case Records of the Massachusetts General Hospital (Case 31451). *New Eng J Med* 233:567-570 1945
5. Waife S. O. and Pratt P. T. Fatal mercurial poisoning following prolonged administration of mercuriophylline. *Arch Int Med* 78: 42-48 1946
6. Fox, T. T. Gold H. and Leon J. Hypersensitivity to mercurial diuretic with observations on its mechanism. *J A M A* 119: 1497-1499 1942
7. Brown G. Friedfeld L. Kassin M. Modell W. and Sussman R. M. Deaths immediately following intravenous administration of mercuripurin. *J A M A* 119: 1004 1942
8. DeGraff A. C. and Nadler J. E. Review of toxic manifestations of mercurial diuretics in man. *J A M A* 119: 1006-1011 1942
9. Wexler J. and Ellis L. B. Toxic reactions to intravenous injection of mercurial diuretics. *Am. Heart J* 27: 86-95 1944
10. Volini I. F. Levitt, R. O. and Martin R. Studies on mercurial diuretics: sudden death following intravenous injection: report of 3 cases with electrocardiographic studies in 2. *J A M A* 128: 12-17 1945
11. Barler M. H. Lindberg H. A. and Thomas M. E. Sudden death and mercurial diuretics. *J A M A* 119: 1001-1004 1942
12. Saxl P. and Heilig R. Über die diuretische Wirkung von Novasuröl und anderen Quecksilberinjektionen. *Wien klin Wchnschr* 33: 943 1920
13. Blumgart, H. L. Gilligan D. R. Levy R. C. and Volk, M. C. Action of diuretic drugs. I. Action of diuretics in normal persons. *Arch Int Med* 54: 40-81 1934
14. Pearlmutter M. Personal communication
15. Cornell University Medical College and New York Hospital. Conferences on Therapy. Use of mercurial diuretics. *New York State J Med* 46: 62-72 1946
16. Modell W. Pearlmutter M. and Clark D. A. Relative importance of digitalis and mercurial diuretics in treatment of advanced heart failure. *Federation Proc* 6: 358 1947
17. DeGraff A. C. and Lehman R. A. Acute toxicity of mercurial diuretics. *J A M A* 119: 998-1001 1942
18. Tyson M. C. Danger of intravenous mercurial injections in nephrosis. *J A M A* 117: 998 1941

### PHYSICAL RISKS OF ELECTROCONVULSIVE THERAPY

RUDOLPH KALDECK, M.D.,\* WILLIAM F. McLAUGHLIN, M.D.,† JOSÉ GURRI, M.D.,‡ AND JOSEPH I. WASSERSUG, M.D.§

BOSTON

ELECTROSHOCK therapy is the most widely used of the somatic methods for the treatment of mental diseases. It is not the purpose of this investigation to describe the therapeutic result achieved or to compare its relative value with other procedures, both somatic and psychotherapeutic. We wish only to evaluate the physical risks involved in this form of treatment. Many papers have been written in the past few years about the subject. Kalinsky and Hoch,<sup>1</sup> in their excellent textbook, summed up their own experiences and reviewed the literature up to 1945. We hope the close cooperation of our medical and psychiatric staff has made it possible for us to add a few findings of practical value.

This report is based on the observation of 628 patients who received 8082 electroshock treatments at the Boston State Hospital during the six-year period from 1942 through 1947. The only fatal case associated with electroshock therapy occurred early in this period.

A twenty-three-year-old man, who had been suffering from paranoid schizophrenia for more than four years, died on March 14, 1942, eighteen hours after the eighth treatment in a second series of electroshock therapy. Autopsy by the state pathologist, Dr. Jetter,<sup>2</sup> who reported the case in detail, revealed an acute glomerulonephritis, which was considered to be of several days' duration, acute focal myocarditis and acute pulmonary edema. Physical and laboratory examination prior to the beginning of the treatment was negative.

Because of this unfortunate experience, we became extremely conservative in the selection of patients. Practically every kind of organic disease and physical defect was considered a contraindication to this form of therapy. However, with increasing experience, it became obvious that such an overcautious attitude deprived too many patients in need of the treatment of its benefit. An increasing number of patients with abnormal findings and advanced age were accordingly treated, without ill effect, although this does not mean that electroshock therapy can be used indiscriminately.

A thorough physical examination of every patient preceded the electroconvulsive therapy. It consisted, in addition to a routine clinical exam-

\*Assistant in psychiatry. Tufts College Medical School senior physician. Boston State Hospital.

†Senior physician. Boston State Hospital.

‡Assistant in psychiatry. Boston University School of Medicine senior physician. Boston State Hospital.

§Instructor in medicine. Tufts College Medical School, visiting physician in tuberculosis. Boston State Hospital outpatient physician. Boston City Hospital, visiting physician. Quincy City Hospital.

ination, of a 7-foot x-ray film of the chest, urinalysis, complete blood count, a serologic blood test and a determination of the blood sugar and non-protein nitrogen. The temperature, pulse, respiratory rate and blood pressure were taken prior to each treatment. Additional tests, such as sputum examinations, sedimentation rate and electrocardiograms, were done when thought necessary. Whenever these examinations justified any doubt, the patient was seen by medical consultants to whom we are very grateful for their help and understanding in weighing the risk of the treatment against the expected therapeutic effect. Definite contraindications were found to be rare.

### AGE

It is now generally accepted that old age in itself is not a contraindication to the use of electroshock therapy. Feldman et al.<sup>2</sup> treated 53 patients over sixty-five years of age, none of whom showed any clinical evidence of injurious effects from the treatment. Thirty-one of our patients were over sixty years old, 4 being sixty-nine and 1 seventy-two. It might be added that during the current year we have already treated 4 patients over seventy. One had diabetes, and several had generalized arteriosclerosis and enlargement of the heart as shown by x-ray study. Marked hypertension was present in 5 elderly patients, the blood pressure was 185 systolic, 110 diastolic, in one, and 172 systolic, 114 diastolic in another. Some had clinical and electrocardiographic evidence of coronary-artery disease. A sixty-nine-year-old woman had had a coronary thrombosis four years previously while a patient in a private mental hospital. Although she was severely depressed and agitated, electroconvulsive therapy was considered too hazardous at the time. Later, transferred to this hospital, she was mentally unimproved, and electrocardiographic examination confirmed the diagnosis of coronary infarction. Her mental condition was markedly improved after thirteen electroshock treatments. This woman and the other elderly patients withstood the treatment well and developed no complications.

As children have not been admitted to this hospital during the past few years, we can report only 1 case—that of an eleven-year-old girl, who was in an extremely stuporous condition and had had to be fed by tube daily for several months. Six weeks prior to admission, a ventriculogram had been performed in another hospital to exclude organic brain disease. As her mental condition did not improve, she was given seven electroshock treatments, with excellent results. She acted and talked like a normal child and was soon back in school.

### UNDERNUTRITION

Undernutrition is a frequent finding among mental patients on account of overactivity and refusal to eat. In the preparation of these patients for shock treatment it is often impossible to improve their nutritional condition. However, it is very important not to treat them in a state of dehydration. This can be averted by tube feedings and parenteral administration of fluids if the patient cannot be induced after the intravenous use of sodium amytal to take nourishment. However, too much time should not be taken in preparing the patients, since it is a common and gratifying experience to find them eating ravenously after one or two treatments. The nutritional condition improves so rapidly in these cases that the treatment can be considered a life-saving procedure. One patient, a twenty-five-year-old woman with catatonic excitement, showed extreme emaciation, amenorrhea, loss of hair, hypotension, subnormal temperature and hyperpigmentation so that an endocrinologic disturbance, such as Addison's or Simmonds's disease, was seriously considered. After seven electroconvulsive treatments, she was in full remission, her physical condition improved rapidly and she was able to leave the hospital.

Another patient, a thirty-one-year-old man who was 6 feet tall, and whose weight was down to 83 pounds, in a catatonic stupor, refused to eat and was fed by tube daily for two months. Permission for shock treatment was received from his family only after his weight had decreased so severely that his condition had become critical. After the second electroshock treatment, he began to eat by himself, and his physical condition improved rapidly. Six weeks after a series of fifteen electroconvulsive treatments, his weight was 125 pounds, he too was able to leave the hospital on a visit. In these 2 cases, the shock therapy was life saving. They indicate that severe malnutrition is no contraindication to convulsive treatment.

Secondary anemia, which is often associated with malnutrition, was found in several patients. Even when the red-cell count was less than 3,000,000, the treatment was not excluded. With better food intake after the electroshock therapy, the condition of the blood also improved. When necessary, the patients received iron and liver medication, but electroconvulsive therapy was not delayed by the medical treatment.

### CARDIOVASCULAR DISEASES

Cardiovascular diseases present the most common cause for withholding electroconvulsive treatment from patients in need of it. However, as early as 1942, Myerson<sup>1</sup> pointed out that the damage to the heart from the psychosis itself put a greater burden on the cardiovascular system than the shock treatment. Among our patients

were 27 in whom enlargement of the transverse diameter of the heart was noted on 7-foot x-ray films. Ten of these patients showed clinical and roentgenologic evidence of arteriosclerotic heart disease, often accompanied by generalized arteriosclerosis. One patient, a sixty-two-year-old woman, with a diagnosis of psychosis with cerebral arteriosclerosis, received twelve electroshock treatments with no untoward physical effects. However, she remained agitated and depressed, and lobotomy was later performed. At operation, the neurosurgeon found advanced arteriosclerosis of the cerebral vessels, with severe atrophy of the brain. After lobotomy, her mental condition showed marked improvement. This is a proved case of advanced cerebral arteriosclerosis in a patient who withstood a course of electroshock treatment without physical damage.

Twenty patients had abnormal electrocardiographic findings, varying from simple left-axis deviation, low voltage and an inverted T wave in Lead 4 to signs of definite coronary-artery disease. The case of a woman with coronary thrombosis was described above among the group of elderly patients. Another patient, who was known to have congenital heart disease (patent ductus arteriosus), received nineteen electroshock treatments. Still another patient, a thirty-seven-year-old woman with a severe agitated depression, had rheumatic heart disease with mitral stenosis and aortic insufficiency. She had a history of several episodes of severe decompensation. After five electroshock treatments, she became decompensated again and had to be digitalized. Her mental condition was markedly improved. All the other heart cases showed no untoward physical effects whatsoever.

Marked hypertension was found in 16 patients, 4 of them with a systolic pressure of more than 200. One woman of fifty-eight with an enlargement of the heart on x-ray study had a blood pressure of 220 systolic, 140 diastolic. Her severe, agitated depression, which did not respond to any kind of sedation, made electroshock necessary in spite of the risk. She had seventeen treatments, and like the rest of the patients with hypertension, did not show any ill effect. In many cases the blood pressure dropped to normal levels when, as a result of the treatment, agitation and tension subsided. Seven patients, who showed very little or no mental improvement, had marked hypertension at the end of the treatment although the blood pressure had been normal at the onset. In 1 patient, a forty-five-year-old woman, the blood pressure, which had been 138 systolic, 92 diastolic, before treatment, rose to 174 systolic, 110 diastolic, after nine electroshock treatments. In a few other patients it went up and down in a way that could not be easily understood, since it was, sometimes, incon-

sistent with the emotional state of the patient. One observation especially appeared to be remarkable. A woman in her middle fifties, in a severe depression very close to complete stupor, had a blood pressure of 158 systolic, 108 diastolic, at the beginning of treatment. After only four treatments she was in full remission, but her blood pressure rose to 220 systolic, 118 diastolic. The patient left the hospital four weeks after the treatment and remained well, both physically and mentally, during a follow-up period of more than a year. Obviously the blood pressure became high when she came out of her stupor, hypertension was normal for her cardiovascular system as soon as compensation was established.

Among 4 patients with hypotension a forty-nine-year-old woman, who had had a blood pressure of 90 systolic, 70 diastolic, showed prolonged cyanosis after the first electroshock treatment. With improvement of her mental condition her blood pressure and pulse pressure went up, and further treatment went on without any incident.

Five or six patients in whom cyanosis and poor quality of pulse persisted for more than a few minutes after treatment had not shown any physical abnormal findings prior to the treatments. They recovered instantaneously after application of oxygen and stimulants.

None of these patients with cardiac findings, hypertension, hypotension or unusual oscillations of blood pressure showed any ill effects from the treatment.

#### PULMONARY TUBERCULOSIS

The high incidence of pulmonary tuberculosis among patients in mental institutions is well known. The question frequently arises whether or not electroshock therapy should be given. Several cases have been reported in the literature with spread or reactivation of the tuberculous lesions after electroconvulsive therapy. The increased intrathoracic pressure, the pulmonary congestion and the anoxia may all have deleterious effects. However, it should be kept in mind that soft and active lesions are prone to spread anyway. There are no investigations available that would demonstrate whether such activations occur more frequently with or without electroshock therapy. Norman and Shea<sup>5</sup> reported from the Foxborough State Hospital the cases of 2 patients who developed active pulmonary tuberculosis after electroconvulsive therapy. Will and Duval<sup>6</sup> described another case from St. Elizabeth's Hospital in Washington, D. C., and reviewed the whole literature up to 1947.

In our own cases we tried to evaluate the criteria of activity or inactivity as much as possible before giving electroconvulsive therapy. It is obvious that x-ray findings are not the sole basis for the

diagnosis Whenever the roentgenologic impression indicated a tuberculous process, the patient was seen in consultation by a tuberculosis consultant, and further laboratory examinations such as examination of the sputum or stomach washings for tubercle bacilli and sedimentation rates were performed

Twenty-five patients had healed pulmonary tuberculosis, the findings in 15 additional cases were considered doubtful All these patients received routine courses of electroshock therapy without activation of the pulmonary process

Eight additional patients were considered to have active pulmonary tuberculosis, and 2 probably active The diagnosis was based on x-ray findings, sedimentation rate and evaluation by the tuberculosis consultant, although acid-fast bacilli could not be found One of these patients, with a manic-depressive psychosis, had an exudative pleurisy of the left side prior to shock treatment After a series of fifteen electroconvulsive treatments, her great overactivity subsided, but she developed a pleuritic exudate on the other side A tuberculous pleurisy often spreads to the other side, and it is difficult to say how much the shock treatment had to do with it The other 7 patients in whom the examination prior to electroconvulsive therapy revealed a tuberculosis of some activity showed mental improvement or at least less agitation after shock treatment This may be the reason why their mild tuberculosis is taking a favorable turn

Another case presented an extraordinarily grave problem an active pulmonary tuberculosis, of serious prognosis in itself, occurred in a patient who was in a state of severe catatonic excitement It was obvious that active therapy had to be started immediately As any therapist in this field may face such a case some day, and will have to make his decision, this case is presented in greater detail

A 20-year-old Negress was admitted in an active schizophrenic attack, which had started a few days before Her catatonic excitement became gradually worse sedation and continuous baths were applied with little success She refused to eat and had to be fed by tube She lost weight and had subfebrile temperatures A chest plate revealed soft areas of infiltration in the right apex and the first right intercostal space The blood sedimentation rate was increased

On July 18, 1947, a right pneumothorax was performed by one of us (J D W) The filling was increased 2 days later and resulted in good collapse of the lung On July 21, she received the first electroconvulsive treatment Subsequently, every other day she had a shock treatment or a fluoroscopic checking of the lungs with refilling of the pneumothorax, when necessary Her condition improved steadily After the first shock treatment she was eating, and the intervals between single treatments could be made longer Altogether she had nineteen electroshock treatments, the last on September 3 One month later, she was released from the hospital, mentally in full remission and with the right lung in good collapse At present she is attending one of the tuberculosis units in this city for maintenance of her pneumothorax and is working as an office clerk

Two patients had had normal chest films prior to electroconvulsive therapy Both had been in mental hospitals for years One, a twenty-eight-year-old woman, with chronic catatonia, had five electroshock treatments without improvement Six months after convulsive therapy, she developed a rapidly progressive pulmonary tuberculosis from which she died three months later The other patient, a sixty-three-year-old woman with agitated depression and confusion, had signs of cerebral arteriosclerosis On account of her severe agitation she received eighteen electroconvulsive treatments within a period of ten weeks without improvement A few weeks after discontinuation of shock therapy, she developed a high temperature, additional chest films showed a bilateral active tuberculosis The pulmonary infection took a rapid course, and she died four months later After the development of the tuberculosis, the chest plates that had been taken of both patients prior to shock treatment were scrutinized again and even then the films had to be considered normal As a certain number of patients with chronic schizophrenia may be expected to develop pulmonary tuberculosis, it remains an open question if and how far the shock treatment should be considered responsible for the activation of the process In any case, as the chest films prior to electroconvulsive therapy were entirely normal, we had no reason to withhold the treatment in these cases

In summary our experiences with the problem of electroconvulsive therapy of mental patients who are simultaneously suffering from pulmonary tuberculosis indicate that the treatment carries definite risks On the other hand, if the patient becomes exhausted by overactivity or refuses to eat, the prognosis of the pulmonary process is in itself very serious In each case it is necessary to evaluate carefully the degree of the tuberculous lesions, their possible aggravation by the psychosis and the result expected from the shock treatment There is a good argument for the use of electroconvulsive therapy in selected cases of pulmonary tuberculosis even if some degree of activity is present If the activity is high or if there is a history of recent hemorrhage, shock should be given only when the pulmonary process has been controlled by some collapse measure, such as pneumothorax There are cases in which collapse therapy and electroshock have to be applied simultaneously

#### BRONCHIECTASIS

Six patients had roentgenologic signs of bronchiectasis without increased secretion They had no ill effects from electroshock therapy

#### ACUTE INFECTIONS

All patients suffering from acute infections should be excluded from electroshock therapy

Whenever any upper respiratory infection was present, treatment was postponed. The same rule was followed in local infections as abscesses or cellulitis. A few patients with chronic otorrhea were given electroshock therapy without ill effects. These cases were evaluated first by clinical examination, x-ray study of the petrous bones, blood sedimentation rate and white-cell count. When any activity of the ear infection was found, the patients were not treated. If there could be any doubt about the rule that patients with acute infections should not be given electroshock treatment, this was re-emphasized by the only fatal case connected with electroshock that occurred in this hospital. As mentioned above, post-mortem examination in that case revealed an acute glomerulonephritis of several days' duration. One of the 2 fatal cases after electroshock treatment recently reported by Riese,<sup>7</sup> was very similar to that discussed above. A thirty-year-old obese woman died forty-eight hours after electroshock treatment. Post-mortem examination showed subacute cystitis and acute pyelonephritis. If any conclusions can be drawn from cases of this kind, they are that intercurrent infections must be watched for during a course of electroshock treatment as well as prior to it. A urine examination should be made at least once a week during a course of treatment.

#### BONE DISEASE, FRACTURES AND DISLOCATIONS

Any kind of bone lesion found prior to electroshock treatment is important, since a higher incidence of fractures can be expected in such cases. A few observations confirmed this opinion. One patient, whose x-ray examination had shown narrowing of the interspaces between the dorsal vertebrae, sustained a fracture of the third dorsal spinous process from electroshock therapy. Another patient, a thirty-eight-year-old woman, had an ankylosis of the right elbow from an old fracture. During the sixth electroshock treatment, she suffered a fracture of the neck of the right humerus, most probably because too much pressure was exerted on the ankylotic limb during shock.

Observations of this kind should not lead to the exclusion of the needed treatment but should indicate that extreme care is necessary in placing such patients on the table and in exerting the proper amount of force in restraining them. As a matter of fact, in our series, numerous patients with bone disease were given electroshock treatment without damage. (A case of spina bifida is described below in the section on central-nervous-system disorders.) One patient had a severe kyphoscoliosis, and shock treatment had been considered in another hospital as too dangerous. As her catatonic excitement persisted, she received a series of electroshock treatments without ill effects. Five patients had scoliosis of moderate

degree, 2 had marked arthritic changes of the spine on x-ray study. One woman, thirty years of age, had multiple areas of increased calcification in the frontal region, which was considered roentgenologic evidence of enostosis frontalis. She received fifteen electroshock treatments without untoward result. Six patients had x-ray findings and histories of fractures prior to the treatment: an elderly woman had sustained a fracture of the jaw in an automobile accident only two and a half months before she had electroshock treatment, another patient, a sixty-five-year-old woman, had had a fracture of the right hip one year previously, 3 patients had old rib fractures, and 1 patient had an old occipitoparietal fracture of the skull, with slight bone depression and negative neurologic findings. All these patients had no ill effects from the treatment.

Fractures due to electroshock treatment occurred in 11 patients, including the 2 cases with previous bone disease mentioned above. Of the 9 patients without previous bone disease, 8 sustained fractures of the spine. As other observers have noted, all these fractures healed with amazingly little discomfort to the patient and without orthopedic treatment. One patient, a young man of nineteen in poor nutritional condition, suffered a fracture of the left acetabulum. Unlike the course in the case reported by Myerson,<sup>4</sup> the head of the femur did not penetrate into the pelvis, and there was no marked displacement of the fragments.

One dislocation of a shoulder occurred in a patient who later gave the information that he had had such an injury before. The humerus was replaced immediately without difficulty. In 3 cases dislocation of the jaw was easily reduced.

When the measures necessary to prevent injuries to the skeletal system are considered, the need of proper placing on the table, with one pillow under the small of the back and another under the knees of the patient, should be stressed. Only moderate restraint should be exerted by the assistants who hold the patient. Another measure, often recommended, is the preliminary administration of curare. As the drug has been tried by us in only a few cases, our experience is not sufficient to justify an opinion about this. However, the observations of other workers seem to show that the dangers of this drug outweigh its advantages. During a twelve-month period, ending June 30, 1946, 3 deaths occurred incident to the administration of electroshock treatment in all mental institutions of Massachusetts, 2 of these were associated with preliminary curare medication.<sup>8</sup> Several other fatal cases after the use of curare are reported in the literature. Of the 2 fatal cases recently described by Riese,<sup>7</sup> 1 was mentioned above in connection with acute infections. The other death occurred in a patient who had received curare prior to electroshock therapy. These and similar reports

explain our reluctance to use curare in the preparation for convulsive treatment

### CENTRAL-NERVOUS-SYSTEM DISEASES

A seventy-four-year-old man with seropositive syphilis and a severe depression had a positive cerebrospinal-fluid Wassermann reaction. Another patient, a woman of forty, had residual poliomyelitis. Both had no ill effects from the shock treatments.

Another patient, a thirty-one-year-old woman with a schizoaffective psychosis, who had not shown any abnormal physical findings prior to shock therapy, developed a transient hemiplegia of three days' duration after treatment. The paralysis disappeared without lasting damage to the patient. As there is still insufficient knowledge of the basic changes in the central nervous system caused by electroshock therapy, such a case might be of value toward a better general understanding of the pathology of electrically induced convulsions. In a separate report an attempt was made to explain this transient hemiplegia on the basis of vascular spasm, causing reversible structural damage in the motor pathways of one side of the brain.<sup>9</sup>

Another patient presented a considerable problem in the decision whether to give her electroshock therapy. She was a woman of thirty, who had a sacral spina bifida with a dorsally protruding meningocele the size of a large hen's egg. Extensive involvement of the spinal cord had caused a spastic paraparesis. Her right leg and several toes of her left foot had been amputated. She had dementia praecox with depressive and paranoid features, and was almost continuously disturbed. She was noisy and threw dishes and similar objects at nurses and doctors. Numerous consultations were had for two years, since we hesitated about giving her shock therapy. Finally, when her mental condition became worse and tube feeding had to be given frequently, a course of electroconvulsive treatment was started. Up to this writing the patient has received twenty treatments with no physical ill effects and marked mental improvement. Although some paranoid trends are still present she is well behaved and laughs and talks with everybody who comes to see her.

### MENSTRUATION AND PREGNANCY

Normal menstruation is no contraindication to the treatment. Only when the hemorrhage was profuse did we wait until it diminished. In the literature are several reports of pregnant women who received electroshock treatment without damage to mother or child.<sup>1</sup> We had no pregnant women in our series.

### DIABETES MELLITUS

Five patients had diabetes mellitus, 1, a woman of sixty with a manic psychosis, had blood sugar values up to 275 mg per 100 cc. She had an excellent remission after nine shock treatments. She, as well as the other diabetic patients, withstood electroshock therapy without untoward physical effects.

### SUMMARY

The physical risks of electroconvulsive therapy are discussed on the basis of a material of 8082 treatments received by 628 patients. Thirty-one of them were over sixty, and 5 over seventy years of age. All these patients responded well to the treatment, as did a child of eleven. Even severe undernutrition is no contraindication to the treatment.

About 50 patients had signs of cardiovascular diseases, such as arteriosclerosis, enlargement of the heart, abnormal electrocardiographic findings, rheumatic heart disease and hypertension. One had definite signs of coronary-artery disease, and another a severe congenital abnormality of the heart. In many patients, the increased blood pressure went down when agitation subsided as a result of electroshock therapy. In a few other cases, the blood pressure went up or up and down in a way that was not always consistent with the patient's emotional state.

Eight patients with active and 25 with arrested pulmonary tuberculosis were treated in this series. Shock therapy of mental patients who are suffering from tuberculosis carries definite risks, but in selected cases, electroshock therapy has to be given even if the tuberculosis is active. If there is a history of recent hemorrhage or if the activity is high, shock should be given only when the pulmonary process has been controlled by collapse therapy. In 1 case electroshock therapy and pneumothorax were applied simultaneously.

Patients suffering from acute infections should be excluded from electroshock treatment, and every effort should be made to discover intercurrent infections prior to and during a course of electroshock. This was emphasized by the one fatal case after electroshock therapy that occurred in this series.

Eleven cases of fractures due to electroshock treatment were observed, 2 of them occurred in patients who had bone disease prior to the treatment. All fractures healed without permanent damage. Regarding the preliminary administration of curare, the opinion is expressed that the danger of this drug outweighs its advantage.

A few patients with diseases of the central nervous system were treated without ill effects. Another patient, who had no abnormal physical findings prior to electroshock treatment, developed a

transient hemiplegia following the treatment, most likely on the basis of vascular spasm, causing reversible structural damage to parts of the brain

### REFERENCES

1. Kalinovsky L. B. and Hoch P. H. *Shock Treatments and Other Somatic Procedures in Psychiatry* 294 pp New York Grune & Stratton 1946
2. Jetter W. W. Fatal circulatory failure caused by electric shock therapy *Arch. Neurol. & Psychiat.* 51 557-563 1944
3. Feldman F. Susselman G. Lipetz, B. and Berrera S. E. Electric shock therapy of elderly patients *Arch. Neurol. & Psychiat.* 56 158-170 1946
4. Myerson A. Further experience with electric shock therapy in mental disease *New Eng. J. Med.* 227 405-407 1942.
5. Norman J. and Shea J. T. Three years experience with electric convulsive therapy *New Eng. J. Med.* 234 857-860 1946
6. Will O. A. Jr. and Duval A. M. Use of electro-shock therapy in psychiatric illness complicated by pulmonary tuberculosis report of case *J. Nerv. & Ment. Dis.* 105 657-646 1947
7. Riese W. Report of two cases of sudden death after electric shock treatment with histopathological findings in central nervous system. *J. Neuropath. & Exper. Neurol.* 7 98-100 1948
8. Yearly report of Massachusetts Department of Mental Health about medico legal deaths in year ending June 30 1946.
9. Kaldeck, R. Transient hemiplegia following electroconvulsive treatment. *Arch. Neurol. & Psychiat.* 59 229-232 1948

## MEDICAL PROGRESS

### X-RAY DIAGNOSIS OF PULMONARY LESIONS

LAURENCE L. ROBBINS, M.D.\*

BOSTON

THE roentgenologic examination of the chest readily reveals abnormality, but the determination of the exact nature of the process is more difficult. One way of approaching the diagnosis is dependent upon a knowledge of gross anatomy, pathology, physiology and x-ray shadows, in addition to having available the brief facts concerning the clinical status of the patient. The material collected for this review is presented on this basis.

From the anatomic standpoint, the recent studies of Boyden and his associates<sup>1-3</sup> of the bronchial and vascular structures of the lung, particularly the relation of the various segments, have been of value. Roentgenologically, Robbins et al.<sup>4-10</sup> have demonstrated the segments as they appear in collapse and the configuration of certain anatomic structures, such as the vascular network and hilar shadows and the interlobar septums or fissures, these have been found to be of importance in diagnosis. Medlar,<sup>11</sup> in a study of 1200 pairs of lungs, found that on the left side the major fissure was complete in 82 per cent, whereas on the right it was complete in approximately 70 per cent, and the minor fissure was complete in 38 per cent, in the other cases, the fissure was partially present (Whether the fissure is complete or not is of relatively little importance in determining its position roentgenologically in the majority of patients).

The azygos septum is important only in that it should not be confused with an abnormal process. Its incidence, as pointed out by Etter,<sup>12</sup> is 1.384 chests examined, Pendler<sup>13</sup> found it to be 1.6 per cent of 25,000 fluororontgenograms.

Lachman<sup>14</sup> reviewed present-day teaching of anatomy from a critical standpoint, stressing the

fact that the dynamic aspects as disclosed by x-ray examination differ considerably from the anatomy of the cadaver. Anatomy is not a fixed study, but one in which there is a good deal of motion of most of the thoracic structures. The posterior reflections of the pleura, sometimes spoken of as the pleuropleural demarcation lines,<sup>15</sup> are of diagnostic importance, loss of visibility of these lines in the roentgenogram may signify enlargement of the heart, pulmonary disease or fluid in the pleural space.

Westermarck<sup>16</sup> has utilized changes in intra-alveolar pressure in diagnosis of pulmonary as well as mitral lesions. He has been able to show that the degree of filling of the pulmonary vessels and of the chambers of the heart is profoundly affected by intra-alveolar pressures. A water manometer with a tube held in the patient's mouth is used so that pressures of water from -15 up to +80 cm are obtained. This method can also supply a rough measurement of the pressure in the pulmonary arteries by determining at which level vessels in the hilus diminish in size.

### TECHNIC OF EXAMINATION

From the technical point of view, there is still a tendency for utilization of the black and white films showing marked contrast. This technic is rather attractive, but unless additional procedures, such as the Bucky or grid films or more complicated methods are used the information that might be obtained by means of the roentgen-ray examination is considerably curtailed. For those who desire as many data as possible from conventional films, the optimum kilovoltage technic, as suggested by Fuchs,<sup>17</sup> will yield a far greater return. This technic produces a film that is rather gray, but all portions of the chest are adequately penetrated so that more

\*Associate in radiology, Harvard Medical School; radiologist-in-chief, Massachusetts General Hospital.

explain our reluctance to use curare in the preparation for convulsive treatment

### CENTRAL-NERVOUS-SYSTEM DISEASES

A seventy-four-year-old man with seropositive syphilis and a severe depression had a positive cerebrospinal-fluid Wassermann reaction. Another patient, a woman of forty, had residual poliomyelitis. Both had no ill effects from the shock treatments.

Another patient, a thirty-one-year-old woman with a schizoaffective psychosis, who had not shown any abnormal physical findings prior to shock therapy, developed a transient hemiplegia of three days' duration after treatment. The paralysis disappeared without lasting damage to the patient. As there is still insufficient knowledge of the basic changes in the central nervous system caused by electroshock therapy, such a case might be of value toward a better general understanding of the pathology of electrically induced convulsions. In a separate report an attempt was made to explain this transient hemiplegia on the basis of vascular spasm, causing reversible structural damage in the motor pathways of one side of the brain.<sup>9</sup>

Another patient presented a considerable problem in the decision whether to give her electroshock therapy. She was a woman of thirty, who had a sacral spina bifida with a dorsally protruding meningocele the size of a large hen's egg. Extensive involvement of the spinal cord had caused a spastic paraparesis. Her right leg and several toes of her left foot had been amputated. She had dementia praecox with depressive and paranoid features, and was almost continuously disturbed. She was noisy and threw dishes and similar objects at nurses and doctors. Numerous consultations were had for two years, since we hesitated about giving her shock therapy. Finally, when her mental condition became worse and tube feeding had to be given frequently, a course of electroconvulsive treatment was started. Up to this writing the patient has received twenty treatments with no physical ill effects and marked mental improvement. Although some paranoid trends are still present she is well behaved and laughs and talks with everybody who comes to see her.

### MENSTRUATION AND PREGNANCY

Normal menstruation is no contraindication to the treatment. Only when the hemorrhage was profuse did we wait until it diminished. In the literature are several reports of pregnant women who received electroshock treatment without damage to mother or child.<sup>1</sup> We had no pregnant women in our series.

### DIABETES MELLITUS

Five patients had diabetes mellitus, 1, a woman of sixty with a manic psychosis, had blood sugar values up to 275 mg per 100 cc. She had an excellent remission after nine shock treatments. She, as well as the other diabetic patients, withstood electroshock therapy without untoward physical effects.

### SUMMARY

The physical risks of electroconvulsive therapy are discussed on the basis of a material of 8082 treatments received by 628 patients. Thirty-one of them were over sixty, and 5 over seventy years of age. All these patients responded well to the treatment, as did a child of eleven. Even severe undernutrition is no contraindication to the treatment.

About 50 patients had signs of cardiovascular diseases, such as arteriosclerosis, enlargement of the heart, abnormal electrocardiographic findings, rheumatic heart disease and hypertension. One had definite signs of coronary-artery disease, and another a severe congenital abnormality of the heart. In many patients, the increased blood pressure went down when agitation subsided as a result of electroshock therapy. In a few other cases, the blood pressure went up or up and down in a way that was not always consistent with the patient's emotional state.

Eight patients with active and 25 with arrested pulmonary tuberculosis were treated in this series. Shock therapy of mental patients who are suffering from tuberculosis carries definite risks, but in selected cases, electroshock therapy has to be given even if the tuberculosis is active. If there is a history of recent hemorrhage or if the activity is high, shock should be given only when the pulmonary process has been controlled by collapse therapy. In 1 case electroshock therapy and pneumothorax were applied simultaneously.

Patients suffering from acute infections should be excluded from electroshock treatment, and every effort should be made to discover intercurrent infections prior to and during a course of electroshock. This was emphasized by the one fatal case after electroshock therapy that occurred in this series.

Eleven cases of fractures due to electroshock treatment were observed, 2 of them occurred in patients who had bone disease prior to the treatment. All fractures healed without permanent damage. Regarding the preliminary administration of curare, the opinion is expressed that the danger of this drug outweighs its advantage.

A few patients with diseases of the central nervous system were treated without ill effects. Another patient, who had no abnormal physical findings prior to electroshock treatment, developed a

result, routine roentgenologic studies of this age group were discontinued. After 1931, the use of stereoscopic films was also dropped since nothing significant could be detected on one film of a stereoscopic pair that was not equally discernible on the other. X-ray examination of nonreactors was found to be noncontributive, and it too was discontinued. Myers stressed the fact that children showing positive tuberculin reactions should be followed for many years with careful checkups. He recommended that no one attempt to make a conclusive diagnosis by an x-ray shadow and decried the possibility of determining the activity of a tuberculous lesion by a single x-ray examination.

It is of interest to note that in Minneapolis the tuberculin test is used as the method of screening in preference to x-ray examination, whereas in China it has been found that tuberculosis is so prevalent that x-ray films are preferred to the tuberculin test.<sup>42</sup>

Reinfection tuberculosis does not always make its first appearance in the upper lobes. Cherry<sup>43</sup> reports that in 1379 known cases of reinfection 152 per cent were discovered to have had a basal onset of the disease. In a survey of 500 cases with skeletal tuberculosis, Mann<sup>44</sup> found that 57 per cent had active pulmonary tuberculosis. He concluded that the skeletal lesion in most children originated soon after the primary infection, whereas in adults it was usually due to reinfection of a previously quiescent focus, which resulted in blood-stream dissemination and subsequent implantation in the bone and lung. Flaxman<sup>45</sup> advocates the use of a modified posterior lordotic projection, sometimes spoken of as the "apical view," for early recognition of tuberculosis in the apical portions of the upper lobes. This position enhances the visualization of the apexes by displacing the shadows of the clavicles away from the area to be studied. Medlar,<sup>46</sup> in an anatomic investigation of lungs of persons who had died unexpectedly, reports that apical scars were present with equal frequency in those who exhibited no microscopical evidence of pulmonary tuberculosis and in those with single and multiple foci. He believes that apical caps are not necessarily related etiologically to tuberculous infection. In tuberculosis, apical scars occur rarely in persons under the age of thirty, over the age of fifty, they are quite frequently due to tuberculosis, and an inequality of these shadows on the two sides should suggest the possibility of a tuberculous lesion.

That bronchial occlusion often accompanies tuberculosis is stressed in at least two reports. Hutchison<sup>47</sup> believes that the extensive shadows seen in primary tuberculosis are due to collapse and do not indicate pneumonic consolidation. Occlusion of the bronchus is most often caused by enlarged lymph nodes in association with sticky mucus from a swollen hyperemic mucous mem-

brane. Guggenheim,<sup>48</sup> investigating pulmonary emphysema and tuberculosis, comes to the conclusion that in only a small minority of the cases can changes be explained on a purely compensatory basis. Localized emphysema, blebs and bullae are due to bronchial changes, the obstruction of the bronchi and bronchioles is caused by exudate, necrotic material, endobronchial tuberculosis, compression, torsion and stretching.

Considerable literature is accumulating that tends to indicate that many of the multiple areas of calcification seen within the lungs are secondary to histoplasmosis rather than to tuberculosis.<sup>49-51</sup> This conclusion is based on a negative tuberculin reaction and a positive reaction to histoplasmin. It is thought that histoplasmosis has a tendency to show the following features: the presence of multiple lesions in the parenchyma, the rather frequent occurrence before the age of one year, and progression of the pneumonic infiltration with the development of new lesions and appearance of calcification over a period of years. It is believed that a far greater number of children, particularly in the Middle West, are sensitive to histoplasmin than to tuberculin. Holt<sup>52</sup> reported the radiologic appearance of the chest in 5 autopsied cases of fatal histoplasmosis. These findings were exceedingly variable. 1 case showed miliary parenchymal lesions with hilar adenopathy; in another, patchy pneumonitis was present; in a third, a large area of consolidation was found in the right upper lobe; a fourth case showed rather widespread dissemination of miliary lesions; and the fifth disclosed extensive consolidation of the right lung. These findings indicate that there is no characteristic roentgenologic appearance to be expected in active histoplasmosis.

Torulosis,<sup>53</sup> aspergillosis,<sup>54</sup> nocardia asteroides infection<sup>55</sup> and the pulmonary manifestations of amebiasis<sup>56</sup> have no typical appearance and are often confused with tuberculosis (or tumor). Another more common chest condition, likewise difficult to distinguish from tuberculosis, is pulmonary coccidioidomycosis.<sup>57-59</sup> Although it has been considered more or less endemic in the Southwest and West, numerous cases of the infection are being found throughout the country in former members of the armed forces. Many of the initial infections are asymptomatic. In symptomatic cases, it has been noted that the onset is often abrupt, resembling an acute respiratory infection. The early roentgenologic picture may be similar to that of an atypical or bacterial pneumonia, the process may be lobular or lobar and enlarged hilar lymph nodes may be present. Occasionally, pleural effusion may accompany and obscure the underlying process. Nodular densities may appear that ultimately break down and form cavities. Resolution, which may take place in from one to three weeks, is some-

structures are visualized on the film than is possible with films of greater contrast. Although the lateral view has long been stressed as necessary, it is still too often neglected. If one is to visualize satisfactorily the septums and locate the various segmental lesions, it is vital to have a lateral projection.<sup>4, 5</sup> Fleischner<sup>18</sup> has recently called attention to the value of the visible bronchial tree on conventional films as indicating pneumonic and other pulmonary consolidations—in other words, if the bronchi are visible, it is indicative of consolidation or a similar process within the adjacent lung, and their visibility distinguishes the abnormality from a pleural effusion or thickened pleura. Intrapulmonary collections of fluid may be readily confused with an elevated diaphragm,<sup>19, 20</sup> and it may be necessary to examine the patient by means of films taken in the lateral decubitus position or after pneumoperitoneum or pneumothorax.

Numerous ways of obtaining satisfactory bronchograms,<sup>21-22</sup> including aspiration, catheter injection and injection under bronchoscopic control,<sup>24</sup> are available. The most important factor from the radiologic standpoint is that the major bronchi of all the lobes be filled in the average case, or that selected bronchi be filled in the special case. The position of the patient during the flow of the oil is of extreme importance. Kooperstein and Bass<sup>25</sup> call attention to 2 cases of bilateral pneumonia following instillation of lipiodol, this complication, however, is unusual.

Laminagraphy, planigraphy and tomography have received a great deal of emphasis in the past few years.<sup>26-29</sup> These procedures are of value in cases in which the patient is not to be bronchoscoped. They may help in demonstrating narrowing or obstruction of the major bronchi, in differentiating enlarged lymph nodes from hilar vascular structures and in disclosing certain cavities. In some cases peripheral masses, when they are benign, may be shown to displace bronchi and vessels, whereas malignant lesions do not displace the bronchi and if they invade the bronchi the latter are narrowed or occluded. Often, the actual tumor within the trachea or bronchus can be clearly delineated, but such a tumor will not be distinguishable from any other mass present within these structures. Laminagraphy can frequently replace bronchography and bronchoscopy when these procedures are impossible, the usual projections, including posteroanterior and lateral, can be used. Amisano<sup>30</sup> utilized transverse laminagraphy of the chest. The patient is in a sitting position with the head flexed on the chest and the film is under the thighs, the axis of rotation of the laminagraph is at the level of the chest to be examined. Considering the long object-film distance the laminagraphs reproduced were surprisingly good.

A recent suggestion for better delineation of chronic draining empyema cavities is mentioned although they are seen less frequently today than in the past, this is the use of a solution of 50 per cent pantopaque (iodophenylundecylate).<sup>31</sup>

Despite all the advances in technical methods, there still remains a large group of lesions that are not yet readily visualized on the roentgenogram. It has been our experience, confirmed by Ritter and Pendergrass,<sup>32</sup> that many of the small lesions of tuberculosis and metastatic nodules even as large as 1 cm in diameter, particularly if they lie against the pleura, may be invisible on the x-ray film.

Mass chest surveys have proved valuable in the discovery of unrecognized cases of tuberculosis and other processes within the chest. A fair trial of photofluorography was given during World War II and is being continued at the present time. Numerous reviews stressing the value of these routine screening methods have been published, approximately 2 to 9 per cent of the films have disclosed pulmonary abnormalities, as many as 5 per cent of which have been found to be due to reinfection of pulmonary tuberculosis. Repeated surveys in industry and elsewhere have shown that active pulmonary tuberculosis developed as a rule at the expected yearly rate, in suspicious cases, serial observations often confirmed the belief that active minimal tuberculosis is asymptomatic and can be discovered only by radiography of the chest.<sup>33-40</sup>

It should be borne in mind that photofluorography is a purely survey procedure rather than one that has accurate diagnostic value. Even with close attention to the use of proper developers, correct type of film and screen to provide excellent contrast and detail, these surveys cannot yield the information furnished by a complete roentgenologic examination of the chest. Another fact to be remembered is that this form of study will pick up many lesions for which the proper method of treatment may constitute a difficult problem for the internist, the radiologist and the surgeon.

#### DIAGNOSIS OF INFLAMMATORY LESIONS

Myers,<sup>41</sup> in a comprehensive article, reviewed the experience of twenty-six years' observation in the city of Minneapolis. The results demonstrated that carefully planned, long-term studies must be undertaken to evaluate such a chronic disease as tuberculosis. As far as the development of radiologic procedures is concerned, the paper films used at first have been succeeded by photofluorographic methods. In the early years there was considerable discrepancy between the findings on x-ray examination and those on tuberculin testing. After ten years, it was found that x-ray inspection of the chest rarely revealed evidence of significant disease in children under twelve or fourteen years of age even though they reacted positively to tuberculin, as a

result, routine roentgenologic studies of this age group were discontinued. After 1931, the use of stereoscopic films was also dropped since nothing significant could be detected on one film of a stereoscopic pair that was not equally discernible on the other. X-ray examination of nonreactors was found to be noncontributive, and it too was discontinued. Myers stressed the fact that children showing positive tuberculin reactions should be followed for many years with careful checkups. He recommended that no one attempt to make a conclusive diagnosis by an x-ray shadow and decried the possibility of determining the activity of a tuberculous lesion by a single x-ray examination.

It is of interest to note that in Minneapolis the tuberculin test is used as the method of screening in preference to x-ray examination, whereas in China it has been found that tuberculosis is so prevalent that x-ray films are preferred to the tuberculin test.<sup>42</sup>

Reinfection tuberculosis does not always make its first appearance in the upper lobes. Cherry<sup>43</sup> reports that in 1379 known cases of reinfection 152 per cent were discovered to have had a basal onset of the disease. In a survey of 500 cases with skeletal tuberculosis, Mann<sup>44</sup> found that 57 per cent had active pulmonary tuberculosis. He concluded that the skeletal lesion in most children originated soon after the primary infection, whereas in adults it was usually due to reinfection of a previously quiescent focus, which resulted in blood-stream dissemination and subsequent implantation in the bone and lung. Flaxman<sup>45</sup> advocates the use of a modified posterior lordotic projection, sometimes spoken of as the "apical view," for early recognition of tuberculosis in the apical portions of the upper lobes. This position enhances the visualization of the apexes by displacing the shadows of the clavicles away from the area to be studied. Medlar,<sup>46</sup> in an anatomic investigation of lungs of persons who had died unexpectedly, reports that apical scars were present with equal frequency in those who exhibited no microscopical evidence of pulmonary tuberculosis and in those with single and multiple foci. He believes that apical caps are not necessarily related etiologically to tuberculous infection. In tuberculosis, apical scars occur rarely in persons under the age of thirty, over the age of fifty, they are quite frequently due to tuberculosis, and an inequality of these shadows on the two sides should suggest the possibility of a tuberculous lesion.

That bronchial occlusion often accompanies tuberculosis is stressed in at least two reports. Hutchison<sup>47</sup> believes that the extensive shadows seen in primary tuberculosis are due to collapse and do not indicate pneumonic consolidation. Occlusion of the bronchus is most often caused by enlarged lymph nodes in association with sticky mucus from a swollen hyperemic mucous mem-

brane. Guggenheim,<sup>48</sup> investigating pulmonary emphysema and tuberculosis, comes to the conclusion that in only a small minority of the cases can changes be explained on a purely compensatory basis. Localized emphysema, blebs and bullae are due to bronchial changes, the obstruction of the bronchi and bronchioles is caused by exudate necrotic material, endobronchial tuberculosis, compression, torsion and stretching.

Considerable literature is accumulating that tends to indicate that many of the multiple areas of calcification seen within the lungs are secondary to histoplasmosis rather than to tuberculosis.<sup>49-51</sup> This conclusion is based on a negative tuberculin reaction and a positive reaction to histoplasmin. It is thought that histoplasmosis has a tendency to show the following features: the presence of multiple lesions in the parenchyma, the rather frequent occurrence before the age of one year, and progression of the pneumonic infiltration with the development of new lesions and appearance of calcification over a period of years. It is believed that a far greater number of children, particularly in the Middle West, are sensitive to histoplasmin than to tuberculin. Holt<sup>52</sup> reported the radiologic appearance of the chest in 5 autopsied cases of fatal histoplasmosis. These findings were exceedingly variable. 1 case showed miliary parenchymal lesions with hilar adenopathy, in another, patchy pneumonitis was present, in a third, a large area of consolidation was found in the right upper lobe, a fourth case showed rather widespread dissemination of miliary lesions, and the fifth disclosed extensive consolidation of the right lung. These findings indicate that there is no characteristic roentgenologic appearance to be expected in active histoplasmosis.

Torulosis,<sup>53</sup> aspergillosis,<sup>54</sup> nocardia asteroides infection<sup>55</sup> and the pulmonary manifestations of amebiasis<sup>56</sup> have no typical appearance and are often confused with tuberculosis (or tumor). Another more common chest condition, likewise difficult to distinguish from tuberculosis is pulmonary coccidioidomycosis.<sup>57-59</sup> Although it has been considered more or less endemic in the Southwest and West, numerous cases of the infection are being found throughout the country in former members of the armed forces. Many of the initial infections are asymptomatic. In symptomatic cases it has been noted that the onset is often abrupt, resembling an acute respiratory infection. The early roentgenologic picture may be similar to that of an atypical or bacterial pneumonia, the process may be lobular or lobar, and enlarged hilar lymph nodes may be present. Occasionally, pleural effusion may accompany and obscure the underlying process. Nodular densities may appear that ultimately break down and form cavities. Resolution, which may take place in from one to three weeks, is some-

times complete, leaving no scar, at other times, there is healing with fibrosis. In the disseminated form, the roentgenologic appearance may resemble other fungous infections, sarcoidosis, miliary tuberculosis or lymphatic spread of metastatic cancer throughout the lungs. The most common error in differentiation is with tuberculosis.

Boyer<sup>60</sup> reported 50 unselected cases of pulmonary tuberculosis in which bronchoscopy was done. Bronchiectasis was demonstrated in 85 per cent, in some cases it had not been suspected clinically. Collapse treatment seemed to bear no relation to the incidence of bronchial dilatation, and the degree of bronchiectasis had no apparent bearing on the amount of sputum.

Some interesting observations on the occurrence of bronchiectasis that was either associated with or the result of a primary tuberculosis were made by Jones and his associates.<sup>61</sup> In 85 of 716 children with pulmonary tuberculosis, a dense homogeneous, and usually segmental or lobar, shadow suggested the presence of an obstructive pneumonitis. Forty-two of the 85 patients were examined bronchoscopically, and 31 were found to have tuberculous involvement of a bronchus in the form of ulceration, granulation tissue, tuberculoma or extrinsic pressure from enlarged lymph nodes. Several years later some of the same children, together with others showing the same phenomena, were studied by bronchography. In 34 of the 37 children examined satisfactory bronchograms were obtained, and in 24 of these bronchiectasis was evident, the pulmonary lesion had been present twelve months or less in 4 of the latter and for thirteen months or longer in the other 20. The bronchographic examination was done at a mean interval of three and a half years after roentgenologic evidence of clearing of the original lesion. From these observations, it was concluded that the duration of the disease was important in the development of bronchial dilatation and that the damage was permanent. There was a preference for localization of the bronchiectasis to the anterolateral branch of the upper-lobe bronchus and the apical branch of the lower-lobe bronchus. The children had symptoms representing both the primary complex and bronchiectasis, but after clearing of the pneumonitis and tuberculosis, there were few symptoms of bronchiectasis.

Bronchiectasis as an entity has received a large amount of study and comment in the past, and since many cases are surgically curable it is desirable that the diagnosis be made promptly. It is the opinion of many that bronchograms are a necessity in making the diagnosis,<sup>62</sup> whereas Good<sup>63</sup> points out that in 75 per cent of the cases it is possible to make a tentative diagnosis of bronchiectasis from the plain films. He cautions also that it may be suspected more frequently from the routine films than can be confirmed by bronchography. Certain

plain films will show no evidence of bronchiectasis even though the disease is actually present, and Good believes that bronchography is necessary in patients who give clinical evidence of it even though no lesion is demonstrable on the plain films. (Usually, it is best that bronchography be instituted at the request of the surgeon who is to perform the operation, inasmuch as the diagnosis will probably have been established by the plain films and the chief object of bronchography will be to furnish the surgeon with an adequate map of the bronchial tree from which he can plan his attack. This procedure also gives him the most accurate means of follow-up studies of the patient in the years to come. Bronchography, performed merely as a diagnostic method without intent of immediate operation, may leave considerable residua within the lungs, which will interfere with follow-up examination.)

Although there is no intention of entering the controversy regarding whether atypical pneumonia causes bronchiectasis, reversible or irreversible, it is to be noted that some cases of bronchiectasis are first discovered during or after an attack of atypical pneumonia.<sup>64</sup> In cases in which the question whether bronchiectasis is associated with the persistence of a pneumonic infiltration arises, it is probably advisable to do bronchography and to follow it with a second bronchogram after a suitable length of time. Royce and Victor<sup>65</sup> believe that an interval of one to three months is sufficient length of time in which to determine the reversibility of the process. Spain and Lester<sup>66</sup> report a case in which bronchiectasis developed distal to a foreign body in a bronchus within a period of seven weeks. It is their belief that early destruction of the musculoelastic layer precludes the possibility of reversibility.

It is of considerable interest that the radiologist sees relatively few cases of lobar pneumonia due to the pneumococcus in this era of antibiotics. Apparently, most of these patients are being treated in the home and are not hospitalized to any extent. As far as diagnosis of lobar pneumonia or of other inflammatory conditions is concerned it is important that the physician follow the patient until the lesion has cleared roentgenologically. It is surprising how many chronic diseases such as bronchiectasis and numerous tumors are first diagnosed as lobar pneumonia or some other inflammatory condition, later, as the symptoms become more severe, these diagnoses must be discarded.

That the roentgenologic appearance of atypical pneumonia may be somewhat bizarre and easily confused with other conditions is a well known fact. Atypical pneumonia may produce collapse rather than consolidation as demonstrated on the roentgenogram, it can cause lesions that involve the greater portion of an entire lobe, one or more segments of a lobe or a diffuse miliary process.

throughout the lung fields. In the last type, the patient is usually seriously ill, and in some cases this diffuse mottling may indicate the beginning of resolution in a process that had shown widespread consolidation. The lateral view is essential to determine adequately the segments involved as well as the amount of atelectasis that is often associated with the disease.<sup>67-70</sup> The pulmonary type of tularemia and Q fever may produce small areas of pneumonitis, which roentgenologically may be confused with pneumonia.<sup>71-75</sup>

A condition that has received renewed interest in the past few years is Loeffler's syndrome.<sup>76-79</sup> The roentgenologic appearance is thought to be due to areas of infiltration or edema that are transitory and tend to migrate to various parts of the lung. No particular lobe is predominantly involved, although when the upper lobe is the seat of the process it may be mistaken for tuberculosis. Clinically, the patients are usually not very ill, a marked eosinophilia is present, and the sputum may contain eosinophils. Loeffler's syndrome may be associated with infestation by *Ascaris lumbricoides*, *Necator americanus* and *Endamoeba histolytica*, strongyloidiasis, allergies, chronic brucellosis and other diseases. As seen in the tropics, the appearance from the roentgenologic standpoint is frequently unique in that it produces a diffuse miliary appearance, which is of transient duration.

Harvey<sup>80</sup> reports 2 cases of clinically proved brucellosis that showed a tendency to multiple small nodular lesions throughout the lung fields. One patient was known to have had previous bilateral hilar-lymph-node enlargement. The radiologic appearance of the chest is very similar to that usually seen in sarcoidosis. McCort et al.<sup>81</sup> describe the findings in the latter condition. Enlargement of the paratracheal lymph nodes was found in all of the 28 cases comprising their series, with enlargement of the peribronchial lymph nodes in 25, pulmonary or parenchymal involvement was evident in 15. In 2 cases there was pleural effusion, and in 1, pericardial effusion, osseous changes were noted in the hands of 6 patients.

Numerous causes of emphysema and pulmonary fibrosis are known. In a recent symposium on so-called idiopathic fibrosis and emphysema, Mallory<sup>82</sup> has shown certain granulomatous or sarcoid-like lesions to be the inciting factor in a small group. The roentgenologic appearance of these cases differs considerably from the usual sarcoid findings, the markings are greatly thickened throughout the lungs, with large areas of intervening rarefaction, apparently representing emphysematous blebs or bullae.<sup>83</sup> Cases of idiopathic fibrosis run a rather severe course with a fatal termination.<sup>84</sup>

Acute pulmonary edema, a frequent accompaniment of acute nephritis, mitral stenosis and certain other conditions, produces fairly characteristic roentgen-ray shadows. In spite of the minimal

signs and symptoms noted clinically, the radiographs usually show massive centrally distributed shadows in the lungs and a somewhat butterfly-like appearance. Doniach<sup>85</sup> ascribes uremic edema of the lungs to capillary permeability and says that it may be seen in other conditions causing heart failure. According to Burford and Burbank,<sup>86</sup> pulmonary edema in some cases is caused by blast injury in which a wave of highly compressed air produces severe changes in the parenchyma, the pleura and even the chest wall. Under these circumstances, the edema in all likelihood is traumatic and not the result of heart failure.

The appearance and technic of demonstration of pulmonary infarcts has been reviewed by Robbins.<sup>87</sup> An interesting but small group of cases are those in which there is infarction of an entire lobe such as that discussed by Rawson and Cocke.<sup>88</sup> Their patient, a thirty-nine-year-old Negro, had complete infarction of the left lower lobe subsequent to long-continued passive congestion, there was aseptic softening, with subsequent rupture into the pleural cavity resulting in hemopneumothorax. They found only 5 other cases of this type previously reported, and it is of interest that all the patients were between twenty and forty-four years of age.

#### PULMONARY LESIONS IN CHILDREN

An excellent approach to the subject of pediatric pulmonary roentgenology has been presented by Blair.<sup>89</sup> He summarizes and classifies in a concise manner the numerous conditions that may be encountered in children.

The surgical aspects of staphylococcal pneumonia in infancy and childhood have been discussed by Blumenthal and Neuhoof.<sup>90</sup> The roentgenologic appearance is that of ordinary suppurative pneumonia, with densities that may be lobular, lobar or segmental in type and with a tendency to cavitation and abscess formation, there may be extension to the pleura. The authors believe that repeated roentgenologic examination is essential in following the course of the disease.

Another form of cavity, termed pneumatocele, presents a thin margin and may contain fluid. It is seen in the course of other types of pneumonia in children and has recently been re-emphasized by Almklov and Hatoft.<sup>91</sup> The pneumatocele develops in an area of consolidation, the time of its appearance, in the authors' series, varied from the second to the twenty-fifth day after onset of the disease. In certain cases more than one pneumatocele were present, these ranged in diameter from 1 to 3 cm., and fluid levels were frequently noted. The pneumatoceles disappeared spontaneously without treatment.

Of particular interest to the radiologist may be the child who is brought for examination of the chest with the question, because of his cyanosis, of pneumonia or heart disease. Recent reports<sup>92-93</sup>

describe such a condition, which has been found to be due to poisoning from wax crayons. These children exhibit rapid respirations, some elevation of temperature and pulse, weakness and listlessness. The striking roentgenologic feature is the apparently normal chest and the finding of opaque material in the stomach and intestinal tract.

Idiopathic pulmonary hemosiderosis or essential brown induration of the lungs has been described by Wyllie et al.<sup>94</sup> All the patients were children ranging in age from a few months to sixteen years, with the exception of 1 man of thirty-eight years. The disease is characterized by recurrent attacks, sudden in onset, of fatigue, cyanosis and pallor, with increasing dyspnea, acceleration of the pulse rate and a high fever. Cough is troublesome, often followed by vomiting, and at times traces or even considerable quantities of blood are noticeable in sputum or vomitus. There may be abdominal pain as well as increased liver dullness and splenomegaly. The most common roentgenologic findings—and these become accentuated during an attack—are mottled shadows, particularly noticeable in the hilar areas, and a diffuse stippling throughout the lung fields. There may be evidence of partial lobar collapse. At first glance the milium nodules suggest tuberculosis, but close inspection is said to reveal small, clear, circular spaces surrounded by thickened opaque walls, giving a pumice-stone appearance, the heart shadow is enlarged, the border extending chiefly to the right, and the pulmonary conus is prominent. The prognosis is poor.

A somewhat similar type of nodular lesion may be associated with mitral stenosis, and in long-standing cases actual calcification or ossification of some of these nodules may occur.<sup>95</sup>

#### OCCUPATIONAL DISEASES

Occupational diseases that cause changes within the chest are numerous. Some of those reported recently have been associated with welding and inhalation of graphite dust and of dust caused by the handling of grains and seeds.<sup>96-101</sup> Bagasse disease of the lungs, or bagassosis, is brought about by the inhalation of dried bagasse dust. There seems to be an insufficient amount of silica present in the dust to cause the signs and symptoms.<sup>102-103</sup> The severity of the disease appears to be directly related to the concentration and duration of exposure to the dust. Some cases end fatally. The roentgenographic appearance differs from that in other forms of pneumoconiosis primarily in that it is reversible, and resolution may be complete in six to eight months.

Exposure to beryllium compounds in industry has attracted considerable attention in the last few years.<sup>104-105</sup> There appear to be two forms of reaction to exposure, the first of which is an acute chemical pneumonitis resulting from exposure to

high concentrations of beryllium compounds including fluoride, oxyfluoride and oxides. There is a definite relation between exposure and the development of the disease, and if the patient recovers, the symptoms clear up with elimination of the exposure. The second form is a delayed chemical pneumonitis, apparently caused by exposure to small amounts of beryllium compounds in the air. This is characterized by delay, which may vary from one month to five years, between exposure and onset of symptoms. The x-ray appearance, as described by Wilson,<sup>106</sup> is very similar to that seen in sarcoidosis.

#### TUMORS

In the present era of thoracic surgery, the roentgenologic diagnosis of tumor of the lung, in an attempt to differentiate benign and malignant lesions, has become primarily of academic interest.<sup>110-113</sup> Bloch et al.,<sup>114</sup> pointing out the difficulties in differential diagnosis of bronchiogenic carcinoma, observe that diagnosis is often impossible by conservative methods and that surgical exploration is indicated. Churchill<sup>115</sup> states that the problem in primary cancer of the lung is the same as that encountered in any other form of cancer—in other words, earlier diagnosis. In his opinion, roentgenologic screening is at present the only way to detect early primary cancer in the apparently well population. This method will disclose silent neoplasms in the periphery of the lung, and in recent years it has succeeded in bringing to light a few asymptomatic cases. It will not, however, disclose the early endobronchial growth that has not yet encroached upon the lumen of the bronchus; these lesions are less likely to be silent, the patient having symptoms at an earlier stage than the one with a peripheral lesion.

Rigler and Kelby<sup>116</sup> have re-emphasized the fact that obstructive emphysema is a valuable early sign of bronchiogenic cancer. This is best demonstrated by roentgenograms during expiration or by fluoroscopy. Transition from emphysema to atelectasis occurs as the tumor grows and completely obstructs the bronchus. Reitz<sup>117</sup> and Oechsh and Olson<sup>118</sup> stress the necessity of adequate x-ray examination as well as the importance of photofluorography. In their opinion, laminagraphy is of definite value when the lesion is beyond the reach of the bronchoscope.

Gerstl and his colleagues<sup>119</sup> discuss 7 cases of coexisting bronchiogenic carcinoma and pulmonary tuberculosis, noting that there was little difficulty in making the diagnosis of tuberculosis but much in that of carcinoma. The x-ray examination was of the greatest assistance in raising the question of cancer. Hilar enlargement or infiltration, evidence of major bronchial obstruction, or a relatively circumscribed mass should, in the authors' experience, arouse the suspicion of carcinoma.

Lymphatic spread of carcinoma throughout the lungs may produce an appearance that is difficult to differentiate from sarcoidosis, silicosis and other primary lesions. Clinically it is characterized by severe, increasing dyspnea in a patient with recognized or unrecognized carcinoma elsewhere.<sup>120-121</sup>

MEDIASTINAL TUMORS

Numerous tumors of the mediastinum are found incidentally on pre-employment or survey examinations. Frequently cases of myasthenia gravis are found to be associated with thymic tumors, and any patient with this disease should have a thorough roentgenologic study of the chest. Bronchiogenic cysts and cysts arising from the gastrointestinal tract are often observed, these cannot readily be differentiated from malignant teratomas, neurofibrosarcomas and other malignant tumors.<sup>122-127</sup> In the differential diagnosis, one should exclude the possibility of aneurysm of the aorta, and this may be done by angiocardigraphic visualization of the heart and great vessels.<sup>128</sup> An intrathoracic meningocele must also be distinguished from neurogenic tumors, this may be accomplished by myelography or possibly by the utilization of the Valsalva test during fluoroscopy.<sup>129</sup> Holt<sup>130</sup> called attention to right-sided epicardial fat pad as a differential point, these may be found in the right anterior costophrenic angle. Often, however fat pads cannot be distinguished from cystic lesions, omental hernias or tumors in this location. The facts that malignant changes cannot be excluded in any mediastinal tumor and that there may be later infection of cystic lesions make it imperative that surgical removal be attempted whenever possible.

SUMMARY

Methods for the roentgenologic diagnosis of pulmonary lesions are steadily improving. There remain, however, a large number of unsolved problems that offer a wide field for future investigation.

REFERENCES

1. Boyden E. A. Intrahilar and related segmental anatomy of lung. *Surgery* 18:706-731 1945  
2. Boyden E. W. and Scannell J. G. Analysis of variations in bronchovascular pattern of right upper lobe of fifty lungs. *Am. J. Anat.* 82:27-74 1948  
3. Scannell J. G. Study of variations of bronchopulmonary segments in left upper lobe. *J. Thoracic Surg.* 16:500-537 1947  
4. Robbins L. L. and Hale C. H. Roentgen appearance of lobar and segmental collapse of lung preliminary report. *Radiology* 44:107-114 1945  
5. Robbins L. L., Hale C. H. and Merrill O. E. Roentgen appearance of lobar and segmental collapse of lung: technic of examination. *Radiology* 44:471-476 1945  
6. Robbins L. L. and Hale C. H. Roentgen appearance of lobar and segmental collapse of lung: normal chest as it pertains to collapse. *Radiology* 44:543-547 1945  
7. *Idem*. Roentgen appearance of lobar and segmental collapse of lung: collapse of entire lung or major part thereof. *Radiology* 45:23-26 1945  
8. *Idem*. Roentgen appearance of lobar and segmental collapse of lung: collapse of lower lobes. *Radiology* 45:120-127 1945  
9. *Idem*. Roentgen appearance of lobar and segmental collapse of lung: collapse of right middle lobe. *Radiology* 45:260-266 1945

10. *Idem*. Roentgen appearance of lobar and segmental collapse of lung: collapse of upper lobes. *Radiology* 45:347-355 1945  
11. Medlar E. M. Variations in interlobar fissures. *Am. J. Roentgenol.* 57:723-725 1947  
12. Etter L. E. Variations in position of azygos septum and its incidence in 50,000 roentgen examinations. *Am. J. Roentgenol.* 58:726-729 1947  
13. Pendley W. O. Azygos lobe in photofluorography. *U. S. Nav. M. Bull.* 46:1920-1927 1946  
14. Lachman E. Dynamic concept of thoracic topography: critical review of present day teaching of visceral anatomy. *Am. J. Roentgenol.* 56:419-440 1946  
15. Billing L. On retrocardiac pulmo-pleural demarcation lines and their diagnostic significance. *Acta radiol.* 27:257-263 1946  
16. Westermarck N. Importance of intra alveolar pressure in diagnosis of pulmonary diseases. *Radiology* 50:610-618 1948  
17. Fuchs A. W. Optimum kilovoltage technique in military roentgenography. *Am. J. Roentgenol.* 50:358-365 1943  
18. Fleischner F. F. Visible bronchial tree: roentgen sign in pneumonic and other pulmonary consolidations. *Radiology* 50:184-189 1948  
19. Jones D. B. Basal pleural fluid accumulations resembling elevated diaphragm. *Radiology* 50:227-233 1948  
20. Tagnuchi J. T. and Dressler S. Intrapulmonary effusion masquerading as elevated diaphragm. *Radiology* 50:223-226 1948  
21. Okell E. Bronchography. *Radiography* 13:62-65 1947  
22. Schmidt H. W. Method of obtaining bilateral bronchograms. *Proc. Staff Meet. Mayo Clin.* 23:71-77 1948  
23. Poppe J. K. Simple and practical method of obtaining complete bronchograms. *Am. Rev. Tuberc.* 54:104-110 1946  
24. Ritchie D. C. Aspiration bronchography. *Brit. J. Radiol.* 19:471-473 1946  
25. Koopstein S. I. and Bass H. E. Pulmonary reaction following intrabronchial instillation of lipiodol in bronchial asthma. *Am. J. Roentgenol.* 56:569-576 1946  
26. Andrews J. R. and Turck R. O. Plasmography. II. Evaluation of method in diagnosis of lower respiratory tract. *Am. J. Roentgenol.* 58:173-182 1947  
27. Tobias J. W. Importancia de la tomografia para el diagnostico de cancer infiltrativo y poliposo estenosante del tercio inferior de la traquea. *Rev. med. cubana* 57:809-810 1946  
28. Nowell S. Value of tomography in lesions of main bronchi and their larger sub-divisions. *Proc. Roy. Soc. Med.* 40:339-405 1947  
29. Ruger, L. G. and Werner T. B. Plasmography in diagnosis of bronchiogenic carcinoma. *Am. J. Roentgenol.* 58:267-276 1947  
30. Amisano P. Transverse laminography of chest. *Radiol. med.* 32:418-421 1946  
31. George M. P., Mahoney E. B., Pearse H. E. and Strain W. H. Indicated organic compounds as contrast media for radiographic diagnosis. VII. Visualization of empyema cavities with aid of ethyl iodophenylundecylate emulsion. *Radiology* 49:137-142 1947  
32. Ritter V. W. and Pendergrass E. P. Personal communication  
33. Russakoff A. H. Tuberculosis in Alabama state hospitals: mass radiography for its control. *Am. Rev. Tuberc.* 55:93-101 1947  
34. Hyde L. and Hyde B. Pulmonary infiltrations on routine chest roentgenograms. *Am. J. Roentgenol.* 58:407-410 1947  
35. Birkelo C. C. et al. Tuberculosis case finding: comparison of effectiveness of various roentgenographic and photofluorographic methods. *J. A. M. A.* 133:359-366 1947  
36. Pratt A. D. Survey of patients from Dachau Concentration Camp. *Radiology* 47:234-238 1946  
37. Elkin W. F., Irwin M. A. and Kritzthalz, C. Mass chest survey in Philadelphia by industries. *Am. Rev. Tuberc.* 53:360-363 1946  
38. Allison C. R. Tuberculosis control in industry: results from 1941-1945. *Occup. Med.* 2:207-213 1946  
39. Wayburn E. Mass miniature radiography survey in United States Army Air Forces. *Am. Rev. Tuberc.* 54:527-540 1946  
40. Kramer M., Constock, G. W. and Stocklen J. B. Evaluation of chest x-ray survey of industrial plant. *Pub. Health Rep.* 61:950-1101 1946  
41. Myers J. A. Establishment and use of fundamental procedures in tuberculosis control. *Pub. Health Rep.* 61:1563-1583 1946  
42. Eng R. T. Tuberculosis survey among Chinese students. *Am. Rev. Tuberc.* 54:385-388 1946  
43. Cherry H. H. Basal onset of reinfection tuberculosis. *Am. J. Roentgenol.* 59:82-86 1948  
44. Mann K. J. Lung lesions in skeletal tuberculosis: review of 500 cases. *Lancet* 2:744-749 1946  
45. Flaxman A. J. Apical tuberculosis: roentgenological technic for its early recognition with some pathogenic applications. *Am. Rev. Tuberc.* 54:1-9 1946  
46. Medlar E. M. Apical scars: their etiologic relationship to tuberculosis infections. *Am. Rev. Tuberc.* 55:511-516 1947  
47. Hutchison J. H. Bronchial occlusion in childhood tuberculosis: its pathogenesis and effects. *Edinburgh M. J.* 54:322-324 1947  
48. Guggenheim A. Pulmonary emphysema and tuberculosis: roentgenological and pathological study. *Am. J. Roentgenol.* 58:64-74 1947  
49. Sontag L. W. and Allen J. E. Lung calcifications and histoplasma tuberculosis skin sensitivity. *J. Pediat.* 30:657-667 1947  
50. High R. H., Zwierling H. B. and Farcolow M. L. Disseminated pulmonary calcification: report of 113 cases. *Pub. Health Rep.* 62:20-29 1947  
51. High R. H. Non-tuberculous pulmonary calcification and histoplasma sensitivity. *Pennsylvania M. J.* 50:384-387 1947

52. Holt, J F Roentgenologic pulmonary manifestations of fatal histoplasmosis *Am J Roentgenol* 58 717-723, 1947
53. Hamilton, J B, and Tyler G R Pulmonary torulosis *Radiology* 47 149-155 1946
54. Gerstl B Weidman W H and Newmann, A V Pulmonary aspergillosis report of two cases *Ann Int Med* 28 662-671 1948
55. Glover R P Herrell W E Heilman F R and Pfuetze K H Nocardiosis nocardia asteroides infection simulating pulmonary tuberculosis *J A M A* 136 172 175 1948
56. Langston H T and Fox R T Pleuropulmonary manifestations of amebiasis *Arch Surg* 55 618 623 1947
57. Bass H E Koopstein S I Friedmann M M, and Kastlin G H Pulmonary coccidioidomycosis *Dis of Chest* 12 371-386 1946
58. Rakofsky M and Knickerhocker T W Roentgenological manifestations of primary coccidioidomycosis *Am J Roentgenol* 56 141-155 1946
59. Charr R Some nontuberculous diseases of lung *M Clin North America* 31 1475-1492 1947
60. Boyer, L B Bronchography to tuberculosis clinical study *Am Rev Tuberc* 54 111-121 1946
61. Jones E M Peck, W M and Willis H S Bronchiectasis following primary tuberculosis *Am J Dis Child* 72 296-301, 1946
62. Sokoloff M J Bronchiectasis *M Clin North America* 31 1418-1431 1947
63. Good C A. Some remarks concerning roentgenologic diagnosis of bronchiectasis *Proc Staff Meet Mayo Clin* 20 22 1945
64. Cohen S Bronchiectasis some medical features among military personnel *Radiology* 49 192-200 1947
65. Royce B F and Victor R G Bronchiectasis following atypical pneumonia *Bull U S Army Med Dept* 8 61-68 1948
66. Spain D M and Lester C W Time element in development of irreversible bronchiectasis *J Pediatr* 32 415-419 1948
67. Loeffler W and Moeschlin S Über miliäre Pneumonie von einartigem schwerem Verlauf (miliäre Virus-pneumonien) *Schweiz. med Wchnschr* 76 815-818 1946
68. Lenk R. Die Bedeutung der Röntgenuntersuchung für die Diagnose und Differentialdiagnose der "Akuten interstiellen Pneumonie." *Acta radiol* 27 115 128 1946
69. Crysler W E Primary atypical pneumonia disease of segmental distribution *Am J Roentgenol* 56 324 336 1946
70. McCoy W C Primary atypical pneumonia report of 420 cases with one fatality during twenty seven months at Station Hospital Camp Rucker Ala *South M J* 39 696-706 1946
71. Robbins F C and Raggan C A Q fever in Mediterranean Area report of its occurrence in Allied troops clinical features of disease *Am J Hyg* 44 6-22 1946
72. Feinstein M Yeener, R and Marks J L Epidemics of Q fever among troops returning from Italy in spring of 1945 clinical aspects of epidemic at Camp Patrick Henry Virginia *Am J Hyg* 44 72 87 1946
73. Commission on Acute Respiratory Diseases Laboratory outbreak of Q fever caused by Baikal gnippe strain of *Rickettsia burnetii* *Am J Hyg* 44 123-157 1946
74. Icons J V, and Hooper J M Q fever in United States II Clinical data on outbreak among stock handlers and slaughterhouse workers *J A M A* 133 815 818 1947
75. Mackinnon A G Pulmonary type of tularemia (two cases) *Canad. M A J* 56 541 1947
76. Henderson A T and Pierce C B Transitory focal pulmonary edema and eosinophilia (Loeffler's syndrome) *Am J Roentgenol* 58 391-406 1947
77. Wright, D O and Gold, E M Loeffler's syndrome associated with creeping eruption (cutaneous helminthiasis) report of 26 cases *Arch Int Med* 78 303 312 1946
78. Elkeles A and Butler N R Transitory pulmonary infiltrations and apical cavitation associated with eosinophilia *Brit J Radiol* 19 512-517 1946
79. Pearlman A W Loeffler's syndrome *Am J Roentgenol* 58 75 1947
80. Harvey W A Pulmonary brucellosis *Ann Int Med* 28 768-781 1948
81. McCort, J J Wood R H Hamilton J B and Ehrlich D E Sarcoidosis choical and roentgenologic study of twenty-eight proved cases *Arch Int Med* 80 293 321 1947
82. Mallory T B Pathology of pulmonary fibrosis including chronic pulmonary sarcoidosis *Radiology* 51 468-476 1948
83. Robbins L L Idiopathic pulmonary fibrosis roentgenologic findings *Radiology* 51 459-467 1948
84. King D S Idiopathic pulmonary fibrosis choical study *Radiology* 51 477-479 1948
85. Doniach I Uremic edema of lungs *Am J Roentgenol* 58 620-628, 1947
86. Burford, T H. and Burhanl, B Traumatic wet lung observations on certain physiologic foodmateals of thoracic trauma. *J Thoracic Surg* 14 415-424 1945
87. Robbins L L Technique of roentgenologic demonstration of pulmonary infarcts *Am J Roentgenol* 56 736-742 1946
88. Rawson A J and Cocke J A Infarction of entire pulmonary lobe with subsequent aseptic softening causing sterile hemopneumothorax *Am J M Sc* 214 520-524 1947
89. Blair I G Interpretation of children's chest x rays *Brit J Radiol* 20 223-237 1947
90. Blumenthal S and Neuhoef H Staphylococcal (suppurative) pneumonia in infancy and to childhood and its surgical aspects *Am J Dis Child* 72-691-719 1946
91. Almklov J R and Hatoff, A Pneumatocele during course of pneumonia in children *Am J Dis Child* 72 521 528 1946.
92. Clark E B Poisoning due to ingestion of wax crayons report of case *J A M A* 135 917 1947
93. Jones J A and Brieger H. Poisoning due to ingestion of wax crayons report of case *J Pediatr* 30 422-427 1947
94. Wylie W G Sheldon W Bowdian M and Barlow, A. Idiopathic pulmonary haemosiderosis (essential brown induration of lungs) *Quart J Med* 17 25 1948
95. Elkeles A Dissemination ossified nodules in lungs associated with mitral stenosis *Proc Roy Soc Med* 40 400-403 1947
96. Doig A T and McLaughlin I G Clearing of x ray shadows in welder's siderosis *Lancet* 1 789 1948
97. Sander O A Benign pneumoconiosis due to metal fumes and dusts *Am J Roentgenol* 58 277-282 1947
98. Shaver C G and Riddell A R Lung changes associated with manufacture of aluminum abrasives *J Indust Hyg & Toxicol* 29 145-157 1947
99. Dunoyer L Hermon R and Bagnall D J T Pneumoconiosis in dockers with grain and seeds *Brit J Radiol* 19.50-511, 1946
100. Dunner L Observations on development of graphitic pneumoconiosis *Brit J Radiol* 21 182 185 1948
101. Gough J Pneumoconiosis in coal workers in Wales. *Occup Med* 4 86-97 1947
102. Lemone D V Scott, W G Moore S, and Koven A L Bagasse disease of lungs *Radiology* 49 556 567 1947
103. Editorial Bagasse disease of lungs *New Eng J Med* 238.378 1948
104. Williams C R Significant aspects of exposure to beryllium compounds in industry *Occup Med* 4 101-110 1947
105. Hardy H L and Tabershaw I R. Delayed chemical pneumonitis occurring in workers exposed to beryllium compounds. *J Indust Hyg & Toxicol* 28 197-211 1946
106. Martland H S Jr Occupational beryllium poisoning in New Jersey with special reference to its incidence diagnosis and compensation *J New Jersey M Soc* 45 5 1948
107. Pascucci L M Pulmonary disease in workers exposed to beryllium compounds its roentgen characteristics *Radiology* 50 23 36, 1948
108. Pyre, J and Oatway W H Jr Beryllium granulomatous alveolar sarcoid Saem sarcoid military sarcoidosis chronic beryllium poisoning or delayed chemical pneumonitis description and report. *Arizona Med* 4 21 1947
109. Wilson S A Delayed chemical pneumonitis or diffuse granulomatosis of lung due to beryllium. *J A M A* (in press)
110. Holle S W Bronchial adenomas *Mil Surgeon* 99.528-554 1947
111. Naclerio E A. and Langer L Adenoma of bronchus review of fifteen cases *Am J Surg* 75 533 547 1948
112. Bartlett, J P and Adams W E. Solitary primary neurogenic tumor of lung report of case *J Thoracic Surg* 15 251 260 1946.
113. Watts C F Clagett, O T and McDonald J R Lipoma of bronchus discussion of benign neoplasms and report of case of endobronchial lipoma *J Thoracic Surg* 15 132-144, 1946.
114. Bloch R G Adams W E Thornton F and Bryant, J E Difficulties in differential diagnosis of bronchiogenic carcinoma. *J Thoracic Surg* 14 83 97 1945
115. Churchill E D Primary carcinoma of lung *J A M A* 137 455 461 1948
116. Rigler L G and Kelby G M Emphysema early roentgen signs of bronchiogenic carcinoma *Radiology* 49.578-586 1947
117. Reitz, H E Review of present methods in early diagnosis of bronchiogenic carcinoma *U S New M Bull* 48 198-200 1945
118. Oechsh W R. and Olson K B Primary bronchiogenic carcinoma mistakenly diagnosed as pulmonary tuberculosis case reports with body section roentgenography *Am J Roentgenol* 57 429-434 1947
119. Gerstl B Warring F C Jr and Howlett, K S Jr Cancer and pulmonary tuberculosis diagnostic problems in patients with cancer of lung in presence of pulmonary tuberculosis. *Am Rev Tuberc* 54 470-487 1946
120. Lamhie C G and Collier J Generalized lymphatic carcinomatosis (cancerous lymphangitis) of lungs with special reference to military carcinomatosis and syndrome of 'granule froide' *M J Australia* 2 439-466 1946
121. Mueller H P and Sniffen R C Roentgenologic appearance and pathology of intrapulmonary lymphatic spread of metastatic cancer *Am J Roentgenol* 53 107 123 1945
122. McNamara W L Sargent, W F and Costuch R J Giant sarcoma of pleura report of case *Arch Surg* 85 632-636 1947
123. Klassen K P Patten R. and Bemen F M Neurofibroma of diaphragm. *J Thoracic Surg* 14 407-413 1945
124. Steele J D and Schmutz, J Mediastinal cyst of gastric origin. *J Thoracic Surg* 14 403-405, 1945
125. Dickson J A Clagett, O T and McDonald J R Intrathoracic gastric cyst. *J Thoracic Surg* 15 318-323 1946
126. Maier H C Bronchiogenic cysts of mediastinum. *Ann Surg* 127 476-502, 1948
127. Bradford M L Mahon, H W., and Grow J B Mediastinal cysts and tumors *Surg Gynec & Obst.* 85 467-491 1947
128. Sussman M L Differentiation of mediastinal tumor and aneurysm by angiocardigraphy *Am J Roentgenol* 58.584-590 1947
129. Sengpiel G W, Ruzicka F F, and Lodmell E. A. Lateral intrathoracic meningocoele *Radiology* 50.515 520 1948
130. Holt, J F Epicardial fat shadows in differential diagnosis *Radiol or*, 48 472 479 1947

## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

EDITH E. PARRIS, *Assistant Editor*

### CASE 34471

#### PRESENTATION OF CASE

*First admission* A seventy-one-year-old woman was admitted to the hospital because of the presence of an abdominal mass.

Eight years before admission the patient noted a walnut-sized mass in the right lower quadrant, which gradually increased in size. Six months before admission she first noted pain at the upper portion of the mass. There was no fever, chills, nausea, melena, night sweats or urinary symptoms.

Physical examination showed some tenderness in the right lower quadrant. A mass was palpable extending laterally into the right flank, and it was felt extending on to the crest of the ilium.

Laboratory examination revealed a negative urine, a white-cell count of 8000 and a hemoglobin of 13.5 gm. A barium enema showed diverticulosis of the sigmoid and upward displacement of the cecum by a large soft-tissue mass in the right lower quadrant. The terminal ileum lay along the medial and inferior margins of the mass.

At operation there was an encapsulated tumor attached to the ureter, bladder, appendix and the large vessels running to the right leg. In removing the tumor the right common iliac artery gave way and it was necessary to ligate it. Following operation she was treated with anticoagulants and exercises, and the leg remained viable. The pathological report on the tumor was fibroma, probably neurogenic.

*Second admission* (two years later) The patient remained well until three and a half months before admission, when she suffered an attack of "grippe." She did not feel that she regained her full strength following this illness and one month later she noted a yellow color to her skin. This was not associated with an acute episode of pain or nausea and vomiting. She did notice postprandial distress associated with belching, a feeling of fullness and bloating. The stools were light, and the urine dark, and there was generalized itching. In the two weeks prior to admission the jaundice lessened in degree and the stools became

darker and the urine lighter. Bilateral ankle swelling was noted.

On examination the blood pressure was 130 systolic, 80 diastolic. The main finding was an abdominal mass with an irregular edge, occupying the right upper quadrant, extending 15 cm below the costal margin. The skin was icteric, and there was ++ edema up to the knees. The temperature was normal.

Laboratory examination revealed a urine specific gravity of 1.017, a + test for albumin and a +++ test for bile, and microscopically there was an occasional white cell and granular cast in the sediment. The white-cell count was 8600, and the hemoglobin 12.5 gm with a normal differential. The van den Bergh test was 10.3 mg per 100 cc direct and 13.2 mg indirect, the prothrombin time was 17 seconds (normal, 16 seconds), and a cephalin flocculation test was ++ at the end of twenty-four and forty-eight hours. The total protein was 6.72 gm, the albumin 3.7 gm, and the globulin 3.01 gm per 100 cc, and the alkaline phosphatase was 24.6 units. A barium enema showed displacement inferiorly of the transverse colon and cecum by a large mass believed to be liver. A gastric series revealed displacement of the stomach and duodenum to the left by a mass in the right upper abdomen. A chest radiogram disclosed a rounded area of increased density, 1.5 cm in diameter, in the left lower lobe, not present two years previously. An intravenous pvelogram demonstrated good function in both kidneys. A retrograde pvelogram showed a normal kidney on the right.

On the eighteenth hospital day a laparotomy was performed.

#### DIFFERENTIAL DIAGNOSIS

DR. CLIFFORD C. FRANSEEN: May we see the x-ray films?

DR. JAMES J. MCCORT: A plain film of the abdomen made on the first admission discloses a large, soft-tissue mass in the right lower quadrant. A barium enema shows diverticula in the sigmoid without signs of inflammation. In addition to that the cecum is elevated and a loop of terminal ileum displaced toward the midline, evidently around the mass. It does not appear to be intrinsic.

When the barium enema was done two years later the barium flowed readily from the rectum to the cecum. The diverticula previously described are filled at this time. However, a large mass is present in the right upper quadrant, displacing the transverse colon downward. Again, there is no evidence that the soft-tissue mass is intrinsic to the colon. A gastrointestinal series done on the second admission shows a suggestion of small varices in the lower third of the esophagus. The stomach is displaced to the left and slightly anteriorly, owing to extrinsic pressure. Studies were made to demon-

52. Holt, J F Roentgenologic pulmonary manifestations of fatal histoplasmosis *Am J Roentgenol* 58 717-723, 1947
53. Hamilton, J B and Tyler G R Pulmonary torulosis *Radiology* 47 149-155 1946
54. Gerstl B Weidman W H and Newmann A V Pulmonary aspergillosis report of two cases *Ann Int Med* 28 662-671 1948
55. Glover R P Herrell W E, Heilmann F R, and Pfuetze K H Nocardiosis nocardia asteroides infection simulating pulmonary tuberculosis *J A M A* 136 172-175 1948
56. Langstoo H T and Fox, R T Pleuropulmonary manifestations of amebiasis *Arch. Surg* 55 618-623 1947
57. Bass H E Kooperstein S I Friedmann M M and Kastlin G H Pulmonary coccidioidomycosis *Dis of Chest* 12 371-386 1946
58. Rakofsky M and Knickerhocker T W Roentgenological manifestations of primary coccidioidomycosis *Am J Roentgenol* 56 141-155 1946
59. Charr R Some oontuberculous diseases of lung *M Clin North America* 31 1475-1492 1947
60. Boyer L B Bronchography in tuberculosis clinical study *Am Rev Tuberc* 54 111-121, 1946
61. Jones E M, Peck W M and Willis H S Bronchiectasis following primary tuberculosis *Am J Dis Child* 72 296-301 1946
62. Sokoloff M J Bronchiectasis *M Clin North America* 31 1418-1431 1947
63. Good C A Some remarks concerning roentgenologic diagnosis of bronchiectasis *Proc Staff Meet Mayo Clin* 20 22 1945
64. Cohen S Bronchiectasis some medical features among military personnel *Radiology* 49 192-200 1947
65. Royce B F and Victor R G Bronchiectasis following atypical pneumonia *Bull U S Army M Dept* 8 61-68 1948
66. Spain D M and Lester, C W Time element in development of irreversible bronchiectasis *J Pediatr* 32 415-419 1948
67. Loeffler W and Moeschlin S Über miliare Pneumonie von eitriger Schwere Verlauf (miliare Viruspneumonien) *Schweiz. med Wchnschr* 76 815-818 1946
68. Lenk R Die Bedeutung der Röntgenuntersuchung für die Diagnose und Differentialdiagnose der Akuten interstiellien Pneumonie *Acta radiol* 27 115-128 1946
69. Cryslar W E Primary atypical pneumonia disease of segmental distribution *Am J Roentgenol* 56 324 336 1946
70. McCoy W C Primary atypical pneumonia report of 420 cases with one fatality during twenty-seven months at Station Hospital Camp Rucker Ala *South M J* 39 696-706 1946
71. Robbins F C and Raggao C A Q fever in Mediterranean Area report of its occurrence to Allied troops clinical features of disease *Am J Hyg* 44 6-22 1946
72. Feinstein M Yessoor R and Marks J L Epidemics of Q fever among troops returning from Italy in spring of 1945 clinical aspects of epidemic at Camp Patrick Henry Virginia *Am J Hyg* 44 72 87 1946
73. Commission on Acute Respiratory Diseases Laboratory outbreak of Q fever caused by Baiken grippie strain of *Rickettsia Burneti* *Am J Hyg* 44 123 157 1946
74. Icons J V and Hooper J M Q fever to United States 11 Clinical data on outbreak among stock handlers and slaughterhouse workers *J A M A* 133 815 818 1947
75. MacKinnon A G Pulmonary type of tularemia (two cases) *Canad M A J* 56 541 1947
76. Henderson A T and Pierce C B Transitory focal pulmonary edema and eosinophilia (Loeffler's syndrome) *Am J Roentgenol* 58 391-406 1947
77. Wright D O and Gold E M Loeffler's syndrome associated with creeping eruption (cutaneous helminthiasis) report of 26 cases *Arch Int Med* 78 303 312 1946
78. Elkeles A and Butler N R Transitory pulmonary infiltrations and apical cavitation associated with eosinophilia *Brit J Radiol* 19 512-517 1946
79. Pearlman A W Loeffler's syndrome *Am J Roentgenol* 58 75 1947
80. Harvey W A Pulmonary brucellosis *Ann Int Med* 28 768-781 1948
81. McCort J J Wood R H Hamilton J B and Ehrlich D E Sarcoidosis clinical and roentgenologic study of twenty-eight proved cases *Arch Int Med* 80 293-321 1947
82. Mallory T B Pathology of pulmonary fibrosis including chronic pulmonary sarcoidosis *Radiology* 51 468-476 1948
83. Robbins L L Idiopathic pulmonary fibrosis roentgenologic findings *Radiology* 51 459-467 1948
84. King D S Idiopathic pulmonary fibrosis clinical study *Radiology* 51 477-479 1948
85. Doniach I Uremic edema of lungs *Am J Roentgenol* 58 620-628 1947
86. Burford T H and Burbank B Traumatic wet lung observations on certain physiologic fundamentals of thoracic trauma. *J Thoracic Surg* 14 415-424 1945
87. Robbins L L Technique of roentgenologic demonstration of pulmonary infarcts *Am J Roentgenol* 56 736-742 1946
88. Rawson A J and Cocke J A Infarction of entire pulmonary lobe with subsequent aseptic softening causing sterile hemopneumothorax *Am J M Sc* 214 520-524 1947
89. Blair I G Interpretation of children's chest x rays *Brit J Radiol* 20 223 237 1947
90. Blumenthal S and Neuhoef H Staphylococcal (suppurative) pneumonia in infancy and in childhood and its surgical aspects *Am J Dis Child* 72 691 719 1946
91. Almilov J R and Hatoff A Pneumatocele during course of pneumonia in children *Am J Dis Child* 72 521 528 1946
92. Clark E B Poisoning due to ingestion of wax crayons report of case *J A M A* 135 917 1947
93. Jones J A and Brieger, H Poisoning due to ingestion of wax crayons report of case *J Pediatr* 30 422-427 1947
94. Wylie W G Sheldon W Bowdian M and Barlow, A Idiopathic pulmonary haemosiderosis (essential brown induration of lungs) *Quart J Med* 17 25 1948
95. Elkeles A. Dissemination ossified nodules in lungs associated with mitral stenosis *Proc Roy Soc Med* 40 403-403 1947
96. Doig A T and McLaughlin I G Clearing of x ray shadows in welder's siderosis *Lancet* 1 789 1948
97. Sander O A Benign pneumoconiosis due to metal fumes and dusts *Am J Roentgenol* 58 277-282 1947
98. Shaver C G and Riddell A R Lung changes associated with manufacture of aluminum abrasives *J Indust Hyg & Toxicol* 29 145 157 1947
99. Dunner L Hermon R and Bagnall D J T Pneumoconiosis in dockers with grain and seeds *Brit J Radiol* 19 503-511, 1946
100. Dunner L Observations on development of graphite pneumoconiosis *Brit J Radiol* 21 182-185 1948
101. Gough J Pneumoconiosis in coal workers in Wales. *Occup Med* 4 86-97 1947
102. Lemcoe D V Scott W G Moore S and Koven A L Bagasse disease of lungs *Radiology* 49 556-567 1947
103. Editorial Bagasse disease of lungs *New Eng J Med* 238 378 1948
104. Williams C R Significant aspects of exposure to beryllium compounds in industry *Occup Med* 4 101-110 1947
105. Hardy H L and Tabershaw I R Delayed chemical pneumonitis occurring in workers exposed to beryllium compounds. *J Indust Hyg & Toxicol* 28 197 211 1946
106. Martland H S Jr Occupational beryllium poisoning in New Jersey with special reference to its incidence diagnosis and compensation *J New Jersey M Soc* 45 5 1948
107. Pascucci L M Pulmonary disease to workers exposed to beryllium compounds its roentgen characteristics *Radiology* 50 23 36, 1948
108. Pyre J and Oatway, W H Jr Beryllium granulomatous alveolitis military sarcoid Salem sarcoid, military sarcoidosis chronic beryllium poisoning or delayed chemical pneumonitis description and report. *Arizona Med* 4 21 1947
109. Wilson S A Delayed chemical pneumonitis or diffuse granulomatosis of lung due to beryllium. *J A M A* (in press)
110. Holley S W Bronchial adeomas *Mil Surgeon* 99 528-554 1947
111. Naclerio E A and Langer L Adeoma of bronchus review of fifteen cases *Am J Surg* 75 533-547 1948.
112. Bartlett J P and Adams W E Solitary primary nonneoplastic tumor of lung report of case *J Thoracic Surg* 15 251 260 1946.
113. Watts C F Claggett, O T and McDonald, J R Lipoma of bronchus discussion of benign neoplasms and report of case of endobronchial lipoma. *J Thoracic Surg* 15 132 144 1946.
114. Bloch R G Adams W E Thornton F and Bryant, J E Difficulties in differential diagnosis of bronchiogenic carcinoma. *J Thoracic Surg* 14 83 97 1945
115. Churchill E D Primary carcinoma of lung *J A M A* 137 455 461 1948
116. Rigler L G and Kelby G M Emphysema early roentgen signs of bronchiogenic carcinoma *Radiology* 49 578-586 1947
117. Reitz, H E Review of present methods in early diagnosis of bronchiogenic carcinoma *U S Nat M Bull* 48 198-205, 1943.
118. Oechel W R and Olson K B Primary bronchiogenic carcinoma mistakenly diagnosed as pulmonary tuberculosis case reports with body section roentgenography *Am J Roentgenol* 57 429-434 1947
119. Gerstl B Warring, F C Jr and Howlett K S Jr Cancer and pulmonary tuberculosis diagnostic problems in patients with cancer of lung in presence of pulmonary tuberculosis. *Am Rev. Tuberc* 54 470-487 1946.
120. Lambie C G and Collier J Generalized lymphatic carcinomatosis (cancerous lymphangitis) of lungs with special reference to milary carcinomatosis and syndrome of granules froide *M J Australia* 2 439-466, 1946.
121. Mueller H P and Sniffen R C Roentgenologic appearance and pathology of intrapulmonary lymphatic spread of metastatic cancer *Am J Roentgenol* 53 107 123 1945
122. McNamara W L Sargent, W F, and Costich K J Giant sarcoma of pleura report of case *Arch. Surg* 55 632-636 1947
123. Klassen K P Patten R, and Bemen F M Neurofibroma of diaphragm *J Thoracic Surg* 14 407-413 1945
124. Steele J D and Schmitz, J Mediastinal cyst of gastric origin. *J Thoracic Surg* 14 403-405, 1945
125. Dickson J A Claggett, O T and McDonald J R Intrathoracic gastric cyst. *J Thoracic Surg* 15 318-323 1946
126. Maier H C Bronchiogenic cysts of mediastinum. *Ann. Surg* 127 476-502 1948
127. Bradford M L, Mahon H W, and Grow J B Mediastinal cysts and tumors *Surg Gynec & Obst.* 85 467-491 1947
128. Sussman M L Differentiation of mediastinal tumor and aneurysm by angiocardigraphy *Am J Roentgenol* 58 584-590 1947
129. Sengpiel G W Ruzicka F F and Loddell E A. Lateral intra thoracic meningocoele *Radiology* 50 515 520 1948
130. Holt, J F Epicardial fat shadows in differential diagnosis. *Radiology* 48 472 479 1947

to suggest any abnormal condition in the stomach. All the x-ray findings suggest pressure extrinsically. If one comes down to an eventual analysis and is forced to choose any particular tumor one might say that this was a malignant tumor of the fibro-cellular group arising in the retroperitoneal structures with metastases to the lung but the metastases to the liver still bothers me. The picture to my mind would better fit something like a new primary tumor in the liver, which could of course go to the lung like this and form this large mass. Nothing is said about ascites. I think we come down to the point where the diagnosis might be academic. One can only prove it by histologic examination. This answer might have been obtained by a peritoneoscopy. Presumably a laparotomy was done with the idea that if the gall bladder was not involved a short-circuiting operation could be done, and the patient could be given some temporary relief from the jaundice. That is as far as I can go toward establishing the histologic diagnosis except to say that the retroperitoneal tumor had apparently involved the liver. If I were to make a choice preoperatively, I would list a primary hepatoma of the liver.

DR. WYMAN RICHARDSON: There is nothing suggested from the history that there was underlying disease of the liver. Usually the primary hepatoma develops on top of it.

DR. FRANSEEN: That is true. The only clue here is the suggestion of esophageal varices.

DR. FRED A. SIMMONS: I operated on this patient at the first admission. She will always remain a graphic case because of the accident to the wall of the internal iliac artery, which was of fairly good size. The tumor encircled the great vessels behind as well as on top. The ureter lay in the curve of the lateral aspect. As the tumor was dissected from the common iliac artery the vessel separated apparently at the site of a calcareous deposit. We altered our technic and the tumor was freed after the hemorrhage had been controlled and transfusion started. The patient's condition was good enough to allow removal of the tumor though we thought we had removed it in its entirety. I am impressed with the careful postoperative handling by the house staff which enabled this woman to keep the extremity. The pathological report was a benign tumor, but my impression at the operation was that it should have been malignant. I could not palpate the liver, since we approached the growth retroperitoneally.

#### CLINICAL DIAGNOSIS

Metastatic fibrosarcoma of liver

#### DR. FRANSEEN'S DIAGNOSIS

Hepatoma of liver

#### ANATOMICAL DIAGNOSIS

*Metastatic fibrosarcoma of liver and lungs*

#### PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: When the patient came back the second time the service asked us to review the slides of the original tumor, which we did, and felt again that from the block we had it looked like a benign fibroma. A peritoneoscopy was unsatisfactory so that a laparotomy was done and a tumor found within the liver, a biopsy of which showed fibrosarcoma. The patient did not do well following that procedure and died.

At autopsy she had a liver that weighed almost 6 kg., being diffusely involved with round nodules

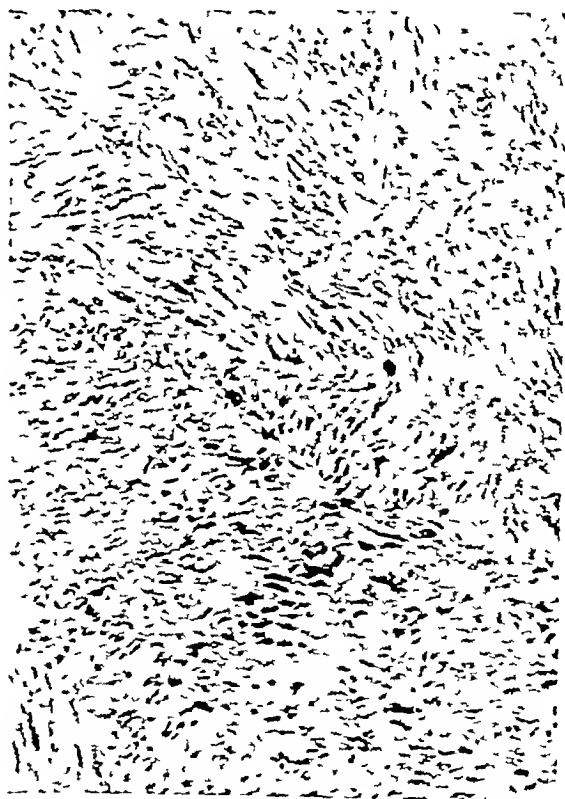


FIGURE 1

of metastatic sarcoma. The metastases were very circumscribed and could easily be shelled out, a feature that distinguishes it from metastatic carcinoma. The jaundice was probably due in part to the neoplastic replacement of the liver, but I believe more likely due to the fact that the caudate lobe was completely involved with tumor and pressed against the common bile duct. There were two nodules in the lungs—one on the pleura of the left lobe and one within it.

strate the right kidney and any possible relation of the mass to the kidney. On an intravenous pyelogram we see a normal outline of the kidney with good filling of the calyces and pelvis and without distortion of these structures. Further study by the retrograde injection of dye in the right urinary tract confirms this. If we compare the films taken on the first and second admissions there is no difference in the appearance of the calyces or in the configuration of the pelvis in two years. We can see the kidney in the later film behind the soft-tissue mass. It is a little lower in the abdomen than it was two years previously. The mass, therefore, is extrinsic to the right kidney and displaces it downward slightly.

There is a small, round area of increased density in the lower lobe of the left lung seen in the chest film taken on the second admission but not present on the chest film taken two years earlier. Otherwise the lungs are clear, the heart and vessels appear normal.

DR. FRANSEEN: Let us go back to the beginning and see what we can make of this tumor. It was evidently one of slow growth and when first noted was a walnut-sized mass in the right lower quadrant. We can tell something about the huge size of the abdomen from the x-ray films. If the patient was able to feel the mass herself through that abdominal wall, we can be sure that the walnut-sized mass was just a knob that protruded above a larger mass beneath. Eight years later she had a large lesion in the right lower quadrant consistent with slow growth. The slow growth was also suggested by the pathological report of a fibroma, possibly neurogenic. We get no exact idea of its site of origin from this record. It was apparently adjacent to or attached to numerous structures. With such soft-tissue tumors, one can cover oneself by saying that, from subsequent events, perhaps a section from another part of the tumor might have shown it to be more malignant than the histologic picture that was reported. In general, in dealing with tumors, if a secondary tumor appears, one should always assume that there was a relation with the first until proved otherwise. It may not have been so in this case. For two years she remained free of trouble. That is not an unreasonable interval for a tumor of this type even though there may have been a recurrence. Although the tumor was reportedly encapsulated, there was considerable difficulty in removing it—that is, it was not clearly encapsulated from a surgeon's viewpoint.

Two years later she had what was thought to be the "grippe," meaning, I suppose, that her family doctor had treated her for "intestinal grippe," and not necessarily an upper respiratory infection. The symptoms related to the stomach could be accounted for on the basis of pressure on the stomach or duodenum since the duodenum was pushed over

to the right on x-ray study. There is no mention of blood in the stools. There is no way of knowing, of course, whether or not this was a second primary tumor, and this always has to be considered. I am assuming all along that this was a tumor. There is nothing to suggest that this was an inflammatory process from the history or the findings at that time, and I think it is safer to go on the assumption that this was a tumor until it has been ruled out, especially in a seventy-three year-old woman. If it turns out to be inflammatory, that is fine. There is nothing here to permit me to suspect that this was due to an inflammatory lesion of the biliary tract or to obstruction on the basis of stone in the common duct. One certainly has to consider that area in the lung as a metastasis and thereby strengthen the suspicion of tumor.

Could all this picture have come from one of the fibrocellular groups of tumors? Metastasis to the liver would be an unusual behavior for it, however. We assume that the palpable mass was the liver, but the mass could have been in the retroperitoneal structures and the lymph nodes, giving the same displacement on x-ray examination, but this would also be somewhat unusual for the type of tumor described, even the malignant forms. The same statement is true of the neurogenic group. In my experience these two often show up in the lung but rarely in the liver. If we dismiss that, we will have to cover ourselves further by saying that it may have been some other form of malignant tumor, possibly a leiomyosarcoma. It would fit in, but not well. So, taking everything into consideration, I think it is safe to assume that a second primary tumor would not be uncommon, especially in a seventy-three-year-old woman.

What primary tumor can cause these findings? We have not much evidence for a malignant lesion anywhere else in the gastrointestinal tract. The jaundice could well have been due to pressure at the hilus of the liver on the bile duct. The only thing I can see against it is that the findings suggest that the jaundice lessened. Almost invariably with malignant tumors jaundice is progressive and becomes complete rather than being intermittent when it is caused by obstruction from a stone. That is the only finding against this idea, however. We must consider other things of course. The whole abdomen is open to suspicion—the gastrointestinal tract and the ovaries, for example. I think we can assume that the breasts and other peripheral sources of origin have been ruled out, or some mention would have been made of them. We assume perhaps that the left kidney was normal. The retrograde pyelogram was done only on the right. Is that correct?

DR. McCORT: Yes.

DR. FRANSEEN: There was no question that function was good in the left kidney. There is nothing

left ureteral orifice. No blood was seen coming from either orifice.

An intravenous pyelogram showed a filling defect measuring approximately 2 cm. in diameter in the left kidney pelvis and in the adjacent inferior major calyx (Fig. 1). In none of the films did the area fill, and one of the calyces was deformed, suggesting the presence of a mass in that region. The lateral margin of the left kidney was not clearly visualized, but there was some suspicion of an increase in size extending outward from the lateral margin in its middle portion. The right kidney was normal in size, shape and position.

On the nineteenth hospital day an operation was performed.

### DIFFERENTIAL DIAGNOSIS

DR. RICHARD CHUTE. To begin with, the fact that this patient was a rubber-factory worker may have been of significance. Although we do not know how long he had been at this work or exactly what he did, the possibility of poisoning with benzol, with an aniline compound or with lead must always be considered in rubber-factory workers. Lead is used in the process of manufacture, benzol is widely used as a solvent, and aniline compounds are employed to accelerate vulcanization. In benzol poisoning the bone marrow is affected, with reduction in platelets and a tendency to abnormal bleeding from the gums, nose and so forth. Frequently there is leukopenia (although the white-cell count may be normal or may be elevated), and there is anemia. In this patient there was no mention of bleeding other than intermittent hematuria, consistent with his bladder tumors, his white-cell count was not remarkable, and there was very little anemia so I believe that benzol poisoning can be ruled out. Also, I feel that lead poisoning can be ruled out, since no colic, weakness, wrist drop, lead line and so forth were mentioned. When it comes to the question of aniline poisoning he was not described as cyanotic like the rubber-factory workers who used to be called "blue boys" in Akron, Ohio. Nevertheless, it is a fact that workers with aniline compounds have a well recognized abnormal tendency to the formation of bladder tumors, which are said to occur in them thirty-three times as frequently as among other people. The tumors usually do not appear until after prolonged exposure—the average time being twelve years. A doubtful privilege of working in plants where a good deal of aniline is used is that of receiving, at the company's expense, periodic cystoscopic examinations. Furthermore, long exposure to aniline is well known to make men irritable and grouchy, and this patient is described as "emotionally unstable." So it is possible that aniline poisoning played a part in this case.

The finding of two pedicled papillary tumors is not surprising in a fifty-five-year-old man with

a history of bladder symptoms and the presence of blood in the urine. In my opinion these are undoubtedly papillary carcinomas, since I know of no other bladder disease that produces this picture. Bilharziasis (schistosomiasis) may produce a somewhat similar appearance, except that the lesions are more sessile and are usually ulcerated, and there are usually more marked symptoms and evidence of inflammation. The finding of only rare white cells in the urine indicates that the lesions in the bladder were not inflammatory. Nothing is said

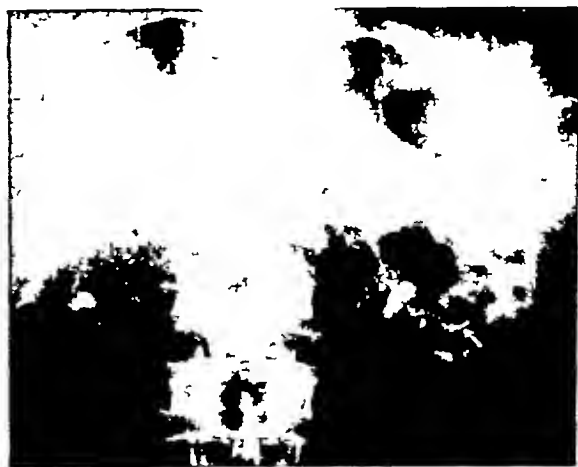


FIGURE 1 Intravenous Pyelogram  
Arrow points to crescentic calyx

about residence in areas of schistosomiasis such as Egypt or of finding the ova of *Schistosoma haematobium* in the urine.

Next we come to consideration of the significance of the filling defect in the left kidney pelvis associated with deformity of a calyx, suggesting a mass. Naturally, from the x-ray reports one thinks at once of a malignant papillary tumor of the kidney pelvis that has invaded the kidney parenchyma. It is well known that papillary tumors of the kidney pelvis often invade the kidney, extend down the ureter and give secondary implants in the bladder. Perhaps the tumors in the bladder were not true implants. Perhaps they occurred simultaneously with the renal tumors, very possibly brought on by the same etiologic factor. At any rate, the association of papillary tumors of the kidney pelvis with papillary tumors of the bladder is a well recognized fact. It is believed that this double lesion is greater in persons exposed to aniline than in others.

The fact that at cystoscopy no blood was seen coming from either ureteral orifice does not rule out the kidneys as a source of bleeding in a case with intermittent hematuria. In this patient the

DR ALLEN G BRAILEY Why did the jaundice lessen?

DR CASTLEMAN Perhaps the caudate lobe flopped around a bit

DR JAMES T HEYL Was there anything left in the right lower quadrant?

DR CASTLEMAN The pelvis was completely free from tumor. The right ureter was thickened on the outside where the tumor apparently had been adherent but there was no evidence of tumor. We



FIGURE 2

took several sections from that area. Here is a photomicrograph of the original fibromatous tumor (Fig 1). It is not very cellular, and the individual cells have single nuclei. In the section of the liver biopsy, on the other hand, the cells have changed. The nuclei are very large, some of the cells have two and three nuclei, and occasional mitoses are seen (Fig 2). It is possible, as Dr Franseen has mentioned, that if more blocks from the original tumor had been taken, we might have found one or two areas with morphologic evidence of malignancy.

DR RICHARDSON Is it possible that this was a new tumor?

DR CASTLEMAN I do not believe so. These certainly were metastases in the liver.

DR FRANSEEN Can you remember how many other times you have seen a fibrosarcoma behave this way?

DR CASTLEMAN I think we have had one other case. However, most of these cases that metastasize go to the lungs.

DR SIMMONS In retrospect, it would have been wise to radiate her.

DR CASTLEMAN No, I do not believe so. The metastases had probably already occurred at the time of the original operation.

DR FRANSEEN I also think that the metastases were there at the time of operation. Again we should emphasize the fact that hepatic metastases alone are not a contraindication to palliative surgery in certain carcinomas and other tumors—for example, cancer of the rectum. In this case it is possible that metastasis to the liver was not recognized at the original operation, and perhaps fortunately so, otherwise there might have been a temptation to abandon the difficult removal, and the patient would thereby have been denied the two years of palliative relief that she obtained.

## CASE 34472

### PRESENTATION OF CASE

A fifty-five-year-old rubber-factory worker was admitted to the hospital because of hematuria.

Approximately five months before entry he began to have intermittent hematuria, with blood clots. This was associated with a low backache and some dysuria. He had no pain in the flanks, loins or lower abdomen. He had nocturia four or five times a night but rarely any urgency. There was no weight loss.

Physical examination revealed a slim, emotionally unstable man who appeared younger than his stated age and who seemed in good physical condition. Aside from a moderately enlarged prostate gland, the physical examination was negative.

The temperature, pulse and respirations were normal. The blood pressure was 130 systolic, 90 diastolic.

Examination of the blood disclosed a white-cell count of 10,000 and a hemoglobin of 12.8 gm. The nonprotein nitrogen was 32 mg per 100 cc. The urine showed a +++ test for albumin, and the sediment contained 100 to 120 red cells and a rare white cell per high-power field. The specific gravity was 1.015. A urine culture grew *Staphylococcus albus* and alpha-hemolytic streptococcus.

Cystoscopy revealed a small, papillomatous growth, measuring approximately 1.5 cm in diameter, just behind the interureteric ridge. Another round mass, measuring approximately 3 cm in diameter and having what appeared to be a larger stalk, was noted just to the left of the

# The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal  
Established 1828

Official Organ of

THE MASSACHUSETTS MEDICAL SOCIETY

and

THE NEW HAMPSHIRE MEDICAL SOCIETY

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND

PUBLISHED WEEKLY UNDER THE JURISDICTION OF THE

COMMITTEE ON PUBLICATIONS

James P. O'Hare, M.D. Richard M. Smith, M.D., *Chairman*  
Oster Cope, M.D. Conrad Wesselhoeft, M.D.  
John Fallon, M.D.

Joseph Garland, M.D., *Editor*

Associate Editors

Thomas H. Lanman, M.D. Henry Jackson, Jr., M.D. Donald Munro, M.D.

Clara D. Davies, *Executive Editor*Robert O. Leary, *Assistant Editor*

Editorial Board

C. Guy Lutz, M.D. Maxwell Finland, M.D.  
Harry R. Viets, M.D. James M. Faulkner, M.D.  
Edward M. Green, M.D. Carroll B. Larson, M.D.  
Dwight O'Hara, M.D. Francis D. Moore, M.D.  
Fletcher H. Colby, M.D. C. Stuart Welch, M.D.  
Robert L. Goodale, M.D. Vernon P. Williams, M.D.  
Charles M. Jones, M.D. Benjamin Castleman, M.D.  
Harvey R. Morrison, M.D. Hugh R. Leavell, M.D.

**SUBSCRIPTION TERMS** \$7.00 per year in advance, postage paid for the  
United States (medical students \$4.00 per year) Canada \$8.00 per year  
(Boston funds) \$9.50 per year for all foreign countries belonging to the  
Postal Union

**MATERIAL** should be received not later than noon on Thursday three  
weeks before date of publication

The Journal does not hold itself responsible for statements made by any  
contributor

**COMMUNICATIONS** including those concerning classified advertising but  
excluding regarding other advertising should be addressed to the *New England*  
*Journal of Medicine* 8 Fenway Boston 15 Massachusetts Telephone  
KE 6-2034

**NEW ENGLAND ADVERTISING REPRESENTATIVE** (except for classified  
advertising) Edwin B. Tyler 89 State Street, Boston Massachusetts  
Telephone LA 3 5516

## TO HIM THAT OVERCOMETH

A SERIES of short papers have appeared this year in the London *Lancet* that are in no sense scientific or technical contributions, nor are they clinical, in that they do not describe from a professional point of view the symptomatology of the disorders discussed, or their treatment. Under the general heading "Disabilities" they consist merely of the patient's own brief chronicle of the disabling features of a disease or an injury, the method of meeting them and the degree of success attained in overcoming them.

The physical means by which some of these disabilities are defeated or their effects mitigated is of interest, the real worth of the articles lies in their

inspirational value — the spiritual lesson that they teach of the strength that comes through the effort of resistance. Each instalment in the series is a chapter from the book of courage.

A girl of twenty-three with a crushed vertebra and a damaged spinal cord copes with the problem of urinary incontinence and forces herself to become again a useful and optimistic member of society. A young man with a lesion of the cauda equina teaches himself to overcome his own bowel and bladder difficulties and learns to walk again. An Englishwoman with disseminated sclerosis, uncoordinated to the point where she reels and staggers like a drunken person, is caught in the German occupation of France. Considered by the conquerors as incapable of resistance she organizes a factory for forging identification papers and with one leg splinted, relearns bicycle riding. Alone she travels through the countryside, picking herself out of the ditch after each of her frequent catastrophes, finds fugitive English and American fivers and arranges for their escape. A victim of the crippling effects of her disease, she apparently finds also some measure of compensation in the emotional exaltation that sometimes accompanies it.

A man with double forearm amputation as a result of a bomb explosion employs to their fullest possibilities the varied mechanical contrivances available for amputees, as well as those that he has himself invented or improved. The best years of his life he finds to be still ahead of him. A patient with congenital cerebral palsy, compounded with infantile paralysis contracted at the age of two, considers life to be a "total war against physical affliction." "When told I cannot do a thing I have sometimes to sit and think out my own way of doing it and then I make this way as much like the normal method as possible." It is this person, once "the peculiar child of all peculiar children" who becomes a lecturer and lay preacher, who teaches himself to ride a bicycle, to drive a car and to manage a horse.

Another victim of a bomb explosion, suddenly and totally blinded at the age of thirty discovers that "one of the compensations of blindness is finding ways of overcoming it." It is this person who, having decided that such recreations as billiards

hematuria could just as well have come from a kidney as from the bladder tumors—very likely from both. Regarding the differential diagnosis of the x-ray picture, blood clot could have caused a filling defect in the kidney pelvis, but I would hardly expect it to deform a calyx or produce a picture suggestive of a mass. However, a tumor with blood clot could give this picture. Other tumors than papillary ones, such as invasive squamous-cell carcinoma of the renal pelvis and, rarely, renal-cell carcinoma (so-called hypernephroma), could also produce this appearance. Renal cyst is another possibility. This could cause deformity of a calyx and the suggestion of a mass, and, if it bled, as they sometimes do, the resulting blood clot could cause a filling defect in the kidney pelvis. Rarely, a staphylococcal abscess of the kidney parenchyma—the so-called renal carbuncle—gives this appearance on x-ray study. In the record no mention is made of the usual preceding history of recurrent furuncles or other infected skin lesions or a paronychia. Also, there was no fever and no mention of pain or tenderness in the left kidney region. The staphylococcus cultured from the urine was *Staph albus* rather than *Staph aureus*, the usual organism in these processes. Therefore, I do not believe that we are dealing with a renal carbuncle.

The final note says that "on the nineteenth hospital day an operation was performed." Since it is most unusual for the Urological Service to wait as long as this to operate, I suspect that there was something very unusual about this case. However, on the basis of the evidence submitted to me, I am making a diagnosis of carcinoma of the left kidney, probably papillary, and papillary carcinoma of the bladder.

DR STANLEY M WYMAN The plain film of the abdomen shows the kidneys fairly well outlined. I am unable to get very much excited about any distortion of the lateral margin of the left kidney. These first three films of the intravenous pyelogram examination are the most striking. There is a crescentic dye shadow overlying the lower major calyx. The appearance is that of compression and displacement of a minor calyx and compression of the pelvis of the kidney. The major calyces, as far as we can see in the upper pole, appear normal. The lowermost calyx and the calyx extending to the left lower quadrant are not adequately seen. From this examination one can assume the presence of a mass, 2 or 3 cm in diameter, compressing the calyces in this region. The last film taken from the retrograde

examination better demonstrates the lower major calyx. I can see no definite intrinsic involvement of this and there seems to be merely pressure on a minor calyx and distortion of the lower major calyx. Again there is possibly a little upward displacement of the major calyx in the midkidney region, giving the impression of something in this region compressing but not intrinsically involving the major calyx. I do not believe that the kidney pelvis per se is involved in this process. I think it is most likely a mass in the parenchyma rather than in the calyx.

DR CHUTE That would throw out papillary carcinoma of the kidney and make a renal-cell carcinoma or cyst a better choice.

#### CLINICAL DIAGNOSIS

Papillary carcinoma of kidney and bladder

#### DR CHUTE'S DIAGNOSES

Renal-cell carcinoma or cyst of kidney  
Papillary carcinoma of bladder

#### ANATOMICAL DIAGNOSES

Cyst of kidney  
Papillary carcinoma of bladder

#### PATHOLOGICAL DISCUSSION

DR BENJAMIN CASTLEMAN The first operation was a biopsy of the tumor of the bladder. This proved to be papillary carcinoma, and following that operation the left kidney was removed. When we received the kidney we found a well encapsulated, previously sectioned cyst about 2 cm in diameter in the midportion of the kidney, extending down and compressing the calyx to the lower pole of the kidney. The cyst had a very thin wall and apparently had been filled with clear, thin fluid. There was a thin layer of cortex over the cyst wall so that I do not believe it had produced much, if any, bulge of the margin of the kidney.

The patient worked in a factory where rubber products, such as raincoats and boots, are made and not in the manufacture of rubber. I should doubt that he was exposed to beta-naphthol, which is the substance in the aniline dyes that is responsible for the development of bladder cancer.

DR ARTHUR W ALLEN What did they do to the bladder tumor?

DR CASTLEMAN It was resected by cautery just a few days ago.

actual scientific valuation. A high premium goes with surgery, with anesthesia, with injections, with anything that the patient can grasp as presenting some definite procedure. A low premium goes with diagnostic skill, commonsense advice or friendly support. Even medical men, being themselves human, are drawn into the same way of thinking.

In discussing the problem at a meeting a surgeon recently said, "You mean the general practitioner is just a medical man who refers everyone to some specialist who can treat him?" In actual fact the family doctor can and should handle 80 to 90 per cent of the patients who consult him. But to treat them adequately he must be well trained in internal medicine, he must be a very good psychiatrist, and above all he must be as interested in the patient as a person as he is in the disease that the patient possesses. To be all of these surely, is a full-time job, one that does not permit the time to acquire technical skills involved in surgical maneuvers. If economics is the prime obstacle to the attraction of men into this branch of medicine, either the family doctor must be content with a lower financial return than his surgical brother, or a utopia must be reached where all men receive their just deserts.

Recognizing the dangers inherent in the distribution of medical care in the complicated structure of modern medical science the attempt is now being made to organize and classify everyone. The specialty boards have become so important and the possession of a certificate so highly prized that the majority of the medical students in the country are now planning their educational program to become certified specialists. But if only 10 to 20 per cent of the patients need a specialist, such a situation is ridiculous. Obviously, something must be done to point up the importance of the family doctor or general practitioner who should take full care of 80 to 90 per cent of the patients.

The establishment of the Section on General Practice in the American Medical Association and the proposal to organize a board of general practice may be steps in the right direction, but one wonders whether these are not moves based on self defense — a kind of guild or labor-union attitude — rather than a desire to advance medical science.

Would it not be more appropriate to reduce the opportunities for specialization to their proper proportions and at the same time to define clearly where the function of the general practitioner or family doctor lies? In addition, should not greater steps be taken to emphasize in hospital training qualities that the family doctor most needs — sound internal medicine and sound understanding of psychosomatic problems? Should not greater attempts be made to educate the public? If these things can be accomplished, general practice or family doctoring will assume its rightful place of esteem, and he who practices this skill will lose his all too frequent inferiority complex.

---

## DIABETES WEEK

THE week of December 6 has been designated as Diabetes Week, an arbitrary unit of time in which every effort will be made to bring under treatment the estimated million undiscovered diabetic patients in the country. This is not, obviously, a task that can be accomplished in a week; the designation is for the purpose of hammering home the existence of the problem and the necessity of meeting it. Considerable assurance was required, as the counselors of the American Diabetic Association know, to launch another special week for observance. In this case at least the cause was justified, and the need may be considered as imperative.

"The Clinical Characteristics of Early Diabetes Mellitus," by Beaser, printed elsewhere in this issue of the *Journal*, is most timely in view of the task that the American Diabetic Association has set. Beaser's statistics also, taken from the Diabetes Clinic of the Beth Israel Hospital, indicate the prevalence of early diabetes and the undesirability of having it go undetected. The task is to make the public aware of the necessity for the early discovery of the disease before overt symptoms have manifested themselves.

Patients can be classified in three groups according to the nature of the first signs or symptoms by which the disease makes its presence known. In the first group are those with frank diabetic symptoms such as polydipsia, polyuria, weight loss, weakness and pruritus. This group comprises

and table tennis are beyond his capacity, turns successfully to high diving, surf-riding and aquaplaning. For him the words of England's blind poet have had peculiar meaning

who best

Bear his milde yoaik, they serve him best

And so the list has grown — the education of a congenitally deaf child as told by its parents, the adjustments made by a nurse who develops epilepsy at thirty, the problems of the tuberculous, the young man crippled by poliomyelitis, the adolescent boy with an ileostomy, the alcoholic who finds his salvation in helping others similarly afflicted

Overcompensated many of these witnesses may be called, and with reason, as the heart hypertrophies that has an extra load to carry. From their achievements, however, a fundamental lesson may be drawn. All forms of life are meant to struggle against their difficulties and to rise above their obstacles or succumb. These that have been presented are only extreme examples culled from recent experiences.

If man, individually or in the aggregate, cannot accept life's challenges he must accept the futility of life. In this season set briefly apart for gratitude let him, then, rather than being thankful only for what apparent good fortune may seem to have overtaken him, be thankful also for the problems, the adversities, the temporary reverses that challenge him.

"To him that overcometh," it is written, "will I give to eat of the hidden manna."

---

## THE FAMILY DOCTOR AND THE GENERAL PRACTITIONER

THE current discussion regarding the role and prestige of the general practitioner has resulted in a certain amount of confused thinking. Some say that he is on his way out and the sooner the better, for things are done differently nowadays than formerly. Others bewail his decline, realizing that he is the most important cog in the organization for the care of sick people.

What are the reasons for these divergent views? They are concerned with semantics, with economics

and with the American obsession to organize and classify.

As to semantics, there is as much confused thinking in the medical profession as in the laity regarding the meaning of the term general practitioner. For purposes of discussion let us assume that a general practitioner is the first-echelon unit of medical care to whom the patient turns when he falls ill — whether such illness is a fever, vague fatigue and boredom with life, a perforated peptic ulcer or a fractured femur. If the patient lives in a small town situated far from a large city, the general practitioner will care for all the above illnesses. He has to be an astute internist to diagnose the fever, a skilled diagnostician and wise psychiatrist to deal properly with the tired patient, a competent surgeon to diagnose correctly and to operate upon the patient with an acute abdominal emergency, and an able orthopedic surgeon. But if the patient lives in a large city, who can deny that the best care requires that the general practitioner be primarily a medical man, and that surgical techniques are of a higher order when practiced by one doing nothing else but surgery? Here the general practitioner, though still the first-echelon unit of medical care, becomes a family doctor who knows how to diagnose and deal with problems but who refers patients requiring technical procedures and special skills to those who practice such procedures every day. In the small isolated community the family doctor and general practitioner are by geographical necessity one and the same. In the large city the general practitioner required by the small isolated community should not exist — he becomes the family doctor or family medical advisor.

Economics enters into the problem in that human beings put a high value on something that can be seen or felt — something producing quick action. They will gladly pay a large sum to a surgeon to take out an appendix or hitch up a uterus, in a mistaken attempt to cure a gastrointestinal neurosis. But they will feel imposed upon if asked to pay ten or fifteen dollars to a physician who spends an hour discussing personal problems and trying to teach the patient how to deal with them himself. The fact is that compensation for medical services is based on what the public values not

actual scientific valuation. A high premium goes with surgery, with anesthesia with injections, with anything that the patient can grasp as presenting some definite procedure. A low premium goes with diagnostic skill, commonsense advice or friendly support. Even medical men, being themselves human, are drawn into the same way of thinking.

In discussing the problem at a meeting a surgeon recently said "You mean the general practitioner is just a medical man who refers everyone to some specialist who can treat him?" In actual fact the family doctor can and should handle 80 to 90 per cent of the patients who consult him. But to treat them adequately he must be well trained in internal medicine, he must be a very good psychiatrist and above all he must be as interested in the patient as a person as he is in the disease that the patient possesses. To be all of these surely, is a full-time job, one that does not permit the time to acquire technical skills involved in surgical maneuvers. If economics is the prime obstacle to the attraction of men into this branch of medicine, either the family doctor must be content with a lower financial return than his surgical brother, or a utopia must be reached where all men receive their just deserts.

Recognizing the dangers inherent in the distribution of medical care in the complicated structure of modern medical science the attempt is now being made to organize and classify everyone. The specialty boards have become so important and the possession of a certificate so highly prized that the majority of the medical students in the country are now planning their educational program to become certified specialists. But if only 10 to 20 per cent of the patients need a specialist such a situation is ridiculous. Obviously, something must be done to point up the importance of the family doctor or general practitioner who should take full care of 80 to 90 per cent of the patients.

The establishment of the Section on General Practice in the American Medical Association and the proposal to organize a board of general practice may be steps in the right direction, but one wonders whether these are not moves based on self defense—a kind of guild or labor-union attitude—rather than a desire to advance medical science.

Would it not be more appropriate to reduce the opportunities for specialization to their proper proportions and at the same time to define clearly where the function of the general practitioner or family doctor lies? In addition, should not greater steps be taken to emphasize in hospital training qualities that the family doctor most needs—sound internal medicine and sound understanding of psychosomatic problems? Should not greater attempts be made to educate the public? If these things can be accomplished general practice or family doctoring will assume its rightful place of esteem and he who practices this skill will lose his all too frequent inferiority complex.

## DIABETES WEEK

THE week of December 6 has been designated as Diabetes Week, an arbitrary unit of time in which every effort will be made to bring under treatment the estimated million undiscovered diabetic patients in the country. This is not obviously a task that can be accomplished in a week; the designation is for the purpose of hammering home the existence of the problem and the necessity of meeting it. Considerable assurance was required as the counselors of the American Diabetic Association know to launch another special week for observance. In this case at least the cause was justified, and the need may be considered as imperative.

"The Clinical Characteristics of Early Diabetes Mellitus," by Beaser, printed elsewhere in this issue of the *Journal*, is most timely in view of the task that the American Diabetic Association has set. Beaser's statistics also, taken from the Diabetes Clinic of the Beth Israel Hospital, indicate the prevalence of early diabetes and the undesirability of having it go undetected. The task is to make the public aware of the necessity for the early discovery of the disease before overt symptoms have manifested themselves.

Patients can be classified in three groups according to the nature of the first signs or symptoms by which the disease makes its presence known. In the first group are those with frank diabetic symptoms such as polydipsia, polyuria, weight loss, weakness and pruritus. This group comprises

some 34 per cent of the total. The second group, making up 19 per cent, is composed of those who first become aware of diabetes because of the onset of one or more of its complications, such as neuritis, infection and cataract. The third, or "casual" group, comprising 47 per cent of the total, is made up of those who, with diabetes unsuspected, are found to be glycosuric on an examination conducted for a purpose unrelated to any suspicion of diabetes. It is to make the public aware of the presence of this group and the means and importance of discovering the persons who compose it that Diabetes Week has been designated.

Certain facts further emphasize the desirability of early diagnosis in diabetes. The longer the condition goes undiscovered, the more severe is its course likely to be, and it is known that sugar may be present in the urine for several years before symptoms pertaining to the disease become evident. This fact also explains its apparent onset with complications in 19 per cent of Beaser's cases—the patients had had diabetes for some time but did not know it.

Single negative urinalyses, moreover, are unreliable for the exclusion of diabetes mellitus. Stated differently, in the words of the author, "Even a single slightly positive test obtained under routine conditions, even though overshadowed by one or more previous, simultaneous or succeeding negative tests, should be taken to mean diabetes unless a glucose tolerance test proves otherwise."

### INCREASE IN TUBERCULOSIS

THE New York Tuberculosis and Health Association has reported a sharp increase in the number of new cases of tuberculosis in that city. For the first nine months of 1948 the total increase has amounted to 12 per cent, with a 17 per cent increase in the borough of Manhattan. The 6433 new cases registered represent an increase of 660 over the same period in 1947.

This increase is viewed with some alarm, and a corresponding increase in the number of deaths is expected, 70 per cent of all new cases registered being usually in an advanced stage of the disease. The patients now hospitalized within New York City number 5485, or 11 per cent more than a year ago. Tuberculosis sanatoriums, far from continu-

ing with the anticipated lightening of their load, are experiencing increased pressure and overcrowding.

New York's death rate for the corresponding period of 1948 was 40.4 per 100,000 population as compared with a rate of 38.9 for 1947. This represents an increase of 4 per cent.

Boston, similarly, according to an unpublished report from the Boston Health Department, has had reported 604 new cases for the first nine months of 1947 and 694 for 1948, an increase of approximately 15 per cent. The death rate in Boston, however, is close to 65 per 100,000, although some improvement in the rate is expected for 1948. The death rate for the country as a whole is well under 40.

### MASSACHUSETTS MEDICAL SOCIETY MALPRACTICE INSURANCE POLICIES

At the present time the office of the Society is receiving many requests for information concerning malpractice insurance policies and for information regarding which company issuing such policies is approved by the Society.

For the protection of the members of the Society, I believe it is best to quote from the recommendations of the Committee to Survey Malpractice Insurance as published in the *New England Journal of Medicine*, issue of December 4, 1947, under "Proceedings of the Council," as follows: "That no one company be recommended exclusively at this time."

This recommendation was adopted by vote of the Council.

H. QUIMBY GALLUPE, M.D., *Secretary*

### ATTENDANCE AT COUNCIL AND COMMITTEE MEETINGS

All too frequently those in the offices of the Society who are responsible for the execution of its official actions are impressed with the lack of information on important issues, and even opposition, to acts of the Society, on the part of fellows who have failed to acquaint themselves with the matters involved.

A more careful reading of the issues of the *New England Journal of Medicine* that pertain to Society activities, and better attendance at meetings of the Council and committees would go a long way toward clearing up these difficulties.

In order that the business of the Society may receive due attention, the Secretary will notify all district secretaries of the attendance at meetings of the Council and of those committees whose members are elected by the districts.

H. QUIMBY GALLUPE, M.D., *Secretary*

## MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

### NEW TYPHOID-VACCINE DOSAGE

The time-honored dosage of typhoid vaccine of three doses of 0.5 cc, 1.0 cc and 1.0 cc given at intervals of seven to ten days is now to be abandoned. For many years it has been suspected that larger amounts of some biologic preparations were being given than were really required. Everyone has been reluctant, however, to reduce doses without good scientific basis, for fear that a decrease in protection would result.

The United States Army Medical Corps has pioneered in the studies regarding typhoid vaccine. Just prior to the war important improvements were made in the production and testing of the vaccine, based on a large volume of research carried out at the Army Medical Center.

Using this vaccine of uniformly high quality, the Army has determined that a smaller dosage schedule is possible. Hereafter the routine will be three 0.5-cc doses administered at intervals of seven to twenty-eight days. The Biologics Control Laboratory of the National Institute of Health has now approved this dosage, and has authorized manufacturers to make this change in the directions accompanying the packages. The Massachusetts Department of Public Health has recommended this dosage as an optional alternative since February, 1948. In line with the policy of the National Institute of Health, it is now recommended that the new dosage schedule be universally adopted. This change may be made with assurance that the immunity produced will be as good as is required. Repeated studies at the Division of Biologic Laboratories have shown that the vaccine made there is equal or superior in potency to all batches obtained to date from other laboratories for comparison.

The recommendations for revaccination have not been changed. Either a subcutaneous dose of 0.5 cc, or an intracutaneous dose of 0.1 cc, given annually, will maintain a satisfactory level of immunity.

## MISCELLANY

### YALE CHILD STUDY CENTER

The appointment of Dr. Milton J. E. Senn as director of the new Yale Child Study Center has been announced by President Charles Seymour. The new center, embracing all the specialties and social sciences that bear on pediatrics, will include also the famous Yale Clinic of Child Development, established by Dr. Arnold Gesell, who retired as professor of child hygiene on July 1.

Dr. Senn, a native of Wisconsin, is retiring from the position of director of the Institute of Child Development and professor of pediatrics in psychiatry at Cornell University Medical College to assume his new post, which will carry with it the Sterling Professorship of Pediatrics and Psychiatry.

### ANNUAL MEETING OF THE SILVER HILL FOUNDATION MEDICAL COUNCIL

The medical council of the Silver Hill Foundation held its annual meeting in New Canaan, Connecticut, October 15 to

17. The members, chosen to serve in an advisory capacity for a period of two years, met first in a scientific session led by Dr. William B. Terhune, medical director of the Foundation. After this meeting, the members and their wives and guests were entertained at the Country Club of New Canaan.

The Silver Hill Foundation is a psychotherapeutic unit devoted to the study, care and treatment of the psychoneuroses where patients are given brief, intensive psychotherapeutic and physiologic aid to re-establish their lives and their ability to work. The medical staff is composed of internists who, although they are diplomates of the American Board of Psychiatry and Neurology, are interested in the eclectic approach to the treatment of the psychoneuroses rather than adhering to any one formal school of psychiatry. The subject for discussion of the Council this year was "What Is the Ideal Method of Treating the Psychoneuroses, Psychosomatic Illnesses and Psychosocial Disorders?" Speakers were Dr. Harold L. Amoss, Dr. Arlie V. Bock, Dr. Walter O. Klingman, Dr. F. C. Redlich and Dr. Edwin G. Zahriskie.

### ADVISORY COMMITTEE TO CHILDREN'S BUREAU

The United States Children's Bureau, now a unit in the Social Security Administration of the Federal Security Agency, has organized an advisory committee to aid in the development of its programs for maternal and child health and crippled children's services. The Bureau is responsible for administering the \$18,500,000 in grants that Congress makes available each year to the states to extend and improve these services.

The committee of forty-seven advisers, appointed by the chief of the Bureau for a three-year term, includes the following New England members: Harriett M. Bartlett, associate professor of social economy, School of Social Work, Simmons College; Dr. Allan M. Butler, professor of pediatrics at the Harvard Medical School; Dr. William T. Green, head of the Department of Orthopedic Surgery of the Children's Hospital, Boston, Massachusetts, representing the American Academy of Orthopedic Surgery; Dr. James R. Miller, of Hartford, Connecticut, trustee of the American Medical Association, representing the Association and Dr. Duncan E. Reid, professor of obstetrics at the Harvard Medical School.

## CORRESPONDENCE

### DIABETES DETECTION DRIVE

*To the Editor:* Will you kindly publish the following open letter to the Physicians of America?

The finding of the million cases of unknown diabetes in this country poses a direct challenge to the American doctor. It is within his power to accomplish this feat. The existence of these cases in the United States has been demonstrated through a series of surveys, the most recent one conducted by the United States Public Health Service. The results of these studies now provide a springboard for organized medicine and a golden opportunity for physicians to seize the initiative on their own in this significant phase of public health.

The American Diabetes Association has planned a campaign to promote the early discovery and prompt treatment of the million undiscovered cases of diabetes. This campaign is unique in professional service, for according to plan the physician himself will be at the helm. Therefore, the plan cannot be prosecuted, or even started, without the endorsement and support of the entire medical profession through its governing bodies, national, state, county and local medical societies.

The plan proposed by the Association is simple, direct and sure. Through local diabetes associations, related to the American Diabetes Association and with the cooperation of local, county and state medical societies over the United States and Canada, it is planned to carry out blood-sugar screening tests by a new five-minute micro-blood-sugar method with simultaneous urinalysis for sugar with attention to the time in relation to the preceding meal. The procedure can be carried out apart from a formal laboratory. The only provision will be that the candidate must name a physician or clinic to which the results of the tests will be mailed for interpretation.

to the patient. *Under no condition* will a report be sent directly to the examinee. The effort is to bring the patient with unknown diabetes under his own physician's care. There will be no statistics and no red tape.

Simultaneously, the American Diabetes Association will carry on an intensive educational campaign directed first toward doctors' postgraduate courses. It will be directed toward the layman by radio, newspapers and other publicity channels in addition to the *A D A Forecast*, the Association's bi-monthly magazine, which brings to the diabetic patient homespun articles on the disease by eminent authorities in the field. At the same time the Association will place in the hands of physicians over the country an authentic *Handbook of Therapy*. Containing the most up-to-date information available, the *Handbook* will assist the physician in treating diabetic patients.

The week of December 6-12, immediately following the interim meeting of the American Medical Association, will be proclaimed as "Diabetes Week." This will be the formal beginning, the kick-off, of the Association's Diabetes Detection Drive. From this start, the program will continue on a long-term basis.

The Association is determined to do its part in finding these million diabetic patients and guiding them to you, their physicians, for treatment. May we count on your support when the matter comes up before your county or local medical society? The success or failure of the Diabetes Detection Drive depends upon you. You stand at the helm, this is *your* project.

HOWARD F. ROOT, M.D., *Chairman*

American Diabetes Association, Inc.

## MEDICINE IN POLAND (1948)

*To the Editor* Assigned to the American Embassy in Warsaw, Poland, on January 2, 1948, as attending surgeon, I had the opportunity of observing and working with Polish doctors for six months. It was necessary for the welfare of the people under my care that I become familiar with the intricacies of the hospitals in Warsaw, that I meet physicians from the different specialties, and that with our own facilities and theirs appreciated a scheme of medical treatment be worked out. My job was a pleasure, and I have many fond memories of time spent with Polish colleagues. It was an academic revelation to visualize their medical setup.

Formal comparison of American and Polish medicine is without real significance. It is of value that the physicians of an international United States of America know the level of medical education, medical care and the type of scientific endeavor in Poland. Understanding can help our outgoing aesculapiads and organizations better to deliver supplies, lecture tours and fellowships, as well as to evaluate better any Polish physician who might manage to leave Poland to apply for licensure in the United States of America. A recent bill before Congress to extend the G. I. Bill of Rights to allow servicemen to enroll in European medical schools makes it seem urgent that a spotlight be thrown on what really exists in these traditionally famous places of learning.

Poland is in general badly smashed after six years of struggle. It was smashed in such a way that its cultural and professional activities were made to suffer most. Eighty to 90 per cent of Warsaw was reduced to rubble—its hospitals, libraries and physicians barely survived the attack. In the Warsaw uprising of 1944 the medical facilities were smothered as 250,000 Poles died. Cracow, always the Polish Vienna, was luckier. Untouched physically, the manpower pipeline and scientific nourishment were cut off. Lodz, Poznan, Wroclaw, Gdynia and Lwow were all punished to some degree—perhaps Warsaw represents a rather high average picture of where medicine stands in Poland today.

In the year following the Allied victory UNRRA gave Warsaw a running start with equipment basic and for daily expenditure. Shortly thereafter the World Health Organization set up its offices and meted out fellowships to Poles eager to sail west across the Atlantic. Many were given the opportunity to go to England, Sweden and Switzerland in like manner, and WHO, together with the Unitarian Committee, sponsored visits from world-renowned specialists, who worked hard on arrival to cover the missing years of scientific improvement. Even now, 15 physicians from England, Sweden, Czechoslovakia and America are touring Poland representing the Unitarian Committee, and their success

so far has been extremely gratifying. Dozens of voluntary philanthropic organizations, such as Brethren Service, Catholic Welfare and the Quaker Mission, continue to advance supplies to Poland's barren armamentarium. The seemingly insurmountable barriers to accomplishment of these missions—finance, customs and politics—were and are being overcome slowly. In like manner is the westward approach to science displacing the old Vienna school of thought and practice.

Against this background one can look out on the field of medicine in Poland, but like the sailor in *Gulliver's Travels*, one must consider whether he is amongst the Lilliputians or Brobdingnagians. It takes time to adjust the sights. It is not merely a question of evaluating the various specialties of medicine. An appraisal of their integration, so vital in American science, must be carried out in detail to arrive at an understanding of where the healing art stands in this land, the battleground between the West and Eurasia.

Unlike Germany, at one time medically self-sufficient, Poland, perhaps since the days of Copernicus, Von Mikulicz and Rydiger, has relied on the importation of science. Thus, most of the men I learned to know and work with spoke either English or German, and often many other foreign tongues. As importers and followers they seldom seem to have excelled. Where greatness existed in a few, schools apparently failed to develop or to foster progress. Under constant duress Polish medicine, along with Poland, failed to gain speed. Facilities remained limited, and ambition to renovate was stifled by traditional professionalism. The backbone of Polish medicine, hardly sturdy before the war, was scourged by an invader nation, which overtly attempted to reduce the rank of this profession, among others of the noblest elements of Poland.

I was carried into the realm of Polish surgery at the Child Jesus Hospital (First Surgical Clinic of Warsaw University) under the direction of Professor Tadeusz Butkiewicz. I was able to work two or three mornings a week in the operating room and to engage in the ward rounds and in some of the conferences. I saw 100 general surgical beds handled by eight or more assistants (men or women averaging thirty or more years of age), most of whom had at least one other job that consumed afternoons and evenings and made their work at the clinic, for a nominal sum, merely a small part of their day. Students were taught on the run and entered into the scheme of things only superficially. Teaching and academic pursuits were borne, when time permitted, by one or two. My friend Dr. Jan Nielubowicz slept little in his devotion to his role of major domo in this realm.

From this department I became acquainted with the roentgenologists and some of the internists and surgical specialists, such as Professor Grucha, a very well trained orthopedist. I found these other fields of medicine more properly tilled, although ancient devices continued to slip into recognized modern forms of therapy. Pneumonias were treated with penicillin and thoracic suction caps called "bankis," because "das alte recht" still clung like a scab to the back of men's minds. But over this lay the pall of no interdepartmental co-operation. I saw that each professor held sway in his realm, irreproachably right, seeking consultation only when a severely ill patient demanded assurance.

In every department of the hospital supplies were short. Much of what they had had been donated by UNRRA and other charitable organizations. Swedish, German and American equipment rounded out the few materials manufactured in Poland. It seemed that politics dictated amounts received from central-government purchases. Yet the wards were fairly tidy and clean, and nursing attendance was quite adequate. No great technical skill was needed in the handling of ward work because many modern devices were as yet lacking.

Results in surgery in this clinic were fair, but much was left undone owing to lack of technique, equipment and knowledge in preoperative and postoperative handling. Follow-up observation was inadequate, so that long-range errors un-revealed did not add to the standard of work. The anesthesia relied on was not only appalling, but in itself limiting. When endotracheal anesthesia was introduced by Dr. Olle Friberg of Stockholm, its application appeared like a rainbow after a dreary rain. There was every indication that, given opportunity, the Poles could come to the fore. There was something to be noted in their traditional professional integrity, which allowed a man to carry on with pride though hindered

from every angle and which allowed even the most trying operation to be performed with practical bravado.

With 500 to 600 beds available in the Child Jesus Hospital the services seldom seemed taxed, although on several occasions there was some overflow into the halls. It was never clear how much of Poland was covered by the 15 or so hospitals in Warsaw, but certainly in some special fields patients covered on clinics here from places 500 to 400 kilometers away, even from cities where medicine was in itself quite capable.

Infrequently, I had the opportunity of visiting other hospitals. At the Wolski Hospital, Professor Landau clearly demonstrated on his sparkling medical service that he had been practicing "western medicine" since 1928. Dr. Mantel in surgery had operating rooms under his surveillance that lacked nothing in equipment, and his reputation in thoracic surgery seemed well deserved.

The few private clinics in which I attended patients now and then did not smack of good medicine, with nursing service makeshift and surgery performed in ancient rooms with such assistance as the attending man might be able to summon if an emergency case appeared. Anesthesia was heartrending in any event. These, then, were the sites where underpaid professors and privileged assistants rounded out their salaries, not happy in their lot, but unable to lift up the scale, being on the pan constantly themselves.

Thus, it was apparent that, as in any other plan of life, varying levels were attained, and medicine and surgery at times even though hard pressed could in capable hands rise above drab surroundings.

When I was permitted to attend the second annual (second since the war) surgical congress in Cracow, April 5-8, 1948, the surgical perspective of this struggling land was revealed. Here 500 of Poland's surgeons gathered, avidly attending Dr. Nowicki's and Dr. Glazka's early morning operating stunts, after which they crammed into a small lecture hall in the well preserved Cracow city hospital for the presentation of papers. Although the orthopedic specialists were to meet separately in the following days, they attended, making the conglomeration complete, and as one of my friends complained as we strove to view the operative site early one morning, "Very few men who could wield a knife were absent."

And yet they seemed to have accomplished little after the heat of enthusiasm had waned. One and a half days were spent in uncritical hickering about treatment of wounds, centering on the role of the sulfonamides and other chemotherapeutic agents. The remainder of the second day lingered on while the surgical treatment of tuberculosis, with endless discussions on the types of operations giving best results in putting the lung at rest, was proffered. Then the mad scramble of the last day, when a rush of unrelated, crowded-out topics appeared, with the scheduled aspirants hoping to find time for their literary work. A few interesting cases were presented, but by and large the series were small with little follow-up observation. Issues were raised that had been better discussed with evidence measured in other lands, as in some instances on spur-of-the-moment investigation. None of the papers bore the earmarks of intensive investigative work. There were no papers on medical-education or surgical-training plans. I was consoled when it became obvious that my friends were no less weary of the haranguing and no less disappointed, although "it was better than the last meeting." They were anxious to learn how a similar surgical congress was handled in America.

I had the opportunity of meeting Duzend Chorobski at this congress, and on my return to Warsaw began to visit his neurosurgical clinic in the Praga portion of town east of the Vistula river. Vigorous and esteemed, having studied and worked in many centers in Europe and in Montreal and Chicago, he demonstrated how much a well trained man could do even in difficult surroundings. Besides turning out much good surgery, Jerzy Chorobski had created a school of neurosurgery amidst ruins and already had two disciples abroad, one in Lodz and another in Cracow. He was constantly buoyed up by the generous gifts of American neurologists — buoyed up spiritually as well as supplied with the physical goods needed to run his service.

In these various clinics mentioned medical students needed some lucky enough to be allowed to do practical things in most instances spending much of their time looking in on rounds in surgery they never approached a sterile field. They complained bitterly, and their few friendly teach-

ers bemoaned the large numbers in general and the expanding female representatives. Their preclinic years were ordinary — once out in the clinic they matured under the existing plan of advancement only after six to eight years. After graduating most of the class turned toward the smaller provincial hospitals for training, where they became eligible after two years to write a thesis for their Polish M.D. A few tough enough to endure obscurity for some years in Warsaw's larger clinics entered into these more academic pursuits.

Lack of reading facilities and medical literature rounded out the difficulties of education, even a master of library technique was often halled in his attempt to hunt up poorly catalogued literature, much missing in confusion and in fact. All libraries closed at eight in the evening, with little help to keep them running.

And where, after all these things were measured, did the Polish patient stand? Theoretically, Poland has a highly developed system of health centers with special setups for tuberculosis control and venereal-disease treatment — much of this exists on paper only. The average worker to enjoy medical care pays 15 to 25 per cent of his earned wage. The peasants, theoretically covered by insurance, were pretty much on their own, and many had to save up for months to pay for treatment of a medical ailment that in the meantime ran its course. They spent many earning hours waiting for care in understaffed clinics. The underpaid physicians, obliged to care for those registered, tended to give better attention to those well off, not covered by an insurance plan, who were willing to pay a reasonable fee. Even in a hospital patients were faced with the frequent necessity of obtaining their own medication on the "open market." Home-cooked food littered the wards to supplement the hospital's meager diets. Dentists, well thought of by most Americans seeking their aid, were overworked and charged a great deal, so that teeth examined in the workers were in the majority either naturally good or from neglect carious. The Poles attending our American hospital in Warsaw seemed amazed at our cleanliness, our armamentarium of drugs and our new equipment.

While I was in Poland, I saw the Unitarian Hospital in Piekary, near industrial Katowice, grow up. I heard of plans to start a large medical center in Lodz. I saw medical students being turned out to ease the burden being borne by 6000 doctors caring for 24,000,000 Poles. I heard of continued efforts to create a system of health centers centrally supported. But above all I had a chance to talk to many young doctors who saw the failure of their old professional system and saw the need for fundamental research, as well as for better medical education and libraries, and these men realized that the West points the way to better medicine. At times they saw that old German dictums and much of Germany's arbitrary medical contributions and outmoded methods had not only led to the downfall of German medicine but also had lagged in progress while a new system of science with perhaps some humanism had grown up to the north and west.

It was all too clear that although daily changes seem to affect the practicing doctors little, their involvement in the catastrophic decline of the nation was complete — he it aggressor or aggrieved. Although Poland demanded consolation by its very plight, it demonstrated how there can prevail a communion of aesculapiads that should be fostered and nourished and looked to for the establishment of world health and peace.

RICHARD H. SEGNIETZ, M.D.

3333 Shepard Avenue  
Milwaukee Wisconsin

## BOOK REVIEW

*Telepathy and Medical Psychology*. By Jan Ehrenwald, M.D. With a foreword by Gardner Murphy. 8<sup>vo</sup>, cloth, 212 pp. New York: W. W. Norton and Company, Incorporated, 1948. \$3.00.

This book is composed essentially of two parts: presentation of proof that telepathy exists as a phenomenon distinct from other psychic processes, and a presentation of the thesis that telepathy is in part or whole the basis of psychopathology.

To prove the first assumption, statistical data and material from case studies are presented in an attempt to put the study

on a scientific basis. In considering statistics, one must remember that they do not by themselves prove a thesis. For a thesis to become a science, two factors must be present: one must be able to predict behavior or performance from the acquired data, and the laws presented must apply to all cases that fall within the limits set up by the thesis. In no way does telepathy fill these requirements since one cannot predict its performance, and there is no explanation of the mechanism of how it works.

Psychiatry in general has fallen into the error of attempting to present itself as more nearly a science by making comparisons with well established scientific, usually physical or chemical, laws. This hook at times does the same thing. One must remember, under these circumstances, that comparisons are only assertions of belief and that comparison in, and of itself, proves nothing and does not make so subjective a field as psychiatry any more scientific than if it were not made.

The second thesis is not documented with a sufficient number of cases. Certainly, in a phenomenon so subjective as the products of mental and emotional functions of the central nervous system, wherein even hallucinations appear to be real, the occasional occurrence of the same thought at the same time to two or more people can be proof of little more than chance. The fact that patients produce material similar to the thoughts of the analyst is not to be wondered at, and has been discussed in numerous books and papers and need not be detailed here. One can only use it to support a belief in telepathy if one believes in telepathy as the dynamic principle. To say that distortion of personality leading to psychoses and neuroses or other functional disturbances is based on telepathic transference of thoughts and feelings is but begging the point. One still has not explained why one person reacts to such influences, if there is such a reaction, and another does not.

The explanation advanced is far too simple. The continuing stimuli from one's environment and from within one's self are so numerous and so varied that personality is always the complex of millions of interlacing threads. One can scarcely ever hope to find the basis of personality disorders in one general underlying principle.

Finally, after the book has been read, an attempt at objective evaluation suggests that little has been added in the way of proof of existence. One still must believe or not according to one's personal bias. As each new section is begun the reader hopes that he is going to have meat to chew on, but at the end of the section there is little more substance than a mouthful of spun candy hought at a fair

## NOTICES

### ANNOUNCEMENT

Dr. Morris Courtiss announces the removal of his office to 314 Commonwealth Avenue, Boston.

Dr. Manuel Kaufman announces the removal of his office from 419 Commonwealth Avenue to 1093 Beacon Street, Brookline, for the practice of internal medicine.

### NORFOLK DISTRICT MEDICAL SOCIETY

A meeting of the Norfolk District Medical Society will be held at the Hotel Kenmore, Boston, on November 23, at 8 p.m.

The program will consist of a "Legislative Meeting," at which members will meet incumbent and recently elected members of the State Legislature.

Physicians and members of the Women's Auxiliary of the Norfolk District Medical Society are invited.

### NEW ENGLAND DERMATOLOGICAL SOCIETY

A regular meeting of the New England Dermatological Society will be held at the Boston City Hospital, Skin Out-Patient Department, at 2:00 p.m. on December 1.

These meetings are open to members and invited guests only.

### INTERNATIONAL CONGRESS ON RHEUMATIC DISEASES

The seventh International Congress on Rheumatic Diseases and the first to be held in the United States will take place

at the Waldorf Astoria in New York City, May 30 to June 3, 1949, inclusive. This congress is sponsored by the International League against Rheumatism. The host is the American Rheumatism Association in co-operation with the New York Rheumatism Association.

Seven scientific sessions are planned, and five one-hour round-table conferences on various clinical topics will be held under the leadership of authorities in the respective fields. Short clinics, papers and reports will be given concurrently at four or five New York hospitals during three afternoons. Evening entertainment will be provided. The registration fee is \$10.00.

Members of the International, the European, and the Pan American Leagues against Rheumatism as well as the Canadian Rheumatism Association, British Empire Rheumatism Council, the Heberden Society of London, and the ten state or city Rheumatism Societies affiliated with the American Rheumatism Association are especially invited.

## SOCIETY MEETINGS AND CONFERENCES

### CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, NOVEMBER 25

#### FRIDAY, NOVEMBER 26

- \*9:00 a.m.-12:00 p.m. Combined Medical and Surgical Staff Rounds Peter Bent Brigham Hospital
- \*12:00 p.m. Clinical Conference on Urology Margaret Jewett Hall, Mt. Auburn Hospital, Cambridge

#### MONDAY, NOVEMBER 29

- \*12:15-1:15 p.m. Clinicopathological Conference Main Amphitheater Peter Bent Brigham Hospital
- 5:15 p.m. Staff Meeting Harris Hall New England Deaconess Hospital

#### TUESDAY, NOVEMBER 30

- \*12:15-1:15 p.m. Clinicorontogenological Conference Peter Bent Brigham Hospital
- \*1:30-2:30 p.m. Pediatric Rounds Burnham Memorial Hospital for Children Massachusetts General Hospital

#### WEDNESDAY, DECEMBER 1

- \*11:00 a.m.-12:00 p.m. Medical Rounds Amphitheater Children's Hospital
- \*12:00 p.m.-1:00 p.m. Clinicopathological Conference (Children's Hospital) Amphitheater Peter Bent Brigham Hospital
- 2:00 p.m. New England Dermatological Society Skin Out Patient Department, Boston City Hospital
- \*2:00-3:00 p.m. Combined Clinic by the Medical, Surgical and Orthopedic Services Amphitheater Children's Hospital

\*Open to the medical profession

OCTOBER 1-MAY 20 Metropolitan State Hospital Page 418 issue of September 9

NOVEMBER 23 and 30 Boston City Hospital House Officers' Association Page 762 issue of November 11

NOVEMBER 17-JANUARY 26 Boston State Hospital Psychiatric Seminar Schedule Page 762 issue of November 11

NOVEMBER 20-23 American Academy of Pediatrics Annual Meeting Chalfonte-Haddon Hall Hotel Atlantic City, New Jersey

NOVEMBER 23 New England Society of Anesthesiologists Page 762 issue of November 11

NOVEMBER 23 Norfolk District Medical Society Notice above

NOVEMBER 30 Hampden District Medical Society Page 492 issue of September 23

DECEMBER 1 New England Dermatological Society Notice above

DECEMBER 2 Suffolk Co. Society Meeting Page 492 issue of September 23

DECEMBER 4 American Federation for Clinical Research Page 644 issue of October 21

DECEMBER 4-9 American Academy of Dermatology and Syphilology Page 728 issue of November 4

DECEMBER 6-8 American Academy of Allergy Fifth Annual Meeting Chalfonte-Haddon Hall Hotel Atlantic City, New Jersey

DECEMBER 7-9 Southern Surgical Association Annual Meeting Page 543 issue of April 8

DECEMBER 9 Recent Advances in Thoracic Surgery Dr. Joseph P. Lynch Pentuck Association of Physicians 8:30 p.m. Haverhill

DECEMBER 9 and 10 New York State Society of Anesthesiologists Page 34 issue of July 1

FEBRUARY 4, 1949 American Board of Obstetrics and Gynecology Inc. Page 244 issue of August 5

MARCH 7-9, 1949 American Academy of General Practice Page 728 issue of November 4

MARCH 28-APRIL 1, 1949 American College of Physicians Page 158 issue of July 22

MAY 16-19, 1949 American Urological Association Biltmore Hotel Los Angeles, California

MAY 26-28, 1949 American Gout Association Hotel Loraine Madison Wisconsin

MAY 30-JUNE 3, 1949 International Congress on Rheumatic Diseases Notice above

NOVEMBER 11-17, 1949 Third Inter-American Congress of Radiology Page 158 issue of July 22

(Notices concluded on page xvii)

## NOTICES (Concluded from page 800)

## DISTRICT MEDICAL SOCIETIES

## HAMPDEN

NOVEMBER 30 8 30 p.m. Academy of Medicine Springfield Car  
cinoma of the Breast Dr Grantley W Taylor

## LIDDLESEX EAST

JANUARY 19  
MARCH 25  
MAY 11

## NORFOLK

NOVEMBER 23

## SUFFOLK

DECEMBER 2 Suffolk Censors Meeting

## WORCESTER NORTH

DECEMBER 15 Leominster Hospital Leominster  
FEBRUARY 25 Burbank Hospital Fitchburg  
APRIL 27 Annual Meeting

## TUFTS COLLEGE MEDICAL SCHOOL

## Postgraduate Division

INTERNAL MEDICINE AS RELATED TO BASIC SCIENCES  
Jan 3-Feb 26 1949 This is a review of anatomy general  
pathology bacteriology physiologic chemistry physiology and  
pharmacology for internists and general practitioners Clinical appli-  
cations are stressed demonstrated with patients The course includes  
lectures cadaver dissection laboratory exercises demonstrations  
It is given by the staff of the Basic Science Departments in collabora-  
tion with the research and clinical departments of the New England  
Medical Center Dr Robert P McCombs in charge Tuition fee \$200  
Minimum enrollment 20 Microscope required Application forms  
must be filed before December 3 Write to POSTGRADUATE DIVI-  
SION 30 Bennett Street, Boston 11 Mass

THE GEORGE WASHINGTON UNIVERSITY  
SCHOOL OF MEDICINE

## Announces

FOURTH ANNUAL SERIES OF INTENSIVE  
POSTGRADUATE COURSES

1	Ocular Pathology Motility and Orthoptics	January 10-14 1949
2	Psychosurgery	January 24-28 1949
3	Psychiatry	January 31-February 11 1949
4	Therapeutics	January 31-February 4 1949
5	Gastrointestinal Problems in Pediatrics	February 7-11 1949
6	Obstetrics	February 14-18 1949
7	Gynecology	February 21-25 1949
8	Anesthesiology	February 28-March 4 1949
9	Surgical Physiology	March 7-11 1949
10	Abdominal Surgery	March 14-25 1949
11	Bone and Joint Surgery	March 28-April 1 1949
12	Neoplastic Diseases	April 4-8 1949
13	Metabolic Diseases	April 11-15 1949
14	Thoracic Diseases	April 18-22 1949
15	Cardiovascular Diseases	April 25-May 6 1949
16	Gastroenterology	May 9-13 1949

By appropriate combinations of the above the following  
longer courses can be arranged  
For the Psychiatrist (Courses No 2 3) January 24-February 11 1949  
For the General Physician (Courses No 4 5 6) January 31-February 18 1949  
For the Obstetrician (Courses No 6 7) February 14-25 1949  
For the Surgeon (Courses No 7 8 9 10 11 12) February 21-April 8 1949  
For the Internist (Courses No 13 14 15 16) April 11-May 13 1949  
Other combinations can also be arranged

A Distinguished Guest Faculty Will Supplement the Local Staff  
Registration in each course is limited

Hotel accommodations are available  
Veterans can use their benefits under the G. I. Bill

For further details write  
DIRECTOR OF POSTGRADUATE INSTRUCTION  
The George Washington University School of Medicine  
1335 H Street N.W., Washington 5 D C

Advertisements



From where I sit  
by Joe Marsh

## Sam's Hens Wear Spectacles!

*Yes, it's a fact! Sam's brood of  
two dozen hens are wearing spectacles  
—which he bought from a mail-order  
house in Capitol City*

Sam says it works (and big poultry  
raisers say so, too) The hens see each  
other through soft colored glasses, and  
instead of fighting and picking at each  
other, they're placid, gain weight, and  
lay more eggs

*Makes me almost wish we could  
have rose-colored glasses for human  
beings, too So that instead of quarrel-  
ing and criticizing, like we generally  
do so much of the time, we'd simply  
live and let live in contentment*

From where I sit, the human race  
wastes a powerful lot of time in wran-  
gling over minor issues whether  
a man should drink beer or cider . .  
whether a woman should wear slacks  
or skirts instead of seeing each  
other through "spectacles" of toler-  
ance that enable us to live-and-let-live  
like Sam's brood of chickens

Joe Marsh

# SHOULD VITAMIN D BE GIVEN ONLY TO INFANTS?

**V**ITAMIN D has been so successful in preventing rickets during infancy that there has been little emphasis on continuing its use after the second year.

But now a careful histologic study has been made which reveals a startlingly high incidence of rickets in children 2 to 14 years old. Follis, Jackson, Eliot, and Park\* report that postmortem examination of 230 children of this age group showed the total prevalence of rickets to be 46.5%.

Rachitic changes were present as late as the fourteenth year, and the incidence was higher among children dying from acute disease than in those dying of chronic disease.

The authors conclude, "We doubt if slight degrees of rickets, such as we found in many of our children, interfere with health and development, but our studies as a whole afford reason to prolong administration of vitamin D to the age limit of our study, the fourteenth year, and especially indicate the necessity to suspect and to take the necessary measures to guard against rickets in sick children."

\*R H Follis, D Jackson, M M Eliot, and E A Park. Prevalence of rickets in children between two and fourteen years of age, Am J Dis Child 66 1-11, July 1943

MEAD'S Oleum Percomorphum With Other Fish-Liver Oils and Viosterol is a potent source of vitamins A and D, which is well taken by older children because it can be given in small dosage or capsule form. This ease of administration favors continued year-round use, including periods of illness.

MEAD'S Oleum Percomorphum furnishes 60,000 vitamin A units and 8,500 vitamin D units per gram. Supplied in 10- and 50-cc bottles and bottles of 50 and 250 capsules. Ethically marketed.

MEAD JOHNSON & COMPANY, Evansville 21, Ind., U.S.A.

WELLESLEY CO

NOV 23 19

LIBRARY

# The New England Journal of Medicine

Copyright 1948 by the Massachusetts Medical Society

Volume 239

NOVEMBER 25, 1948

Number 22

## THE SURGICAL TREATMENT OF MITRAL STENOSIS\*

### I Valvuloplasty

DWIGHT E. HARKEN, M.D.,† LAURENCE B. ELLIS, M.D.,‡ PAUL F. WARE, M.D.,§  
AND LEONA R. NORMAN, M.D.¶

BOSTON

NEARLY fifty years ago the possibility of relieving the obstruction to blood flow through a narrowed mitral valve was first suggested. Subsequent attempts have been made to accomplish this.<sup>1-16</sup> The surgical technics employed in these bold but disappointing adventures have been variously described as valvulotomy and valvulectomy. Much of the discussion of the theoretical value of this procedure has been concerned with the problem whether the patient would tolerate a surgically induced mitral insufficiency better than his existing stenosis. This, however, is an oversimplification of the situation. Many factors produce the symptoms and determine the course of the disease in patients with mitral stenosis. Among these are not only the degree of obstruction and of insufficiency of this valve but also the tendency to tachycardia or arrhythmia and the ease of its control, associated valvular defects, the activity of rheumatic disease, the damage to the myocardium of the two ventricles and alterations, functional or organic, in the pulmonary vascular circuit. Clearly, the problem of surgery in mitral stenosis is not simply that of breaking down a barrier to the flow of blood through a stenotic orifice.

At the present time, there are technics for studying cardiopulmonary dynamics that are vastly more extensive and more accurate than those available

to earlier students of this problem. They provide objective data for the evaluation of the patient before operation and the assessment of the result of surgery. In our opinion, the undertaking of surgery of such an experimental and hazardous nature in a complex physiologic situation without complete, objective studies is entirely unjustified.

It is the purpose of this first report to set forth certain preliminary impressions concerning the selection of patients for operation, the nature of the operation of choice and the surgical handling of the patient. In particular, a technic of direct valvuloplasty for mitral stenosis is presented.

### SELECTION OF PATIENTS AND CHOICE OF OPERATION

In brief, patients selected for operation should give unequivocal signs of mitral stenosis, should not have any significant degree of involvement of other valves or any other type of cardiovascular disease and should not present evidence of active rheumatic carditis or bacterial endocarditis. They should not have associated disease in itself incapacitating, but should have cardiac symptoms that are disabling and intractable to medical therapy. These patients suffer from profound pulmonary symptoms in various combinations, not only dyspnea, on exertion and at rest, and orthopnea, but also paroxysmal dyspnea, pulmonary edema, hemoptysis and chest pain. They may or may not have right-sided heart failure with peripheral venous congestion, hepatomegaly and peripheral edema.

Certain basic factors involved in the physiologic state of the circulation in mitral stenosis must be considered in selecting patients for operation and in choosing the surgical procedure most likely to be beneficial. These are the ability to maintain an adequate resting cardiac output and to increase it on exertion, the basic cardiac rhythm and the resting heart rate, the change on exertion, emotion and so forth, and the degree to which tachycardia can be controlled by medical means, the ex-

\*From the Eighth Surgical Service and the Surgical Research Laboratory, Boston City Hospital, and the Department of Surgery, Tufts College Medical School.

The medical evaluation of patients and cardiac catheterization studies were carried out at the Thorndike Memorial Laboratory, Second and Fifth Medical Services (Harvard), Boston City Hospital and the Department of Medicine, Harvard Medical School.

This study was supported by The Heart Institute of the Sias Laboratories, Brookline, Massachusetts, by The Charlton Fund of Tufts College and by The Life Insurance Medical Research Fund.

†Assistant professor of surgery, Tufts College Medical School, visiting surgeon for thoracic surgery, Boston City Hospital, senior associate in thoracic surgery, Peter Bent Brigham Hospital, thoracic surgeon, Mt. Auburn and Malden hospitals.

‡Assistant clinical professor of medicine, Harvard Medical School, associate physician, Thorndike Memorial Laboratory, Boston City Hospital, assistant visiting physician, Boston City Hospital.

§Assistant to visiting surgeon for thoracic surgery, Boston City Hospital (on leave of absence), fellow in surgery, Smithwick Foundation, Massachusetts Memorial Hospitals.

¶Charlton Research Fellow in Cardiac Surgery, research fellow in heart surgery, Heart Institute of Sias Laboratories, Brookline Hospital.

tent of elevation in pressure in the left auricle and pulmonary veins at rest, during exercise and tachycardia, and the relative importance of mitral regurgitation in the increase in this pressure, the degree of right ventricular failure, and the problem of organic disease in the pulmonary circulation. Since the patients who are under discussion had clinical signs of endocarditis confined to the mitral valve alone and no evidence of active myocarditis, neither the effects of disease involving other valves nor the possibility of left ventricular failure need be considered.

With these factors in mind, a preliminary classification of patients into three groups has been made.

#### *Group A*

This group includes patients with a low resting cardiac output, which is unchanged or even decreased on exercise, and with an elevated pulmonary-artery pressure. Signs of right ventricular failure may appear in addition to the pulmonary symptoms. For such patients, the operation of "valvuloplasty" may be helpful since the available evidence indicates that mitral obstruction is of major importance in their clinical condition.

#### *Group B*

In this group are patients whose resting cardiac output is within normal limits and usually increases with exercise. In spite of the adequate cardiac output, they often have as severe pulmonary symptoms as those in Group A, and the pulmonary-artery pressure is also elevated. The pathophysiologic mechanism in these cases may be a predominance of mitral regurgitation over the element of stenosis, or it may be that a high left auricular pressure maintains flow through narrowed mitral orifices to an adequate level. Secondary organic pulmonary vascular changes may also occur as an important element in producing the pulmonary symptoms. These patients may be benefited by the production of an artificial interatrial septal defect, which will decompress the left auricle and the pulmonary venous hypertension, especially at high peaks during periods of strain. This operation is probably not suitable for patients who have had right ventricular failure because of the added burden produced in the right ventricle by the recirculation of blood through this chamber and the pulmonary circuit. Such an operation may be contraindicated for patients in Group A, in whom too great a proportion of blood may be diverted through the shunt, and with decreased left atrial pressure, blood flow through the stenotic mitral orifice would be reduced still further to a level incompatible with life.

#### *Group C*

This category includes patients whose incapacitating symptoms, particularly attacks of pulmonary edema, are associated with rapid heart action that cannot be controlled by medical measures. The cardiac output may be normal or low, and the pulmonary-artery pressure elevated, the patients are not deemed suitable candidates for either of the operations mentioned above because of the extent and severity of their disease. The occasional patient with mitral stenosis who has attacks of severe chest pain, especially "hypercyanotic angina," may also fall into this group.<sup>17</sup> For these patients, a palliative procedure may be the removal of the cardiac sympathetic accelerator and afferent nerves. In 2 successive operations, the inferior cervical ganglion and the first four or five dorsal sympathetic ganglions are removed from each side through a small cervical incision. The relief afforded is through the production of a slower heart rate or the interruption of pain fibers. It is also possible that some additional direct effect on the pulmonary circulation is produced. A patient on whom such a denervation was performed has had dramatic relief from attacks of pulmonary edema for eleven months.

It is likely that the eventual surgical management of mitral stenosis will include combinations of these three operations. At the present time, however, it seems safest for the patient and consistent with the clearest understanding of the potentialities of each operation to carry them out singly. Again, it should be emphasized that the evaluation of the indications for these operative procedures and of their results should be kept on an objective basis, all the investigative tools that are available being used.

We have now treated 5 patients with mitral stenosis surgically. Two of these patients have had valvuloplasty, 2 have had atrial septal defects created, and 1 has had cardiac denervation. There has been 1 death, this was the first patient on whom a valvuloplasty was performed. This case is reported in detail below. It was from our experience in this operation that we came to appreciate the devastating effects of tachycardia in the presence of mitral stenosis and regurgitation. All the other patients are living and have had subjective improvement of their symptoms. Preliminary follow-up studies in 2 cases indicate that the objective improvement is considerably less striking than the subjective benefit.

#### SURGERY OF MITRAL STENOSIS IN THE PAST

During the latter part of the nineteenth century, the physiology of the circulation and of artificially produced valvular defects was the focus of some attention. The progress made in these studies culminated in the suggestion by Brunton<sup>1</sup> in 1902 that stenosis of the mitral valve might be relieved

surgically. Experimental support of this thesis came from the work of Haecker,<sup>2</sup> Bernheim,<sup>3</sup> and Cushing and Branch.<sup>4</sup> Surgical technic was studied by Schepelmann,<sup>5</sup> and later by Carrel and Tuffier.<sup>6</sup> During the decade from 1920 to 1930, clinical trial of mitral-valve surgery was made.

The most extensive experience was that of Cutler, Levine and Beck,<sup>7-12</sup> who operated on 7 patients of whom only the first survived. Cutler and his group attempted incision of the valve with a tenotomy knife in their first 3 operations. Further consideration of the thick, tough, calcareous valves made it obvious that incisions in the stenotic funnel were probably impossible and certainly inadequate. A cardiovalvulotome utilizing the principle of counterpressure was developed. Unfortunately, none of the patients on whom this instrument was used survived. Allen and Graham,<sup>13-14</sup> Souttar<sup>15</sup> and Pribram<sup>16</sup> reported 1 case each. Of these, only Souttar's patient survived, however, he had but "dilated" the mitral ring with his finger, whereas the others had attempted incision by cardiovalvulotome.

Instruments for direct visualization and manipulation within the heart have been used in cardiac

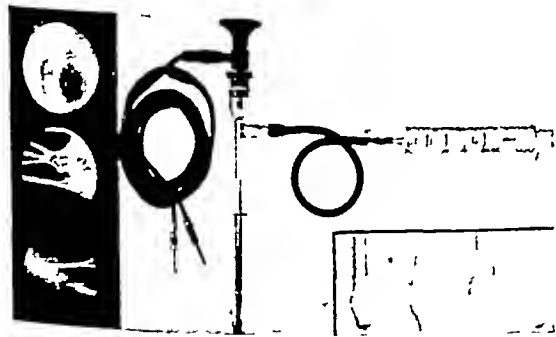


FIGURE 1 Assembled Cardioscope, with Sketches of a Pulmonary Vein, Mitral-Leaflet Edge and Papillary Muscle, as Seen through the Instrument

Insert elastic plastic, transparent balloons that fit on cardioscopic carrier. These, distended with saline solution, displace blood and allow intracardiac inspection. (Reproduced from Harken and Glidden,<sup>18</sup> by permission of the publishers.)

operations.<sup>13-18</sup> (Fig 1), but it is our opinion that the limited vision afforded by them does not warrant the increased operative hazard. To be sure, the ultimate technic in intracardiac surgery will embrace good endoscopic visualization or the utilization of a temporary mechanical substitute for the heart and lungs, allowing direct open operation on the interior of the heart during the period of suspended function.

## BASIC PRINCIPLES AND TECHNIC OF VALVULOPLASTY

The efforts of Cutler and Beck at correcting mitral stenosis formed the basis of our interest in this field. Discussion of the subject with Dr. Cutler before his death made it possible to correlate his experience with our own in cardiac manipulation. The rationale for valvuloplasty was predicated on this experience<sup>19-23</sup> and extended as the result of our first and only fatal operation.

In their operations, Cutler and Beck<sup>11</sup> employed a technic in which the heart was rotated forward and outward from the position of optimum function (Fig 2). One of us (D. E. H.) had found in

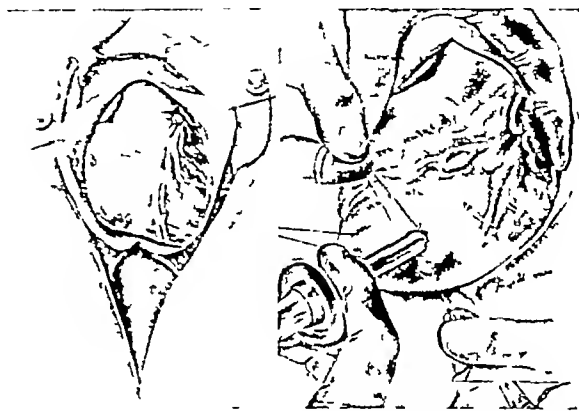


FIGURE 2 Illustrations Demonstrating the Exposure of the Heart and the Dislocation of the Heart from the Position of Optimum Function to Introduce the Valvulotome through the Ventricle. (Reproduced from Cutler and Beck,<sup>11</sup> by permission of the publishers.)

operating on hearts of otherwise robust American soldiers in the course of removing foreign bodies that this very sort of dislocation was invariably associated with violent disorders of rate, rhythm and output. These have been discussed in a previous publication<sup>21</sup> and documented in a motion-picture film in color.<sup>24</sup> If healthy hearts could not tolerate this dislocation, it is hardly likely that hearts damaged by rheumatism associated with far advanced mitral stenosis would fare better, much less tolerate the added insult of insertion of the valvulotome through the left ventricle. Indeed, it seems likely that a high mortality might result in these patients from dislocation of the heart alone, without any intracardiac manipulation.

The first principle is as follows: *the operation should be performed without dislocation of the heart from the position of optimum function.*

Again with the work of Cutler and Beck in mind, it was evident that it was most difficult to strike the apex of the stenotic funnel satisfactorily from

its ventricular aspect (Fig. 3). However, any instrument introduced from the auricular side tends to find the fish-mouthed opening with great ease. The objection to using the auricular appendage had been that it was often too thin and dilated to permit safe surgical entrance. It has been our experience that it is not often too thin for such an approach, if such a situation were encountered, the left superior pulmonary vein or a branch thereof could be used as a port of entry (Fig. 4).

The second principle is as follows: *the button-hole opening of the stenotic mitral valve should be approached from the auricular side so that the funnel directs the cutting instrument to the leaflet margin.*

In spite of these attractive technics for approaching the mitral funnel from above without displacing the heart, there still remains the question that has haunted all discussions of this subject: Is it physiologically advantageous to convert tight mitral stenosis into free regurgitation? Clinicians have been arguing for forty-six years whether mitral regurgitation is better borne than stenosis or the reverse. It is apparent that complete stenosis is

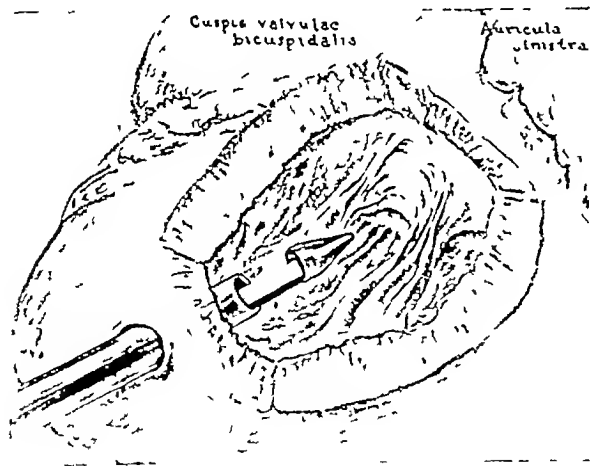


FIGURE 3 Diagrammatic Representation Suggesting Difficulty of Finding the Apex of the Stenotic Funnel Blindly. The dotted line indicates that the surgeons planned to remove a segment of the anterior mitral leaflet. (Reproduced from Cutler and Beck,<sup>11</sup> by permission of the publishers.)

incompatible with life. Conversely, complete regurgitation is promptly fatal to the experimental animal, and patients tolerate marked degrees of mitral insufficiency poorly. Thus, either stenosis or regurgitation in advanced stages can cause the patient's death. The questions before the surgeons are: Is there any compromise between too small an opening in stenosis and a slightly larger opening at the cost of more regurgitation? Is there any way to restore some valvular action to the damaged

valve? Are some types of insufficiency better borne than others? Ideally, surgical intervention should restore perfect valvular action, then the correction of obstruction in the light of the associated degree of insufficiency that is immediately produced would

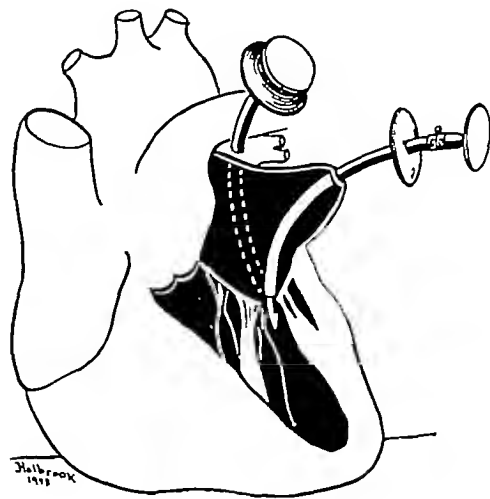


FIGURE 4 Cardiovalvulotome in Position after Insertion through the Left Auricular Appendage and the Alternate Approach through a Branch of the Pulmonary Vein (Dotted Line). The cutting edge is in the ventricle, directed toward the fused posterolateral commissure of the stenotic funnel.

not come under consideration. Unfortunately, that quality of valvuloplastic technic has not been attained.

During early work in our laboratory concerned with the experimental production of bacterial endocarditis,<sup>23</sup> the impression was gained that more than twice as many animals died from the destruction of the anterior mitral leaflet as from a corresponding destruction of the posterior leaflet. More recently, in 4 animals, it was found that left-auricular-pressure increments were roughly twice as high (equivalent to 10 to 20 as opposed to 5 to 10 cm. of saline solution) when anterior defects were produced as contrasted with posterior defects, and these changes were further increased during tachycardia. This suggested that insufficiency produced in various ways had different effects on the cardiac output and on the degree of regurgitation. Studies on a post-mortem human heart preparation supported the hypothesis that there was more regurgitation from an anterior than a posterior defect. These experiments seem interesting to us but are not yet sufficient to be regarded as conclusive. They only support a theory that can be presented diagrammatically.

In Figure 5 it is apparent that the anterior leaflet acts as a baffle that deflects blood toward the aorta,

whereas the posterior leaflet acts as an obstruction directly in the path of blood flow from the ventricle to the aorta. If the anterior leaflet is cut, the baffle or shunt to aortic output is compromised, and yet the obstruction of the posterior leaflet remains. Conversely, if the posterior leaflet is resected, the obstruction is removed, but the outflow through the aorta is less affected.

Direct palpation of the mitral leaflets throughout the cardiac cycle offers another type of informa-

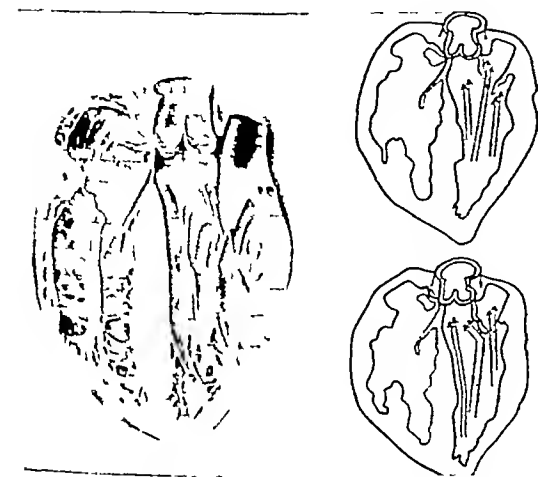


FIGURE 5 Cross-Section of Heart, Showing the Relation of the Mitral Leaflets to the Aortic-Outflow Tract  
The upper diagram illustrates the outflow tract broken by anterior valvulotomy, the posterior-leaflet obstruction remains. The lower diagram demonstrates the anterior leaflet intact as the wall of the outflow tract, the "selective insufficiency" being produced by removal of the posterior leaflet.

tion in this regard. When the exploring finger is introduced through the left auricular appendage of a dog, the anterior leaflet swings free throughout the cycle, but the posterior leaflet is squeezed and buttressed by the posterolateral wall of the left ventricle in systole. In diastole, the myocardium swings away from the normal veil-like posterior mitral leaflet. Again, it seems advantageous to remove segments from the posterior leaflet on its lateral margins in the stenotic funnel, such defects may correct obstruction during diastole (auriculo-ventricular flow) and yet may be occluded by the contracting, buttressing myocardium during systole, allowing less regurgitation (ventriculoauricular flow) than a surgical defect in the anterior mitral leaflet. Thus, some degree of insufficiency having been accepted as unavoidable after surgical enlargement of the mitral orifice, the theory of "selective insufficiency" was evolved as being the most likely to benefit selected patients. Such insufficiency was produced in the first patient operated on. At the present time, the posterior defects and selective

insufficiency are so created that the two commissures are cut away by wedge-shaped resections, with a view toward restoring some valvular action to the distorted, thickened leaflets. The wedge resections attempt to remove the fused zone that immobilizes the leaflets. This is the simplest form of "valvuloplasty" (Fig 6).

The third principle is as follows: *surgical enlargement of the stenotic orifice should be so planned that there is minimal burden from the associated regurgitation (selected insufficiency) and maximum restoration of valvular function (valvuloplasty).*

Our experience with the first patient on whom operation was performed led to a fourth principle. The case history of this patient is as follows:

CASE 1 J. B., a 26-year-old tool grinder, was referred to the Boston City Hospital on March 12, 1947\*. The present illness dated from April, 1946, when for the first time, he coughed up small amounts of pink frothy sputum. Massive hemoptysis occurred in December, 1946, and recurred in February, 1947. Both episodes lasted for 10 days. The second episode was especially severe, producing shock and depleting the patient to half normal erythrocyte and hemoglobin levels. There was no dyspnea, orthopnea or chest pain.

The past history revealed frequent sore throats in childhood, but no definite history of rheumatic fever. The patient had been active and in good health and had passed a life-insurance examination in 1939 without difficulty. In 1942 he was told that he had rheumatic heart disease when he was rejected by the Selective Service board.

Physical examination revealed the maximal apical impulse 7.5 cm left of the midsternal line in the fifth interspace, the midclavicular line was at 8.5 cm. The mitral first sound was increased. There was a Grade II blowing systolic and a rumbling diastolic murmur, with presystolic

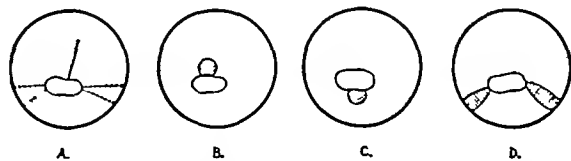


FIGURE 6 Diagrammatic Representation of Various Operations on the Stenotic Mitral Ring as Seen from Above  
A, anterior valvulotomy (dotted lines indicate zones in the solid stenotic funnel that were commissures in the predisease state). B, anterior-leaflet valvulotomy. C, posterior-leaflet valvulotomy. D, "selective insufficiency" and "valvuloplasty" by resection of the immobilizing commissure bridges.

accentuation. The lungs were clear to examination. There was no evidence of venous congestion, hepatomegaly, ascites or peripheral edema. The blood pressure was 118/70. Teleroentgenography showed slight increase of the hilar shadows, normal lung fields and a heart that was somewhat enlarged with a contour consistent with mitral stenosis. There was no evidence of pulmonary disease by bronchoscopy and bronchography. The electrocardiogram was consistent with right ventricular enlargement, and the broad, notched P waves were suggestive of auricular enlargement. The circulation time (arm to tongue) was 16 seconds (calcium gluconate). The venous pressure was equivalent to 95 mm of water. Examination of the blood disclosed a red-cell count

\*Referred by Dr. Sidney Solomon of Everett, Massachusetts.

of 3,850,000, and the hematocrit was 34 per cent. Catheterization of the right side of the heart showed an increased pulmonary-artery pressure of 55/30, with a mean pressure of 42. The right ventricular pressure was 50/7 (elevated). The resting cardiac output was within normal limits (5.95 liters per minute). A diagnosis of rheumatic heart disease with mitral stenosis, pulmonary hypertension and hemoptysis was made. It was decided to perform partial mitral valvulotomy on March 22.

Preoperative medication included 0.40 gm of nembutal, 150 mg of demerol and 0.65 mg of scopolamine. The patient received quinidine (0.4 gm) on the morning of operation. Immediately before induction with pentothal (2.5 per cent solution), 0.65 mg of atropine was given intravenously. Then curare, 30 units, was given and repeated in 10 minutes. An endotracheal tube was then inserted, and the balloon inflated. Shortly thereafter, ether was added slowly to the anesthetic mixture. Continuous electrocardiographic recordings were made throughout the procedure.

The operation was performed with the patient on his back, with the left side elevated 30°. The head of the table was also elevated 30°. The incision in the third intercostal space extended from the sternum to the left anterior axillary fold.

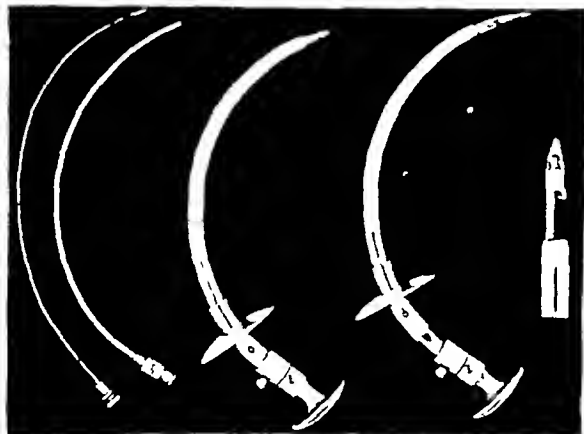


FIGURE 7 Photograph of the Cardiovalvulotome

On the left the trocar and cannula used in pressure determinations are illustrated. In the center the cardiovalvulotome in closed and open positions is shown. On the right, the detail of the cutting edge is demonstrated.

The pectoralis major and minor muscles were split. The mammary vessels were ligated and divided. The second and third costal cartilages were cut, the pleura incised, and the ribs spread. The thoracic inlet was infiltrated from within with 2 per cent procaine. The left superior pulmonary vein was isolated distally from the pericardium up to and including the anteromedial vein. Hemostatic traction sutures of No. 5 silk were looped around these veins. Transverse hemisection in the anteromedial vein between the control sutures allowed insertion of a No. 10 ureteral catheter into the left auricle. A mean pressure equivalent to 450 mm of water was recorded. The valvulotome (Fig. 7) was then inserted, and a segment was taken from the posterior leaflet of the mitral valve. The interauricular pressure was then recorded as equivalent to 470 mm of water. The valvulotome was reintroduced, and another disk removed from the posterior leaflet. Auricular pressure after this resection of the valve overflowed the 500-mm water manometer. The rise in left auricular pressure was completely incomprehensible at this time, and it was deemed unsafe to resect any more of the leaflet. The ureteral catheter was removed, and the vein was ligated. It was estimated that less than 100 cc of blood was lost in the five intracardiac manipulations. The chest was closed in layers with interrupted

sutures. During operation, the patient received 40 cc. of plasma, 150 cc of 5 per cent dextrose in water and 800 cc. of whole blood. His initial pulse was 78, but it rose to levels of 110 during induction of anesthesia. Shortly after the pleura had been opened and the ribs spread, the pulse gradually climbed to 140, remaining at this level throughout the remainder of the operative period, at all times it was regular. The blood pressure was constant at 100/60 to 110/70. Immediately after operation, the blood pressure was normal, the pulse 150 to 160, and the color fair. After the operation, the patient was observed on the operating table for 2 hours. The pulse remained unchanged, the systolic blood pressure gradually fell to 100. At this point, he was returned to the ward, where cyanosis of the nail beds and ears, with mottling of the forehead were noted. A positive-pressure mask was adjusted to provide 4 cm of expiratory resistance for 15 minutes of every hour.

The temperature gradually rose to 106.6°F 6 hours after operation, and at the same time, the systolic blood pressure dropped to 50. The clinical condition varied from minute to minute. Whole blood in small amounts was given to elevate the blood pressure, but signs of pulmonary congestion developed. The positive-pressure mask was poorly tolerated, and the resistance had to be eliminated. Rectal administration of aspirin and constant alcohol sponging reduced the temperature to 102.2°F, and it was maintained at this level. With the onset of hyperpyrexia, the patient became completely comatose, with a flaccid paralysis. There were no localizing signs. Eight hours after operation, intravenous metrazol was given with dramatic response, the patient became rational and conscious, talked fluently, moved all extremities and had normal reflexes. However, the systolic blood pressure never rose above 80, and cyanosis persisted. Shortly after the metrazol, the patient relapsed into unconsciousness, and the metrazol was repeated in 1-cc doses, intramuscularly, every hour thereafter, with temporary return of consciousness and activity. The patient continued to exhibit varying degrees of peripheral vascular collapse, pulmonary edema and anoxia. He succumbed in respiratory collapse and pulmonary edema approximately 24 hours after operation.

Autopsy revealed that the heart weighed 380 gm. The leaflets of the tricuspid valve and the cusps of the pulmonary and aortic valves were thin and delicate. The chordae tendineae of the tricuspid leaflets were of normal appearance. The trabeculae carneae and papillary muscles of the right ventricle were moderately hypertrophied. There was some thickening of the wall of the right ventricle. The left auricle showed hypertrophy and dilatation of its wall. The leaflets of the mitral valve were interadherent with a resulting stenosis. The lumen, fish-mouthed in character, had a circumference of 3 cm. The chordae tendineae of the valve were markedly thickened and shortened. An operative defect in the medial portion of the base of the posterior leaflet measured 0.6 cm by 0.3 cm, it extended completely through the thick valve from the auricular to the ventricular surface. Grossly, the lungs were unusually firm. Microscopical examination revealed thickening of the alveolar walls, dilatation of the capillaries and increase in the interstitial tissue and pericapillary edema. These findings were consistent with those described by Parker and Weiss.<sup>29</sup> The spleen, kidneys, liver and gastrointestinal tract showed chronic passive congestion. Gross and microscopical study showed no abnormalities in the brain.

This case illustrates how completely even a carefully planned procedure can miscarry. The intended manipulation was carried out with dispatch, and the changes in the interauricular pressure were recorded. The result was disastrous. Even at autopsy it was not clear why the operation had caused a rise rather than a fall in the left auricular pressure and had resulted in pulmonary edema and death in twenty-four hours.

The anesthesia chart showed a pulse rate fluctuating from 90 to 110 at induction of anesthesia. The operation had started with a rate of 110, and the

rate had risen to 135 per minute before the intra-cardiac portion of the procedure was undertaken. It then rose steadily after the operation. This tachycardia had not been prevented by us, no doubt, the use of barbiturates, atropine and direct vagal block had increased the heart rate.

In the presence of tachycardia when the mitral orifice is stenotic or regurgitant, it seems possible that three factors tending to increase pulmonary vascular pressure can operate

The stenotic mitral orifice permits blood to drain through it at a limited maximum rate only. The flow from auricle to ventricle occurs only during diastole. The duration of each systolic contraction is essentially the same whether the heart rate is fast or slow, therefore, the increased total systolic time of tachycardia is at the expense of the total diastolic time. With a reduced total diastolic period, there is less time for auricle-to-ventricle drainage or flow. Thus the obstructive effect of a stenotic mitral valve is greatest during periods of rapid heart action.

The undamaged right ventricle may pump more blood into the lungs during tachycardia.

The total volume of regurgitant blood is a function of the number of systolic contractions. The more rapid the heart, the more numerous are the regurgitant jets and, in general, the greater insufficiency in terms both of volume of regurgitant blood and of effect of regurgitant pressure on the left auricle and pulmonary circulation.

In short, tachycardia tends to increase pulmonary blood pressure by greater obstruction to forward flow, greater pulmonary filling from the undamaged right ventricle and increased regurgitation or backward flow from the left ventricle.

These factors, simple as they seem now, were not fully appreciated until the disastrous effects of tachycardia in the first patient were observed. Subsequent animal experiments have confirmed their importance, and these will be reported later. It is evident that during any operation on patients with mitral stenosis and regurgitation, a slow heart rate must be maintained.

These considerations have a bearing, too, on the selection of patients for operation. Patients in Group B who are able to maintain a normal resting cardiac output may have predominant mitral regurgitation. If so, their condition would only be made worse by an increase in the degree of insufficiency surgically, by tachycardia or particularly by a combination of these. For the patients in Group C, the operation of cardiac denervation is a direct attempt to diminish the hazard that tachycardia presents. The more closely we observe patients with severe mitral disease, the more conspicuous is the association of tachycardia with bouts of "pul-

monary decompensation" such as paroxysmal dyspnea, pulmonary edema and hemoptysis.

The fourth principle is as follows: *in the presence of mitral obstruction or regurgitation, a rapid heart rate must be avoided, tachycardia tends to increase pulmonary vascular pressure and is associated with attacks of pulmonary edema or "pulmonary decompensation"*

The course of the second patient on whom valvuloplasty was performed illustrates that the procedure is feasible in human beings, perhaps the survival of this patient was aided by the measures taken to reduce tachycardia.

CASE 2 G A C, a 27-year-old man, was referred to the Boston City Hospital in June, 1948\*. The chief complaint was that of pain at the angle of the right scapula. Since the age of 8 years, he had had six attacks of "rheumatic fever," characterized by fever, chills and bone pain. With one episode he developed chorea and tender subcutaneous nodules. He had suffered from exertional dyspnea, palpitation of the heart and easy fatigability for 10 years at least. He had taken maintenance doses of digitalis since the early attacks in childhood. A chronic cough with occasional streaking of blood had occurred 3 years previously. At about that time, pain in the back of the right side of the chest started. This was nonradiating and could be relieved at first by changes in position. However, it had become progressively worse during the 2 months prior to admission and was constant at the time of entry. The patient was almost completely invalided during this period.

Physical examination revealed an emaciated young man with a *cafe-au-lait* complexion. There was slight venous distention in the neck. The heart was greatly enlarged to the right and left, and the rhythm was typical of auricular fibrillation with a rate of 110 and some pulse deficit. A soft diastolic rumble was heard from the lower end of the sternum to the apex. Near the apex, the murmur was loud and rough and there was a pronounced diastolic thrill. The pulmonic second was greater than the aortic second sound. The area of liver dullness appeared to be increased. There was no peripheral edema. The blood pressure was 110/65.

Six-foot teleroentgenograms revealed a greatly enlarged heart to both right and left. The left auricle was markedly enlarged. There was fluid in the right costophrenic angle. Films showed areas of patchy density in the right-middle and lower-lung fields, probably owing to atelectasis. The electrocardiograms showed auricular fibrillation and diphasic T waves, with low origin of Leads 1, 2 and 4. The venous pressure was equivalent to 180 to 230 mm of water. The circulation time was 12 seconds (arm to lung) by the ether method. The hematocrit was 36 per cent. The vital capacity was 2.7 liters and dropped to 2 liters after exercise, when the pulse rate was elevated to 140. Measurement of the resting cardiac output by cardiac catheterization showed it to be low (3.4 liters per minute with a cardiac index of 2). With mild exercise the stroke volume decreased from a resting level of 52 cc. to 29 cc. The pulmonary-artery pressure was elevated (71 systolic, 39 diastolic and 51 mean) and showed a further increase during exercise. Evidence of right ventricular failure was afforded by the elevated resting right auricular pressure (8 mm of mercury), which increased to 9.5 mm after 1 minute of mild exercise and to 18.5 mm on manual pressure over the right upper quadrant.

In view of the general condition and the results of the physiologic studies, valvuloplasty was considered indicated.

Operation was performed on June 16. Premedication included 100 mg of seconal, 100 mg of demerol and 0.5 mg of scopolamine. Induction was uneventful with nitrous oxide and cyclopropane, endotracheal anesthesia was maintained with ether. The heart rate was followed continuously by electrocardiographic tracings. The patient was placed in the dorsal decubitus position. A left anterior intercostal approach through the third space was carried out, with division of the second and third costal cartilages at the sternum. Firm adhesions held the lung to the chest wall. The pericardium was opened transversely down to

\*Referred by Dr. Sawyer Foster of Boston, Massachusetts.

the phrenic nerve. The left lateral aspect of the left auricle and the left auricular appendage were exposed by freeing diffuse adhesions to the pericardium. A pulmonary conus perhaps three times the normal size presented anteriorly. Three No. 000 silk purse-string hemostatic sutures were placed around the auricular appendage at the projected cardiomyotomy site. Through this prepared site in the tip of the left auricular appendage a trocar and cannula (Fig. 7) were then introduced, the trocar was removed, a manometer was attached to the cannula, and the interauricular pressure found to be equivalent to 450 mm. of saline solution at a pulse rate of 92. The cardiovalvulotome (Fig. 7)



FIGURE 8 Patient in Case 2 Two Months after Mitral Valvuloplasty

was introduced with the cutting edge directed at the lateral commissure, the valvulotome hook engaged, and the instrument closed. The cutting sensation and sound were elicited, but the segment was not recovered. The maneuver was repeated with the instrument directed at the medial commissure. Finally, a segment of the stenotic funnel was removed in a third maneuver directed at the posterior aspect of the lateral commissure. After these three intracardiac cutting manipulations, the interauricular pressure was again taken and found to be equivalent to 400 mm. of saline solution even though the pulse rate had risen to 108. During these five intracardiac procedures, 40 mg. of procaine was given twice intravenously. Upon completion of the intracardiac manipulations, the instruments were withdrawn, and the cardiomyotomy site was sealed by tying the purse-string sutures. The closure of the auricle was reinforced by the pericardial closure in that zone. The remainder of the pericardial incision was loosely closed to allow the escape of any effusion. The anterior thoracotomy incision was closed in layers in a routine fashion, without drainage.

The postoperative course was uneventful, and the patient was subjectively improved during his immediate hospital convalescence. The pain that represented his chief complaint on admission disappeared, and he seemed to have an increased exercise tolerance.

The first objective studies made since the operation show little improvement in cardiac function over that prior to operation. The size of the left auricle has not diminished. Follow-up studies will be reported.

This operation was directed at increasing the size of the mitral orifice itself. That the patient would benefit by this procedure was suggested by the low cardiac output and the stroke volume that decreased with exercise. The principle of increasing the size of the mitral orifice and yet producing "selective insufficiency" was combined with an attempt at removing the immobilizing commissures, the current crude form of "valvuloplasty." Intravenous procaine was given during the operation to reduce myocardial irritability and as a part of the effort to maintain a slow heart rate. The operation was uneventful, and the pressure studies at the time suggested a favorable response. Since operation, the patient has been dramatically improved subjectively, although such objective studies as have been made show little change from the earlier investigations.

Before operation it was known that the general condition of this patient made him a much worse operative risk than the first patient. However, operation was elected after the poor prognosis, the progression of symptoms despite a rigid medical regime and catheterization studies that suggested possible benefit through valvuloplasty had been considered. The four principles of surgery on the mitral valve were applied, and the commissures and one segment of the posterior leaflet of the stenotic funnel were removed. This patient is alive today, symptomatically improved, five months after operation (Fig. 8).

#### SUMMARY AND CONCLUSIONS

Numerous complex physiologic and morphologic factors are concerned in the production of symptoms in patients with mitral stenosis.

A preliminary classification is presented of patients incapacitated by mitral stenosis, who may be benefited by different types of surgery. Group A, patients with low fixed cardiac output—mitral valvuloplasty, Group B, patients with normal cardiac output—artificial interatrial shunt, Group C, patients with uncontrollable tachycardia or with anginal pain—cardiac denervation.

Five operations have been performed. Mitral valvuloplasty was performed in 2 patients of Group A, with 1 death. Artificial interatrial defects were produced in 2 patients of Group B, with survival in each case. Denervation of the heart by bilateral removal of the inferior cervical and dorsal first to fourth ganglions in 1 patient of Group C was followed by improvement.

These cases are now reported only to indicate the ability of such patients to withstand operation. The evaluation of any long-term benefits attributable to these procedures — and, indeed, of the ultimate position of surgery in mitral stenosis — must rest on objective criteria gained from hemodynamic studies carried out before and after operation. Subjective selection of patients and assessment of results lead to dangerous competitive exercises in surgical technics rather than to fundamental advances in therapy.

Four principles of the surgery of mitral stenosis have been evolved: the operation should be performed without dislocation of the heart from the position of optimum function, the button-hole opening of the stenotic mitral valve should be approached from the auricular side so that the funnel directs the cutting instrument toward the leaflet margin, surgical enlargement of the stenotic orifice should be so planned that there is a minimum burden from associated regurgitation ("selective insufficiency") and maximum restoration of valvular function ("valvuloplasty"), and in the presence of mitral obstruction or regurgitation, undue acceleration of the heart rate must be prevented — tachycardia increases pulmonary vascular pressure and is associated with attacks of pulmonary edema and other forms of "pulmonary decompensation."

An unsuccessful attempt at producing "selective insufficiency" is presented. It is suggested that tachycardia was an important factor in the disastrous outcome.

A case report is presented of the survival of a patient with mitral stenosis following an operation designed to produce "selective insufficiency" and "valvuloplasty" of the mitral valve.

The need for more extensive and more effective valvuloplastic technics is suggested.

We wish to express our appreciation for criticisms and suggestions to the following members of the Board of Consultants of The Heart Institute of the Sias Laboratories: Drs. Burton E. Hamilton, Frederic Parker, Jr., Richard Schatzki, and Paul M. Zoll.

## REFERENCES

1. Brunton L. Preliminary note on possibility of treating mitral stenosis by surgical methods. *Lancet* 1:352 1902. Surgical operation for mitral stenosis. *Ibid* 1:547 1902.
2. Haecker R. Experimentelle Studien zur Pathologie und Chirurgie der Herzens. *Arch f klin Chir* 84:1035-1098 1907.
3. Bernheim B M. Experimental surgery of mitral valve. *Bull Johns Hopkins Hosp* 20:107-110 1909.
4. Cushing H and Branch J R B. Experimental and clinical notes on chronic valvular disease in dog and possible relations to future surgery of cardiac valves. *J N Research* 12:471-486 1907-1908.
5. Schepelmann E. Versuche zur Herzchirurgie. *Arch. f klin. Chir* 97:739-751 1912. Herzklappen Chirurgie. Experimentelle Untersuchungen. *Deutsche Zeitschr f Chir* 120:562-579 1913.
6. Carrel A and Tuffier T. Étude anatomopathologique et expérimentale sur la chirurgie des orifices du cœur. *Presse med* 22:173-177 1914.
7. Cutler E. C. and Levine S. A. Cardiomyotomy and valvulotomy for mitral stenosis. Experimental observations and clinical notes concerning operated case with recovery. *Boston M & S J* 185:1023-1027 1923.
8. Cutler E. C. Levine S. A. and Beck, C. S. Surgical treatment of mitral stenosis: experimental and clinical studies. *Arch Surg* 9:689-821 1924.
9. Beck, C. S. and Cutler E. C. Cardiovalvulotomy. *J Exper Med* 40:375-379 1924.
10. Cutler E. C. Surgical aspect of mitral stenosis. *Arch. Surg* 12:212-229 1926.
11. Cutler E. C. and Beck, C. S. Surgery of heart and pericardium. In *Nelson's Loose Leaf Living Surgery*, Edited by A. O. Whipple and F. B. St. John. Vol. 4. 712 pp. New York: T. Nelson & Sons, Chap. IV. Pp. 286-320 1927.
12. *Idem*. Present status of surgical procedures in chronic valvular disease of heart: final report of all surgical cases. *Arch. Surg* 18:403-416 1929.
13. Allen, D. S. and Graham E. A. Intracardiac surgery — new method preliminary report. *J A M A* 79:1028-1030 1922.
14. Allen D. S. Intracardiac surgery. *Arch. Surg* 8:317-326 1924.
15. Souttar H. S. Surgical treatment of mitral stenosis. *Brit M J* 2:603-606 1925.
16. Pnhrum B. O. Die operative Behandlung der Mitralstenose. *Arch. f klin Chir* 144:458-465 1926.
17. Burgess A. M. Jr. and Ellis L. B. Chest pain in patients with mitral stenosis with particular reference to so-called "hypercyanotic angina." *New Eng J Med* 226:937-941 1942.
18. Harken D. E. and Glidden E. M. Experiments in intracardiac surgery. II. Intracardiac visualization. *J Thoracic Surg* 12:566-572 1943.
19. Harken D. E. Foreign bodies in and in relation to thoracic blood vessels and heart. I. Techniques for approaching and removing foreign bodies from chambers of heart. *Surg Gynec & Obst.* 83:117-125 1946.
20. Harken D. E. and Williams A. C. Foreign bodies in and in relation to thoracic blood vessels and heart. II. Migratory foreign bodies within blood vascular system. *Am. J Surg* 72:80-90 1946.
21. Harken D. E. and Zoll P. M. Foreign bodies in and in relation to thoracic blood vessels and heart. III. Indications for removal of intracardiac foreign bodies and behaviour of heart during manipulation. *Am. Heart J* 32:1-19 1946.
22. Harken D. E. Review of activities of Thoracic Center for III and IV hospital groups 160th General Hospital European Theater of Operations June 10 1944 to Jan 1 1945. *J Thoracic Surg* 15:31-43 1946.
23. *Idem*. Experiments in intracardiac surgery. I. Bacterial endocarditis. *J Thoracic Surg* 11:656-670 1942.
24. Color sound moving picture. Foreign bodies in pericardium and heart (demonstration of heart operations). U. S. Army Signal Corps. Production misc. No. 1238.
25. Donovan T. J. and O'Brien R. Unpublished data.
26. Parker F. Jr. and Weiss S. Nature and significance of structural changes in lungs in mitral stenosis. *Am J Path.* 12:573-598 1936.

# MEDICAL SCHOOLS AND THE QUALITY OF MEDICAL CARE\*

## A Survey of Recent Trends

E RICHARD WEINERMAN, M D , M P H †

BERKELEY, CALIFORNIA

**I**NCREASING attention has been paid in recent years to the economics of medical care. Proposals for newer health-service programs have stimulated a voluminous literature, and many important experiments in organized medical care have been developed to meet the increasing public demands.

Few students of the problem would quarrel with this emphasis upon costs and distribution of care. Ready access to adequate health services must exist for all the people.

The removal of economic barriers, however, would in itself not provide the whole answer to the medical needs of the country. There remains the challenging task of improving the *quality* of the service that is to be more equitably distributed. A serious gap persists between the standards of the teaching medical centers and the quality of care rendered in outlying and underprivileged communities.

In the effort to improve the general quality of medical care throughout the country, the medical schools are realizing the significance of the role they must play. This concept has been clearly expressed by the chairman of the Council on Medical Education of the American Medical Association<sup>1</sup> and by the secretary of the Association of American Medical Colleges.<sup>2</sup> In their emergence from the isolation of the last century, the schools developed close relations with universities and teaching hospitals. Now, such affiliations are beginning to extend to public health and social agencies, to smaller hospitals and health centers, and to practicing physicians in the surrounding area.

If improved quality is to accompany the better financing of medical care, and if the influence of the medical schools is to bear on the problem, this new and broader concept of the function of the school must be universally adopted. The basic functions of teaching and research expand to include the concept of service to the community, of active identification with the medical life of the surrounding region. The modern medical center becomes the hub of continuous postgraduate educational activities, of regional medical-service programs

reaching to outlying rural areas and of functional relations with all community health facilities. Thus, the quality of medical care may be enhanced throughout the region of the teaching center.

Such a development is neither new nor visionary. Many medical schools in this country have accepted responsibilities for improving medical standards in their areas. Several of the foreign nations are developing health-service regions around medical teaching centers. This report includes descriptions of some of the projects already underway in the United States in one phase or another of the general movement. Through broader orientation toward the preventive and social aspects of medicine, through continuous education of the physician and his technical aides and through functioning affiliations between metropolitan and small community hospitals, the quality of medical care available to the public is being steadily improved.

## UNDERGRADUATE MEDICAL TRAINING

In the fifty years since the development of the modern medical course, there have been vast and fundamental additions to the medical sciences. Whole new fields have opened up in nuclear physics, nutrition, tropical medicine, antibiotics, neurologic surgery and endocrinology—to mention but a few. Yet the “modern” medical curriculum existed in 1891, and prevailed in all schools by 1915. Since then, such development as has occurred has been somewhat haphazard and unplanned—often involving cumbersome additions to a fixed structure.<sup>3, 5</sup>

Increasingly apparent, moreover, in an industrialized, mobile society have been the interpersonal, social and environmental aspects of health and disease. The tremendous growth of organized systems of prepayment medical care, group practice, health units and preventive medical programs has changed the face of medicine, without producing very extensive alterations in the countenance of the medical schools. Notable exceptions to this rule are described below.

Such developments require parallel readjustments in the medical curriculum.<sup>6</sup> Fifty years ago, Johns Hopkins University School of Medicine made such a break with the educational *status quo* in introducing the “modern” curriculum. The stage is now set for the next step forward.

\*From the Department of Public Health Practice, Division of Medical Care, Harvard School of Public Health.

Much of the material in this paper was derived from the report on regional medical centers to the New York State Temporary Commission on Need for a State University (Young Commission) and is used with the permission of the Commission.

†Associate professor of medical economics, School of Public Health, University of California, formerly fellow Harvard School of Public Health.

### *Interdepartmental Integration*

The rapid growth of each field of medicine has often resulted in rigid compartmentalizing of the curriculum, with relatively isolated academic divisions each competing for the student's time and attention. If better equipped physicians are to be produced for modern medical practice, heed must be paid to the pleas of medical leaders for the development of integrated "vertical" medical courses.<sup>7-9</sup> Such a curriculum would stress the importance of "dynamic units of study"<sup>8</sup> instead of traditional departmental boundaries. Eadie and Davison<sup>10</sup> have urged a general course structure that is completely functional in concept, whereby each of the separate disciplines contributes to the total understanding of the subject under study.

Integration activities at the Bowman Gray School of Medicine may be mentioned by way of example of efforts in this field.<sup>11</sup> At this new school studies in basic science are being related to their sick-bed implications through medical and surgical clinics designed to illustrate the principles under discussion. The preclinical faculty members make hospital ward rounds, and residents in the various specialties are given teaching assignments in the basic-science courses. Departmental autonomy is increasingly relinquished. Similar efforts are under way at the Western Reserve University School of Medicine<sup>12</sup> and at a few others.

### *New Emphasis in the Curriculum*

Such general integration of the curriculum can go a long way toward improving the quality of the training offered. However, the requirements of modern medicine call for the addition of some specific new elements and the strengthening of others in the general medical courses. These are, significantly enough, the disciplines that examine the relations of the sick man to his fellows and his community. Their influence on the quality of professional care is fundamental.

### *Psychiatry*

Although the teaching of psychiatry has progressed in recent years, medical students are often inadequately provided with training in the understanding of the personal and emotional relations in health and disease. Undergraduate training in this field is too often restricted to a few mental-hospital case studies and a disjointed series of lectures on psychiatric disorders. A recent statement by nineteen medical-school deans declared "There are not five medical schools in the United States with Departments of Psychiatry adequately endowed."<sup>13</sup>

Still entirely undeveloped is the potentially much more productive field of mental hygiene. The medical student is now rarely impressed with an appreciation of the gigantic task to be performed through

preventive psychiatry — especially in childhood — in the control of mental disorders that fill no less than half the hospital beds of the nation. The recently passed National Mental Health Act provides funds for research and training in this field, and should serve as the needed stimulus to expanded undergraduate activity.

The teaching of psychiatry at University of Louisville School of Medicine exemplifies commendable efforts now underway in some schools.<sup>14</sup> Here psychiatric instruction permeates the entire course. The city mental-hygiene clinic is a part of the Department of Psychiatry, which includes three full-time teachers. The program involves seminars, clinical clerkships, home visits, observations of therapeutic interviews, participation in nursery-center operations and the like. Student participation remains the key to the program. More recently, sweeping reorganization of the psychiatric teaching program has been instituted at Yale University School of Medicine.

### *Preventive Medicine*

In a medical philosophy focused on disease and its treatment, the promotion of health and the prevention of illness receive country-cousin attention. Almost every medical educator has been constrained to point out that a fundamental preoccupation with disease — to the exclusion of efforts to prevent it — is a primary weakness of modern medicine.

A recent report<sup>15</sup> indicates that twenty-eight of the eighty-seven schools in the United States and Canada have no organized program for instruction in prevention, and most of the schools do not regard such emphasis as important. Teaching hours are often those that no other department wants, and the median number of clock-hours total only 1.9 per cent of the general curriculum. Little or no instruction is incorporated into the preclinical years, and such instruction as was reported is usually didactic, with little relation to the clinic, the health center or the community.

The recommendations of the Committee on the Teaching of Preventive Medicine and Public Health recognized that the objective was not to produce junior health officers but to imbue the embryo physician with the concept of positive health and with the philosophy of preventive medicine. A separate department with a full-time chief, having 4 per cent of the curriculum hours and 5 to 8 per cent of the total budget, was urged for all schools. Teaching in the preclinical years and full co-ordination with other clinical departments was strongly recommended. This seems modest indeed.

Dublin<sup>16</sup> has described the specific accomplishments of a forward-looking department of preventive medicine at Long Island College of Medicine. His course in preventive medicine embraces the full facilities of the nearby community public-health

center and is closely correlated with clinical teaching. Senior students spend full time for four weeks in this work—participating in health clinics, field activities, seminar discussions, home visits and social-work programs.

Similar affiliations of local health units with departments of preventive medicine operate at Louisville, Cornell, New York University, Alabama, Manitoba and a few other schools of medicine. In this connection, Goodenough<sup>17</sup> and many others have stressed the very real importance of student health services as a practical demonstration of preventive technics and an opportunity for student participation in a program of health conservation.

### *Social and Economic Aspects of Medicine*

By the intelligent development of courses in socioeconomics, medical schools can overcome the single most serious deficiency in the modern system of medical education. The need for such new emphasis has been succinctly expressed by LeBlanc<sup>18</sup>

Somewhere along the line of medical education, the embryo doctor should come in contact with the economic facts of life. Medical students are, from an economic standpoint, a favorably selected group. They come from higher strata rather than the lower. It is not only likely, but experience has shown it to be true, that they know little or nothing about the economically underprivileged. Even in their dispensary work they are seeing their patients in a frame far more flattering than normal. They have never seen or smelled bad housing, they know nothing of the reality of bad diets, of broken homes, of unemployment, of what it means when the breadwinner is sent to a hospital for a long stay, of the thousand and one things never seen at the hospital bedside or in the dispensary.

Yet, in twenty-two of the schools no time is devoted to medical socioeconomics, and the over-all number of clock hours devoted to the subject is 3.9 (median number = 1.5).<sup>19</sup> A recent statement by a medical student highlights the situation: "When confronted with the question 'What information would you like to have included in a course on health economics?', many of the students immediately retorted, 'What is health economics?'"<sup>20</sup>

Similarly, a survey conducted by the Association of Internes and Medical Students revealed an overwhelming desire on the part of the student sample for more instruction in these matters.<sup>21</sup> At Harvard, student interest manifested itself in a highly successful series of medical-sociology seminars organized and run as an extracurricular activity.

Many voices have been raised in recognition of this need. Allen,<sup>7</sup> Leavell,<sup>22</sup> Means,<sup>23</sup> Goldmann,<sup>24</sup> Gregg<sup>25</sup> and others<sup>26</sup> have forcefully stressed the need for the teaching of medical socioeconomics. Oxford University and the University of Brussels have established well known chairs in social medicine, as have other leading schools in Europe and Canada. A few of the schools in this country have already organized some instruction in this field.

One of the best known courses has been that at Yale, where—until recently—regular seminars have been offered in the subject.<sup>24</sup> A briefer orientation course is available at the University of Minnesota Medical School,<sup>27</sup> and a ten-hour elective is being offered at the University of Colorado School of Medicine.<sup>28\*</sup>

Medical socioeconomics should include instruction in the organization and administration of medical-care programs if new graduates are to be able to find their way logically through the turmoil of public discussion of these problems. The medical student should be acquainted with such modern phenomena as Blue Cross plans, group-practice associations, union medical-care projects, rural health co-operatives, veterans' services and welfare medical programs. The experience of foreign health-insurance systems should be analyzed, and current national legislation studied. Effective medical-care teaching can obviously be done best when the school itself is actively involved in the development of medical-service programs in which the students can participate. The value of medical-care activity in the medical school has been discussed in detail for Cornell University Medical College and New York Hospital by Pastore.<sup>29</sup> The affiliation of the New York University Medical Group with the health-insurance plan of Greater New York and of both Johns Hopkins and Maryland medical schools with the new Baltimore plan are cases in point.

In 1940, Gregg<sup>30</sup> gave the sharpest possible emphasis to this phase of medical training: "I venture to say that the order in which medical schools in this country organize seminars and courses on social medicine will be a serial registrar of the relative alertness of their administration."†

### *Community and Field Work*

Training in modern medicine is enhanced by the personal introduction of the student to the various health and medical activities of the community. Work in local health centers, public-health laboratories, social-welfare agencies, group-practice organizations, private practitioners' offices, industrial clinics and the like is invaluable experience for the developing practitioner. Similarly important are student visits to the home and job environments of the patients and co-operation with medical social workers. There seems to be a good reason for the suggestion that the summer months of medical school be devoted to such field observation and training<sup>8</sup> and not wasted during a generally overcrowded curriculum.

\*Greater attention to the subject of health economics and medical care is paid at some of the schools of public health, particularly at Michigan and more recently at Harvard. Plans for expanded work in health economics are now underway at Johns Hopkins, North Carolina and California Schools of Public Health.

†A careful study of social medical teaching in all American medical schools and a strong exposition of its importance has been recently released by an expert Committee of the Association of American Medical Colleges and the American Association of Medical Social Workers.<sup>31</sup>

Some of the schools have taken important initial steps to introduce their students to the extrahospital aspects of health and disease. At Harvard teaching centers (Massachusetts General and Beth Israel hospitals), special sessions are devoted during the clinical clerkship to the social and environmental aspects of the cases assigned for student work-up.<sup>23-26</sup> At the University of Pittsburgh, joint case investigations by both medical and social-work students have been organized.<sup>22</sup> The University of Syracuse has developed a plan whereby each clinical clerk must study intensively the complete socioeconomic background of at least one hospital patient, including contacts with appropriate community agencies.<sup>23</sup> Dalhousie University in Halifax requires that students visit patients' homes together with the public-health nurse and report on the implications of their findings.<sup>24</sup> At California and Wisconsin, fourth-year students are given opportunity to spend time with practicing rural doctors.

An approach to the goal of "harmonized" community health services has recently been described at the new four-year Medical College of Alabama.<sup>25</sup> The offices of medical school, teaching hospital, local health department, outpatient clinics, county hospital and medical society are physically as well as functionally united. Incorporated in the school buildings are also the offices of the voluntary health agencies and living quarters for students, staff and hospital residents.

## GRADUATE MEDICAL TRAINING

### *Internship and Residency*

The institution of intern and residency training marked a major step forward in medical education. Six schools in the United States and four in Canada require a year's internship for the degree of Doctor of Medicine, and twenty-three states have made it a requisite for the medical license. Today there is need for further improvement in the graduate training system. Medical schools have important opportunities for improving the quality of medical practice by broadening the scope of the hospital affiliations in which they are involved.

Of the 6280 registered hospitals in the United States, only about 300 are affiliated for teaching purposes with medical schools.<sup>26</sup> Yet over 1000 hospitals are approved by the American Medical Association for residency training,\* and over 800 for intern training.<sup>27</sup> It is apparent that significant improvements could be achieved if the medical schools were to increase their influence on the standards of graduate education in the nonaffiliated hospitals. Thus, both resident and visiting staffs would benefit from regular exposure to the best of clinical instruction. The concept of regional-

hospital networks, described below, lays the basis for such supervised training programs.

Jensen<sup>28</sup> has reported a valuable experiment in the provision of follow-up medical service for discharged hospital patients by a resident staff member. This experience not only improved the care of chronic cases and reduced the number of readmissions, but served to highlight the complex social and economic factors in each case. Similarly, some of the better teaching hospitals are attempting to improve the scope and vision of their graduate training programs by establishing domiciliary services, clinic experience and social-service conferences for the house staff. Plans for the rotation of the house staff through outlying local hospitals have been reported at Alabama, Michigan, Colorado, Tulane and Rochester and at many of the other schools described below.

## POSTGRADUATE EDUCATION AND COMMUNITY SERVICE

The most obvious and immediate contribution that a medical school can make to the quality of medical practice is in the field of postgraduate medical education. In a swiftly developing profession such as medicine, the greatest impediment to high standards of practice is the difficulty in keeping abreast of the times. The medical schools are therefore paying more and more attention to their postgraduate obligations.

The foundation of an effective system of postgraduate training again rests squarely upon the establishment of a co-ordinated regional network of health and hospital facilities—starting with the rural and community health centers, feeding into larger district hospitals, and converging upon a central base institution affiliated with a medical school. In such functional systems, continuous professional education can be carried on, and the influence of the best medical centers can reach the rural and suburban areas.

### *Regionalism in Health Services*

In a health-service region, the functionally unified medical "trade area" replaces the often unwieldy political unit. An integrated network of hospitals and health centers takes the place of the present haphazard relation of medical facilities. Throughout the nation, health-service regions can be delineated on the basis of such factors as administrative relations, geographic and population characteristics, transportation facilities, established health resources, natural lines of trade movements and current flow of patients to practitioners and hospitals. Within these broad regions, functional subdistricts can similarly be defined.

Each health-service region can develop within itself the elements of a self-sufficient and comprehensive health system. Community clinics, hospitals, public-health units, nursing homes and other

\*Including Army, Navy, Veterans Administration and Public Health Service hospitals.

facilities can co-ordinate into a service network that provides the individual practitioners with complete facilities and reaches all the people with adequate health care. The outlines of such a concept have been worked out by the United States Public Health Service,<sup>39</sup> a Senate committee on Wartime Health and Education<sup>40</sup> and the National Commission on Hospital Care,<sup>41</sup> among others. This principle has been given national impetus by the recent passage of the Hospital Survey and Construction Act, and has already been worked out in some detail by several states.

### *The Role of the Medical Center in the Health Service Region*

The hub of the proposed system of regionalized health services is the medical teaching center. The base hospital is the university-connected institution where teaching, research, specialized medical care and consultation services are integrated. The co-ordinated network of community-hospital and health-center facilities affords the school an ideal opportunity for student training in the socioeconomics of health and in the problems of everyday practice. In turn, the scientific activities at the teaching center stimulate improved standards of medical care throughout the region.

The flow becomes a two-way affair. Consultants and instructors can visit the community institutions, bringing to the local practitioners the needed professional contacts and opportunities for refresher training. Students and graduate trainees can participate at all levels of the system, carrying with them the freshness of recent studies, and learning at first hand about the opportunities and responsibilities of local practice. Laboratory, administrative and library aids can become available to the peripheral institutions.

On the other hand, there can be a steady in-flow of referred patients, diagnostic materials and health personnel from the outlying areas. Special laboratory and radiologic services can be concentrated at the regional centers. Physicians, dentists, nurses and auxiliary technicians can travel to the center for advanced training, refresher courses and special conferences. Co-ordinated record-keeping becomes possible. The teaching center can realize its fullest opportunities for continuous professional education and for service to the outlying areas of the region.

Such regional affiliations can do much to overcome the reluctance of younger, well trained physicians to settle in rural areas. Continuous contacts with the teaching center, available consultants, more adequate laboratory and x-ray aids and better local hospital facilities contribute to more desirable professional conditions. The attraction of competent practitioners to rural communities is an absolute essential in any effort to improve health services for the nation.

Finally, the regional system of co-ordinated metropolitan, district and local hospitals can approach the goal of group medical practice for sparsely settled and outlying areas. Obviously, a working group of physicians cannot be supported in a small, rural community. Through regional affiliations, however, specialists in the district and base centers can effectively co-ordinate with general practitioners in the rural localities. The high standards of modern, scientific teamwork medicine can thus be approached throughout the region.

Description of some of the existing experiments in regional planning may serve to illustrate this concept.

*The Bingham plan.* With the financial support of the Bingham Associates Fund, the Joseph H. Pratt Diagnostic Hospital and Tufts College Medical School have undertaken to co-ordinate medical care in nearby rural areas of Maine and Massachusetts.<sup>42</sup> Outlying community hospitals affiliate with regional hospitals in the larger cities. The teaching center in Boston is the hub of the system. Proger<sup>43</sup> has described the plan as one involving diagnostic hospital service, hospital extension services and postgraduate courses. Laboratory and diagnostic services are promoted in the periphery. Patients are referred centrally for diagnostic and occasional therapeutic aid. Local doctors and ancillary personnel move to the regional and Boston institutions for consultations, conferences and instructional courses. A centrifugal flow of technical aids and teaching personnel proceeds concurrently.

Emphasis is placed upon continuous education of the community physician through detailed case reports, follow-up literature, visiting ward rounds, conferences and refresher courses. Tufts medical students are to be given experience in rural clinical clerkships, and plans are developing for the rotation of medical and surgical residents through the community hospitals.

*The Rochester plan.* A similar regionalization project has been financed by the Commonwealth Fund, centered around the University of Rochester Medical School and six hospitals in the City of Rochester, New York.<sup>44</sup> Seventeen community hospitals in the area have voluntarily affiliated in a regional scheme that involves referral of difficult patients to the medical center, travel by visiting consultants and professors from the University to the outlying districts, rotation of residents through the local hospitals, fellowships for local doctors, nurses and technical personnel to study at the center, and continuous teaching programs designed to meet the needs of busy practitioners. Grants of funds for plant expansions are available to the affiliated community hospitals. A somewhat smaller project at the Medical College of Virginia in Richmond incorporates the same principle.

*The Michigan plan.* For some years the University of Michigan has operated a program of affilia-

tion with outlying community hospitals. Clinical professors conduct "circuit courses" in the local institutions, and resident physicians from the smaller units return to the medical center for eight months of training in the basic sciences.<sup>45</sup> A similar plan for interns at small hospitals is now under discussion.

The University of Michigan Medical School, in conjunction with the State Medical Society, has also maintained since 1927 a department of postgraduate education. Brief refresher courses, summer-session institutes and individual instruction for practitioners have been part of a regional system since 1934. In the academic year 1937-1938 a total of 1957 practitioners participated in the program. A formal certificate of postgraduate education is now awarded for attendance at 60 per cent of the short courses over a four-year period.

*Other postgraduate programs.* The University of Minnesota has maintained a center for continuation study on its campus, where local practitioners may actually reside while taking short refresher courses.<sup>46</sup> In ten years of operation, 2700 postgraduate students have participated. Recently, this institution has pioneered in the training of general practitioners in psychiatry.

New York University has recently inaugurated a system of community-hospital affiliations with institutions suburban to the metropolitan center. With the aid of the Kellogg Foundation a program of residency training includes one year of academic study at the School and assignment of teaching consultants for periodic visits to the affiliated small hospitals.<sup>47</sup>

At the University of Colorado — again with Kellogg funds — a similar regional plan will co-ordinate rural hospitals with the university center. House officers preparing for general practice spend two years at the University Hospital and rotate through selected community hospitals during a third year. The medical school establishes standards and furnishes visiting teachers and consultants for resident (and visiting) staff instruction. This plan is a co-operative venture of the State Medical Society, the Hospital Association and the University.<sup>48</sup>

The Universities of Tennessee and Vanderbilt have co-operated with the Tennessee State Medical Society, the State Health Department and the Commonwealth Fund in supporting circuit courses for general practitioners throughout the State. The first circuit was attended by 46 per cent of the physicians in the State.<sup>49</sup> Fellowships are also available for more extensive courses of study.

A 1946 report of the New York State Health Preparedness Commission<sup>49</sup> has described in great detail the possibility for health regionalization throughout the State, again with the recommendation that the base centers be established in the medical schools.

Experiments in regionalism and postgraduate education have also been undertaken at Tulane, Bowman Gray, Iowa and Wisconsin. Several of the foundations, in addition to those already mentioned, have contributed to the support of these medical-school-hospital-service programs. The Duke Endowment has stimulated hospital co-ordination in the Carolinas, as has the Kellogg Foundation in Michigan. Various state medical societies have sponsored postgraduate sessions for local practitioners, including Connecticut, Idaho and North Carolina. In Canada, both Manitoba and Saskatchewan are developing provincial health services on the regional network principle.

*The North Carolina proposals.* The medical commission chosen to consider the question of expanding to a full four-year school the present basic-science course at the University of North Carolina rendered an affirmative majority report primarily on the basis of the potential value of a state-wide health-service program that could be centered in the new school.<sup>50</sup> It was pointed out that new graduates could not be held in rural areas (a primary need in the State) unless a program were established to provide them with the necessary facilities and professional contacts.

The plan as outlined includes an interrelated hospital network centered around the state medical school, similar in design and function to the program at Tufts. One weakness of existing regional programs has been recognized in the Commission's strong recommendation that close co-ordination with the preventive services of public health agencies be maintained at every level.

An important additional feature, moreover, has been proposed to overcome the economic weakness of the other regional projects. Basic financial problems have continually threatened the success of existing hospital network and postgraduate educational systems. Outlying physicians are not always anxious to refer patients to district medical centers if this entails "losing" the case. Large numbers of the people cannot afford to utilize the hospital network even when it does exist. New health centers and local hospitals cannot be constructed and maintained in communities with deficient medical purchasing power, just as the best of regional plans will not attract to rural areas the doctors who cannot obtain decent incomes there.

Essential to the success of the new concept, therefore, is the establishment of organized systems of group prepayment and tax-supported medical care. Such a unified state-wide plan of financing is the recommendation of the North Carolina Commission. Thus, the facilities can be fully utilized by all the people of the region, and physicians would face no great economic hardships in choosing for practice the particular localities most in need of their services.

facilities can co-ordinate into a service network that provides the individual practitioners with complete facilities and reaches all the people with adequate health care. The outlines of such a concept have been worked out by the United States Public Health Service,<sup>39</sup> a Senate committee on Wartime Health and Education<sup>40</sup> and the National Commission on Hospital Care,<sup>41</sup> among others. This principle has been given national impetus by the recent passage of the Hospital Survey and Construction Act, and has already been worked out in some detail by several states.

### *The Role of the Medical Center in the Health Service Region*

The hub of the proposed system of regionalized health services is the medical teaching center. The base hospital is the university-connected institution where teaching, research, specialized medical care and consultation services are integrated. The co-ordinated network of community-hospital and health-center facilities affords the school an ideal opportunity for student training in the socioeconomics of health and in the problems of everyday practice. In turn, the scientific activities at the teaching center stimulate improved standards of medical care throughout the region.

The flow becomes a two-way affair. Consultants and instructors can visit the community institutions, bringing to the local practitioners the needed professional contacts and opportunities for refresher training. Students and graduate trainees can participate at all levels of the system, carrying with them the freshness of recent studies, and learning at first hand about the opportunities and responsibilities of local practice. Laboratory, administrative and library aids can become available to the peripheral institutions.

On the other hand, there can be a steady in-flow of referred patients, diagnostic materials and health personnel from the outlying areas. Special laboratory and radiologic services can be concentrated at the regional centers. Physicians, dentists, nurses and auxiliary technicians can travel to the center for advanced training, refresher courses and special conferences. Co-ordinated record-keeping becomes possible. The teaching center can realize its fullest opportunities for continuous professional education and for service to the outlying areas of the region.

Such regional affiliations can do much to overcome the reluctance of younger, well trained physicians to settle in rural areas. Continuous contacts with the teaching center, available consultants, more adequate laboratory and x-ray aids and better local hospital facilities contribute to more desirable professional conditions. The attraction of competent practitioners to rural communities is an absolute essential in any effort to improve health services for the nation.

Finally, the regional system of co-ordinated metropolitan, district and local hospitals can approach the goal of group medical practice for sparsely settled and outlying areas. Obviously, a working group of physicians cannot be supported in a small, rural community. Through regional affiliations, however, specialists in the district and base centers can effectively co-ordinate with general practitioners in the rural localities. The high standards of modern, scientific teamwork medicine can thus be approached throughout the region.

Description of some of the existing experiments in regional planning may serve to illustrate this concept.

*The Bingham plan.* With the financial support of the Bingham Associates Fund, the Joseph H. Pratt Diagnostic Hospital and Tufts College Medical School have undertaken to co-ordinate medical care in nearby rural areas of Maine and Massachusetts.<sup>42</sup> Outlying community hospitals affiliate with regional hospitals in the larger cities. The teaching center in Boston is the hub of the system. Proger<sup>43</sup> has described the plan as one involving diagnostic hospital service, hospital extension services and postgraduate courses. Laboratory and diagnostic services are promoted in the periphery. Patients are referred centrally for diagnostic and occasional therapeutic aid. Local doctors and ancillary personnel move to the regional and Boston institutions for consultations, conferences and instructional courses. A centrifugal flow of technical aids and teaching personnel proceeds concurrently.

Emphasis is placed upon continuous education of the community physician through detailed case reports, follow-up literature, visiting ward rounds, conferences and refresher courses. Tufts medical students are to be given experience in rural clinical clerkships, and plans are developing for the rotation of medical and surgical residents through the community hospitals.

*The Rochester plan.* A similar regionalization project has been financed by the Commonwealth Fund, centered around the University of Rochester Medical School and six hospitals in the City of Rochester, New York.<sup>44</sup> Seventeen community hospitals in the area have voluntarily affiliated in a regional scheme that involves referral of difficult patients to the medical center, travel by visiting consultants and professors from the University to the outlying districts, rotation of residents through the local hospitals, fellowships for local doctors, nurses and technical personnel to study at the center, and continuous teaching programs designed to meet the needs of busy practitioners. Grants of funds for plant expansions are available to the affiliated community hospitals. A somewhat smaller project at the Medical College of Virginia in Richmond incorporates the same principle.

*The Michigan plan.* For some years the University of Michigan has operated a program of affilia-

4. Atchley, D. W. Orientation of undergraduate medical curriculum. *Science* 104:67-70 1946
5. New York Academy of Medicine. Committee on Medicine and the Changing Order. *Medicine in the Changing Order*. 240 pp. New York Commonwealth Fund 1947. Pp 126-128
6. Epstein, H. E. Trends in medical education: program for new medical school. *Bull. Hist. Med.* 9:177-198 1941
7. Allen, R. B. *Medical Education and the Changing Order*. 142 pp. New York Commonwealth Fund, 1946
8. Steehan, D. Medical education of future. *M. Woman's J.* 51:17-25 1944
9. Greene, J. A. Coordination of clinical teaching: methods and results of experiment. *J. A. Am. M. Coll.* 20:129-154 1945
10. Eddie, G. S. and Davison, W. G. Postwar medical education. *J. A. Am. M. Coll.* 20:1-11 1945
11. Carpenter, C. C. Experiments in medical education and medical care in new medical school. *South. M. J.* 39:515-518 1946
12. Wearn, J. T. Challenge of functional disease. *J. A. M. A.* 134:1517-1518 1947
13. Cited by Valentine, A. Privately endowed medical school. *J. A. M. A.* 137:15 1948
14. Ackerly, S. Teaching of psychiatry to undergraduate medical students. *J. A. Am. M. Coll.* 18:167-173 1943
15. Association of American Medical Colleges. Final report of Committee on Teaching of Preventive Medicine and Public Health. *J. A. Am. M. Coll.* 20:152-165 1945
16. Dublin, T. Experiment with social approach. In *Proceedings of the Conference on Preventive Medicine and Health Economics*. 245 pp. Ann Arbor: University of Michigan School of Public Health 1946. Pp 101-106.
17. Ministry of Health, Department of Health for Scotland. *Report of Inter-Departmental Committee on Medical Schools*. 312 pp. London: His Majesty's Stationery Office 1944
18. LeBlanc, T. J. Community obligations of preventive medicine. In *Proceedings of the Conference on Preventive Medicine and Health Economics*. 245 pp. Ann Arbor: University of Michigan School of Public Health 1946. P 57
19. Grant, J. Toward health—certain trends. In *Proceedings of the Conference on Preventive Medicine and Health Economics*. 245 pp. Ann Arbor: University of Michigan School of Public Health 1946. Pp 7-17
20. Stern, J. Medical student view-point. In *Proceedings of the Conference on Preventive Medicine and Health Economics*. 245 pp. Ann Arbor: University of Michigan School of Public Health 1946. P 163
21. Association of Interns and Medical Students. Replies to questionnaires on medical education. July 1945
22. Leavell, H. R. Teaching of preventive medicine. In *Proceedings of the Conference on Preventive Medicine and Health Economics*. 245 pp. Ann Arbor: University of Michigan School of Public Health 1946. Pp 23-40
23. Means, J. H. Clinical teaching of social medicine. *Bull. Johns Hopkins Hosp.* 98:96-111 1946
24. Goldmann, F. Teaching health economics in medical schools. In *Proceedings of the Conference on Preventive Medicine and Health Economics*. 245 pp. Ann Arbor: University of Michigan School of Public Health 1946. Pp 173-176.
25. Gregg, A. Transition in medical education. In *Proceedings of the Conference on Preventive Medicine and Health Economics*. 245 pp. Ann Arbor: University of Michigan School of Public Health 1946. Pp 18-22.
26. Cohen, E., and Derow, H. A. Teaching medical students objectives for care of patients and social aspects of illness. *Arch. Int. Med.* 56:351-359 1935
27. Weaver, M. M. Teaching health economics in medical schools. In *Proceedings of the Conference on Preventive Medicine and Health Economics*. 245 pp. Ann Arbor: University of Michigan School of Public Health 1946. Pp 177-181
28. Flono, L. How much time should be allotted to health economics? In *Proceedings of the Conference on Preventive Medicine and Health Economics*. 245 pp. Ann Arbor: University of Michigan School of Public Health 1946. Pp 197-201
29. Pastore, J. B. *Medical Care Program*. Report to Committee on Future Plans of New York Hospital and Cornell University Medical College. New York 1945
30. Gregg, A. Addenda to agenda for decade 1940-1950. *J. A. M. A.* 114:1158-1141 1940
31. Joint Committee of the Association of American Medical Colleges and the American Association of Medical Social Workers. *Widening Horizons in Medical Education*. 228 pp. New York: Commonwealth Fund 1948
32. Colwell, A. H. Social and environmental factors in medicine. *J. A. Am. M. Coll.* 19:159-166 1944
33. Weiskotten, H. G. Experiment in medical care: outgrowth of teaching exercise in clinical medicine. *J. A. Am. M. Coll.* 19:159-166 1944
34. Grant, H. G. Influence of social and economic factors upon illness and its prevention. *J. A. Am. M. Coll.* 18:291 1943
35. Kracker, R. R., and MacQueen, J. W. Developments in Medical College of Alabama. *South. M. J.* 39:8-12 1946
36. Arestad, F. H., and Westmoreland, W. G. Hospital service in United States: report of Council on Medical Education and Hospitals of American Medical Association. *J. A. M. A.* 133:1055-1154 1947
37. Arestad, F. H., Reid, E. K., and Levermore, E. H. Approved internships and residencies in United States. Annual Report of Council on Medical Education and Hospitals of American Medical Association. *J. A. M. A.* 137:23-29 1948
38. Jensen, F., Weiskotten, H. G. and Thomas, M. A. *Medical Care of the Discharged Hospital Patient*. 94 pp. New York: Commonwealth Fund 1944
39. Monahan, J. W., Pennell, E. H. and Hoke, V. M. *Health Service Areas: Requirements for general hospitals and health centers*. 68 pp. United States Public Health Bulletin No. 292. Washington D. C.: Government Printing Office 1945
40. United States Senate Committee on Education and Labor. Subcommittee on War-time Health and Education. *Interim Report No. 3*. United States Senate, 78th Congress, 2nd Session, pursuant to S. Res. 74. Washington: January 1945. Pp 10-17
41. Commission on Hospital Care. *Hospital Care in the United States: A study of the function of the general hospital, its role in the care of all types of illness, and the conduct of activities related to patient service, with recommendations for its extension and integration for more adequate care of the American public*. 631 pp. New York: Commonwealth Fund 1947. P 23
42. Proger, S. Medical education and care. *Hospitals* 20:48-54 1946
43. *Idem*. Distinction of medical care: postgraduate program to fit pattern of medical practice. *J. A. M. A.* 124:823-825 1944
44. Council of Rochester Regional Hospitals. *The Regional Hospital Plan*. 79 pp. Rochester 1946.
45. Bruce, J. D. Continuing professional education. In *Proceedings of the Annual Congress on Medical Education and Licensure*. 70 pp. Chicago: American Medical Association 1938. Pp 34-38
46. Committee on Graduate Medical Education. *Graduate Medical Education*. 300 pp. Chicago: University of Chicago Press 1940
47. New York University. *The Regional Hospital Plan of the New York University College of Medicine*. 1947-48
48. Colorado State Medical Society. Colorado State Hospital Association. Colorado University. *Proposed Three Year Residency in the Field of General Practice*. Denver: Colorado. December 1 1947
49. New York State Health Preparedness Commission. *Planning for the Care of the Chronically Ill in New York State—Regional Aspects*. 85 pp. Albany: Williams Press Inc. 1946.
50. Official Report of the Medical Care Commission on the Expansion of the Medical School of the University of North Carolina. Raleigh 1947
51. Long Island College of Medicine. *Bringing Modern Medicine to the People*. 64 pp. Brooklyn: Privately published 1947
52. Dolman, C. E. *Report on a Survey of Medical Education in Canada and the United States*. 53 pp. Vancouver: University of British Columbia 1946

*The Long Island proposals* Similar vision has been evidenced in the comprehensive program recently announced by the Long Island College of Medicine.<sup>51</sup> This project envisages a regional system throughout the Brooklyn and Long Island area, financed by voluntary prepayment and served by group-practice units in co-ordinated health centers. Major emphasis is laid on preventive services and family-health maintenance. Continuing professional education would be carried on throughout the region. Courses for nurses, technicians, dietitians and so forth would be regularly available.<sup>51</sup>

#### FINANCIAL CONSIDERATIONS

Serious discussion concerning the development of all such programs must, unfortunately, be prefaced with a word concerning finances. Any effort to extend the effective sphere of influence of the medical school must face the facts of budgetary handicaps in current training programs. The financial situation of the American medical schools is "desperate," according to the recent conference of the Council on Medical Education and Hospitals.<sup>13</sup> In a recent volume Allen<sup>7</sup> has declared that "the medical schools of this country will need to double their budgets for teaching and research by 1960." Certainly, any significant progress in medical education depends upon far more adequate financial support.

In 1943 the most heavily endowed institutions had ten times the operating budget of the poorest schools, and expended six times as much per student.<sup>52</sup> Private endowments and foundation funds are diminishing. Tuition fees are at an all-time high and yet cover only 28 per cent of total costs.<sup>13</sup> In this situation, much consideration is being given to the advantage of federal and state aid for medical education and research. Ample precedents for such orderly, acceptable and "nonregimenting" public aid exist in the thirty-odd state-university medical schools and in the grant programs of the United States Public Health Service and the Veterans Administration. Without some source of increased funds, the schools will find it difficult to meet the vast challenges of the day.

There is much to justify the application of public resources to the training of professional personnel. Medicine is being increasingly recognized as a "social" as well as a "natural" science—a discipline that must be as devoted to the protection of the health of the community as to the care of the sick individual. As health administrators, as advisers to statesmen, educators and law courts and as attendants in every phase of community life, physicians must fulfill an ever-expanding public role. New trends in medical-care planning, in industrial health programs and in international organizations call for even greater numbers of publicly responsible doctors. It does not seem inappropriate,

therefore, that society assume a share of the responsibility for training these kinds of physicians, and that the medical school devote itself actively to the broad social orientation of its students and to the promotion of the highest standards of medical service throughout the region. A medical school endeavoring to serve as the focal point of a regional medical-care plan that involves care of welfare clients, co-ordination with public agencies and general service to the community would logically qualify for public financial assistance.<sup>51</sup>

The democratic principle of full and equal opportunity for persons from minority and economically underprivileged groups who wish to study medicine is, of course, another powerful justification for such aid. Only through more adequate financing of medical schools can adequate scholarship grants and loans become available to those now unable to overcome the financial barriers to medical education.

#### THE MEDICAL SCHOOL OF THE FUTURE

The portrait of the new university medical school can now, perhaps, be drawn. Basically a service to the entire community, such a medical school will exist as the hub of a network of interrelated hospitals and health centers extending to the most isolated districts. Co-ordination with public-health and private-health and medical-care agencies will reflect the co-operative relations fostered between physicians and other health personnel. The students, chosen on the basis of broad academic preparation, demonstrated intellectual ability and qualities of personal integrity, will train in unified and noncompartmentalized courses that give adequate stress to the social and economic implications of modern medicine. Graduate and postgraduate educational programs will bring the knowledge of recent advances to local practitioners and afford younger residents some experience with the problems of rural and urban extrahospital practice. Research activities will continually elevate the standards of service. Through the co-ordinated network of medical facilities, the school will participate directly in the promotion of health and the provision of medical care throughout the area. Augmented public and private financial support to medical teaching centers will demonstrate an increased awareness of the broad social values that will accrue.

Thus, teaching centers may contribute effectively, continuously and lastingly to the quality of the medical service that is rendered to the people.

#### REFERENCES

- 1 Weiskotten, H. G. Current problems in medical education. *J A M A* 133:1045 1947.
- 2 Cited in The Official Report of the Medical Care Commission on the Expansion of the Medical School of the University of North Carolina. Raleigh 1947. P. 60.
- 3 Davison, W. C. Future of medical education. *J A Am. M. Coll* 21:223-235 1946.

and a physical examination performed. All were found free of a history of liver disease and of significant physical abnormalities. Blood counts, a bromsulphalein excretion test (using 5 mg of dye per kilogram of body weight) and an initial sedimentation rate were found to be normal in all (Table 1). Also, routine urinalysis on each subject was entirely normal.

On completion of these examinations, each subject was put on a daily dose of dicumarol. Daily prothrombin times were determined on the undiluted plasma of each, with the use of thromboplastin prepared in our laboratory from human brain by a method derived from the Quick<sup>3</sup> acetone extraction technic. The prothrombin concentrations were maintained so far as possible, between 30 per cent and 10 per cent of mean normal, since these are the levels most commonly accepted as the limits of therapeutic range. All subjects tolerated the drug well, and were carried on it for twenty-five consecutive days. The sedimentation rates were determined on twenty-one of the twenty-five days, by the use of the Westergren method, in which the upper limit of normal in male subjects is considered as 15 mm per hour and 4 mg of po-

tassium oxalate and 6 mg of ammonium oxalate per each 5 cc of blood being used as anticoagulant.

## RESULTS

In none of the 5 subjects was there an elevation of the sedimentation rate above the upper limits of the normal range (Table 2).

## SUMMARY

The results of this study indicate that dicumarol administered in therapeutic dosage for twenty-five consecutive days has no significant effect on the erythrocyte sedimentation rate in normal men. It is possible that the results of this study cannot be applied to the interpretation of the effect of dicumarol on the sedimentation rates of patients with associated diseases that are known to affect the sedimentation rate.

## REFERENCES

1. Barker, N. W. Clinical use of dicumarol. *N. Clin. North America* 29:920-937, 1945.
2. *Idem*. Personal communication.
3. Quick, A. J. Nature of bleeding in jaundice. *J. A. M. A.* 110:166-1662, 1938.

# MEDICAL PROGRESS

## OTOLARYNGOLOGY

CARLYLE G. FLAKE, M.D.\*

BOSTON

IT IS the purpose of this review to present in summarized form certain papers on subjects of current concern in the field of otolaryngology and others that may be of more general interest. These papers appeared in the literature for the year 1947.

### THE EAR

#### Fenestration Operation

Moorhead<sup>1</sup> reported a series of 123 patients upon whom the fenestration procedure had been performed. The results were estimated on the basis of audiometer readings taken at 512, 1024 and 2048 cycles. In this group 29 per cent of patients failed to recover satisfactory hearing for any of the three tones. Forty-seven per cent recovered serviceable hearing with perception at the 30-decibel level or better for all three tones. Fifteen per cent improved to the extent that their threshold for two or three tones reached the level of 30 decibels or better.

\*Instructor in Laryngology, Harvard Medical School; chief, Division of Otolaryngology, Children's Hospital; otolaryngologic surgeon, Peter Bent Brigham Hospital.

In general 76 patients (62 per cent) were classed as having had successful results. The two main causes cited for poor results in suitable patients were closure of the new window by formation of new bone or by the development of fibrous tissue or both, and secondary postoperative serous labyrinthitis. No deaths occurred in this series, and although 2 patients developed facial paralysis, this complaint was transient.

From the many reports of the fenestration operation that have appeared in the literature, it becomes evident that satisfactory results may be achieved in a sufficiently high percentage of cases to warrant the operation in suitable patients. According to Lindsay<sup>2</sup> the three problems that remain to be solved are the establishment of criteria for assessing the possibilities of improvement in each case, the maintenance of a fenestra that will give maximum function and the prevention of injury to the sense organ of the ear as a result of the operation. In Lindsay's experience, patients most suitable for operation are young persons with relatively

# THE EFFECT OF DICUMAROL ON THE ERYTHROCYTE SEDIMENTATION RATE IN NORMAL MEN\*

JAMES L. PALMER, M.D.,† AND SVEN M. GUNDERSEN, M.D.‡

HANOVER, NEW HAMPSHIRE

OUR interest in the possible effect of dicumarol [3, 3'-methylenebis (4-hydroxycoumarin)] on the erythrocyte sedimentation rate in human beings was aroused when we began to use the drug in an increasing number of cases of acute myocardial in-

had no answer for it, and were unable to find a satisfactory answer in the literature.

Current opinion holds that the erythrocyte sedimentation rate is determined in large measure by the various fractions of the plasma proteins. Since

TABLE 1 Data before the Administration of Dicumarol

SUBJECT	AGE	RED-CELL COUNT	HEMOGLOBIN	WHITE CELL COUNT	BROMSULFALEIN RETENTION		INITIAL SEDIMENTATION RATE
					AT END OF 45 MIN.	AT END OF 60 MIN.	
	yr		gm/100 cc				mm/hr
R A H	20	4 830 000	14.8	6 000	0	0	1
L N P	21	5 000 000	15.5	7 700	0	0	2
C S	21	5 0 0 000	14.3	6 400	0	0	2
W D W	23	5 000 000	15.3	8 100	0	0	1
D M W	27	5 500 000	15.7	10 000	0	0	1

fraction. Experience suggested that the sedimentation rates in the patients receiving dicumarol remained elevated over a longer period than would otherwise have occurred, especially when judged in terms of general clinical progress. As is well

dicumarol affects the level of at least one of these fractions — that is, prothrombin — it seemed logical to assume that it might in some manner affect the sedimentation rate. Barker<sup>1</sup> stated in 1945 that dicumarol probably increased the sedimentation

TABLE 2 Prothrombin Concentrations and Sedimentation Rates after the Administration of Dicumarol

DATE	R A H		L N P		C S		W D W		D M W		CONTROL	
	PRO-THROMBIN CONCEN. TRATION	SEDI-MENTATION RATE	PRO-THROMBIN CONCEN. TRATION	SEDI-MENTATION RATE	PRO-THROMBIN CONCEN. TRATION	SEDI-MENTATION RATE	PRO-THROMBIN CONCEN. TRATION	SEDI-MENTATION RATE	PRO-THROMBIN CONCEN. TRATION	SEDI-MENTATION RATE	PRO-THROMBIN CONCEN. TRATION	SEDI-MENTATION RATE
	%	mm/hr	%	mm/hr	%	mm/hr	%	mm/hr	%	mm/hr	%	mm/hr
5/12/48	90	1	94	2	84	2	79	1	92	1	83	—
5/13/48	84	1	85	2	82	3	72	1	80	2	76	3
5/14/48	70	2	31	2	37	2	42	1	48	3	87	2
5/15/48	34	1	41	2	36	2	28	2	25	1	87	2
5/17/48	20	2	17	2	21	2	23	2	21	1	87	2
5/18/48	21	1	18	2	19	2	22	1	22	1	85	2
5/19/48	24	1	20	2	25	2	24	1	24	2	80	2
5/20/48	26	1	21	2	24	2	25	1	25	2	83	—
5/21/48	22	2	19	2	22	2	24	2	23	2	83	3
5/22/48	21	2	19	2	20	3	19	1	19	1	83	—
5/23/48	21	2	17	1	19	—	21	2	22	2	85	2
5/24/48	21	1	19	2	19	2	19	1	19	1	83	3
5/26/48	23	2	21	2	21	—	20	1	24	1	85	5
5/27/48	21	1	22	4	20	5	20	1	22	2	83	4
5/28/48	22	1	23	8	20	5	22	1	25	4	80	4
5/29/48	24	2	21	9	21	5	21	1	28	2	83	13
5/31/48	20	1	19	10	21	2	21	2	30	2	82	3
6/1/48	20	7	19	4	23	3	19	1	40	—	74	—
6/3/48	22	2	25	2	25	3	20	2	22	3	80	—
6/4/48	21	2	21	4	21	3	20	3	28	2	76	3
6/5/48	24	2	23	3	24	2	22	2	24	1	83	9

known, the sedimentation rate is one of the most valuable of the available tests in following the course of these patients. When the question of the influence of dicumarol on this test was raised, we

rate, but he now believes that it probably does not.<sup>2</sup> Because of the dearth of information on the subject, we decided to test the effect of the drug on the sedimentation rate of normal persons.

## METHODS

Five healthy medical students volunteered as subjects. On each a thorough history was taken,

\*From the laboratories of the Mary Hitchcock Memorial Hospital and Dartmouth Medical School.

†Resident in medicine, Mary Hitchcock Memorial Hospital.

‡Physician, Mary Hitchcock Memorial Hospital and Hitchcock Clinic.

mechanism is intact and that the cochlear mechanism is not necessarily lost, for hearing islands may develop later in such patients. Deafness in children should be diagnosed, and the educational treatment started before three years of age. Even the completely deaf child can be taught lip reading and effective speech, and the use of a hearing aid enables those with some residual hearing to learn intelligible and not unpleasant speech. It has been proved practicable to teach an entirely deaf child about 1350 words so that he can speak 500 or 600 words when ready for the first grade. Oral communication is now recognized as the only rational approach for the deaf child. Lip reading is being replaced by speech reading because the development of speech is almost impossible without it. Effort is made to teach the deaf child to read the play of expressions on speakers' faces in terms of concept. The child must learn to hear with his eyes and reply in speech. The parents of deaf children must be taught to treat their children as normal and talk to them as much as possible.

### *Pellagra*

Observations made on the effects of starvation diets in a group of prisoners of war in Java, Batavia and Sumatra were reported by de Raadt.<sup>6</sup> From an otoneurologic viewpoint the chief symptoms were vertigo, nystagmus, headache, hearing impairment and weakness of lateral gaze and of convergence. Of 160 patients showing this syndrome, 101 complained of dizziness. Of the latter, 39 had typical rotary labyrinthine vertigo. The attacks varied in intensity and lasted from a few minutes to several days. At times the additional symptoms of nausea, vomiting, tinnitus and deafness were present. Profuse sweating and headache were often noted. Nystagmus was always present, generally of the first degree and in both directions. All forms of dizziness, especially the rotary vertigo, were initiated or increased by conjugate movement of the eyes. Forty-five patients complained of deafness, which was generally moderate and not annoying. One prisoner of war with perfect hearing when he entered the camp became totally deaf for conversational voice but subsequently almost completely recovered his hearing when nutritional conditions improved. Studies showed that the lesion in these patients was localized to the brain stem and that pellagra was the causative factor. The symptom complex observed was an early manifestation of that disease. It was suggested by de Raadt that any patient showing idiopathic vertigo of central origin should receive anti-pellagra therapy until the origin of the vertigo was determined.

### *Associated Keratitis*

Lewis<sup>7</sup> reported a clinical syndrome occurring in three young women and consisting of bilateral acoustic neuritis associated with interstitial kera-

titis. Allergy, dietary deficiency, syphilis and other chronic diseases were ruled out. In each patient the syndrome was characterized by a nonsyphilitic interstitial keratitis, vertigo, tinnitus and deafness. The acoustic neuritis terminated after a few months in complete bilateral nerve deafness and loss of vestibular function. The keratitis did not change appreciably in a year. The etiology was not determined, and the possibility of a virus infection could not, therefore, be excluded. In 1 patient cervical sympathetic ganglionectomy was performed early in the course of the disease without beneficial effect.

### *Multiple Sclerosis*

Hearing defects in patients with multiple sclerosis were studied by Von Leden and Horton.<sup>8</sup> Fifty-seven per cent of a series of 92 patients had normal hearing, whereas the remainder showed a measurable degree of deafness (25 decibels or more) in one or both ears. Of a similar group of normal healthy subjects tested under the same standard conditions, 18 per cent showed slight changes in auditory acuity in contrast to the varied changes found in 43 per cent of the patients with multiple sclerosis. Different types of auditory involvement were noted, including moderate to severe unilateral field defects up to 70 decibels. The decreased hearing in the speech range did not extend beyond the critical level of 70 decibels. This retention of hearing in the conversational range accounts for the fact that only 12 patients complained of poor hearing and that only 7 of these actually had defective hearing. This dissociation of subjective and objective disturbances is characteristic of multiple sclerosis. No relation appeared to exist between the hearing impairment and the severity of the disease. It was noted that disturbances of vestibular function provide a fairly accurate indication of changes in the patient's general condition.

### THE LABYRINTH

#### *Streptomycin*

A series of 81 patients from a large military hospital who had been treated with streptomycin for a variety of diseases were examined by Fowler and Seligman<sup>9</sup> for evidence of changes in the hearing and vestibular function. Those with known disease of the ear were excluded from the study. The diseases for which streptomycin had been given included osteomyelitis (71.6 per cent of cases), urinary infections (16.3 per cent) and miscellaneous conditions. The daily dose was usually 3 gm of streptomycin administered intramuscularly in divided doses. Total individual dosage was small in comparison with that given in tuberculosis and ranged from less than 10 gm to 49 gm, although 1 patient received a total of 141 gm. The interval between cessation of treatment and the initial otologic examination varied from one day to six months. Fifteen of the patients

better hearing for high tones than for low tones and a bone-conduction threshold within the normal range up to the 4000-cycle frequency or beyond. The hearing in this type of patient may, postoperatively, reach within 15 decibels of normal in the speech frequencies. The main problem in estimating bone conduction in otosclerosis arises when there is much asymmetry between the two sides. The bone-conduction threshold is then likely to reflect the better ear unless masking is adequate. It is questionable whether masking can be reliably carried out for bone-conduction sounds. It is also questionable whether an air-conduction hearing loss of over 60 decibels can occur without some impairment of the perceptive apparatus. In the series of cases reported the consistent finding of a depressed threshold for bone-conducted sound proved to be a reliable indication of the possible failure to obtain adequate and permanent improvement by fenestration. The possibility of improvement in speech perception appears to be most accurately indicated by the preoperative bone-conduction threshold values of 2048 and 1024 cycles

#### DEAFNESS

##### *Occupational*

MacLaren and Chaney<sup>3</sup> found, in a noise survey in an industrial plant, that sounds at levels of above 100 decibels are common in metal fabrication and that riveting is an important source of half this noise. Industrial noise also appears to be of the broad-spectrum variety, without prominent frequency peaks or narrow frequency bands. The borderline between relatively harmless noise and that which produced steady deterioration was found to lie in the region of 100 decibels. An analysis of 5000 audiograms made on workers in an airplane manufacturing plant showed that certain types of hearing loss increased greatly in the presence of intense noise. The greater portion of hearing loss took place within a few days or even a few hours of exposure and, at first, involved frequencies above 2048 cycles per second. Later, the loss extended to lower frequencies but at a much slower rate. After removal from the noise the lower tones were the first to return, followed by recovery of the high tones provided the damage had not been too great. In every group there were persons who did not show acoustic trauma even at the highest level encountered, fewer such cases were found as the noise intensity rose. Ear protectors that attenuated the higher frequencies, enough to bring over-all loudness below 100 decibels, allowed a measure of recovery from the trauma. The presence of conductive deafness did not seem to be an important factor in relation to development of occupational deafness. It was thought that the defect of conduction might result in some protection to the cochlear mechanism and that persons with this form of hear-

ing loss probably do not need to be excluded from noisy areas. As a preventive measure the authors recommended that when noise levels regularly exceed 100 decibels pre-employment audiograms be obtained, audiometric studies should be repeated at monthly intervals until it is determined what sort of equilibrium the employee can attain. Progressive deafness after six months calls for transfer to quieter surroundings. Should an early marked loss appear in the region below 2048 decibels, the worker should be removed to a quieter place.

##### *Rubella*

Further confirmation of the results of maternal rubella in producing deaf mutism in the offspring is reported from England by Clayton-Jones.<sup>4</sup> In a small school with 18 children the mothers of 8 gave a definite history of rubella in the second to fourth month of pregnancy, 1 mother gave a probable history. All the 8 children were born between August and October, 1940. In three larger schools a history of rubella was obtained from the mothers of 11 of 123 children. The 11 children were born between October, 1940, and February, 1941. Deafness noted in these children was bilateral and of the inner-ear type. It was incomplete and usually fairly uniform throughout the frequency range. Difficulty in feeding during infancy was commonly reported, and examination showed a tendency to deformity of the jaw, pigeon chest and atonic musculature. Intelligence appeared to be unaffected. No cataract or definite heart lesion was detected. The health records of the city of Manchester, England, show that the rubella epidemic of 1940 was peculiar in that an unusually high proportion of young women were affected.

##### *Pre-School*

Goodhill<sup>5</sup> states that hearing tests in children are based on psychologic principles since audiometry is useless up to the age of three and of limited value in children three to four years of age. Young infants are examined by the eye-reflex test. Various sounds are made by an assistant, who stands behind the child while the latter's attention is diverted. Hearing is indicated by involuntary blinking or jerking of the eyeball. The attention of a child two or more years old is diverted, and his name called in various tones. Hearing is demonstrated by eye responses or turning of the head toward the sound. Drums, whistles, bells and other sound-producing sources are used to test the frequency-response ranges, or a frequency-modulated loud speaker may be used. It is important that vestibular function be estimated in children who do not respond to sound stimuli, to detect possible hearing islands that may be amplified by a hearing aid in future training. The Kobrak cold-stimuli test can easily be done even on an infant. A normally active response indicates that the vestibular neurologic

night or during periods of inactivity. Warning of an impending attack, which was noted in about 50 per cent of the patients, took the form of an alteration in the character of the tinnitus or deafness and, in some patients, of a feeling of fullness or numbness behind the affected ear. Vertigo was the major symptom and consisted of a sensation of movement of surrounding objects—less commonly, of the subject himself rotating. Duration of the attacks varied from a few moments to several days and in severity from momentary inconvenience to helplessness. Unconsciousness occurred in only 2 cases. The caloric test rarely failed to reveal a lack of balance between the two labyrinths, the commonest finding being a depression of function on the side of deafness. In approximately 10 per cent of the patients in this series the caloric test revealed definite bilateral vestibular involvement. Medical treatment was given a trial in all cases and in the majority was sufficient to control the attacks. Phenobarbital and small doses of hyoscine were often helpful in modifying the attacks. Exclusion of salt and salty foods from the diet together with the limitation of fluid intake offered more relief than any other form of conservative treatment. When the attacks could not be controlled by medical means, surgical ablation of the offending labyrinth was carried out in patients in whom only one vestibular labyrinth was affected. This procedure was employed in 116 patients without any untoward operative results. After operation some residual dizziness, particularly on sudden head movements, was generally experienced. However, most patients were well enough to return to work within a period of two months of their operation.

Since various conditions causing vertigo are difficult to differentiate, Williams<sup>12</sup> suggests that a diagnosis of endolymphatic hydrops (Ménière's disease) should not be made until certain diseases and conditions have been ruled out. These are as follows: the presence of impacted foreign bodies or inspissated serum in the external auditory canal, obstruction of the eustachian tube on the affected side, multiple sclerosis, and Brun's syndrome of occlusion of the fourth ventricle by cysticercosis. The methods of medical treatment that have succeeded in relieving symptoms of endolymphatic hydrops have been based on the conception that this condition is a form of allergy. In acute attacks a few minims of epinephrine given intravenously have proved effective, as have rather large doses of atropine (0.86 mg). Benadryl has been found moderately effective in some patients. Williams has found that with either nicotinic acid or histamine results superior to those obtained by controlling water and electrolyte metabolism may be obtained. However, there is no obvious reason why these various methods should not be combined. It was therefore suggested that the total fluid intake be limited to 3000 cc daily, preferably less, that care be taken that the drinking water does not

contain excessive amounts of the sodium ion and that salty foods and the addition of salt to cooked foods be avoided. Potassium nitrate, 1 or 2 gm in enteric-coated tablets, is given three times a day with meals, and nicotinic acid is administered subcutaneously, starting with 25 mg and increasing by this amount with each injection until a dose that relieves symptoms is reached. In most instances this has been found to be 100 mg. However, some patients are unable to tolerate this amount, whereas others may require doses as high as 200 to 300 mg daily. Treatment with the vasodilators should not be continued longer than six months, without a rest period of several weeks since many of the vasodilators lose their efficiency when administered for longer periods. On this regimen and with judicious psychiatric treatment to relieve the anxiety-tension state, approximately 80 per cent of patients were relieved of their symptoms. In cases in which all types of medical treatment had failed, ablation of the labyrinth has proved the most effective treatment.

The vertigo<sup>14</sup> of Ménière's disease (labyrinthine hydrops) is so characteristic that it should not be confused with any other type. The typical symptom is a violent vertiginous seizure, which is paroxysmal and disabling. In contrast the vertigo in intracranial disease is more in the nature of a swimming, giddy or unsteady feeling, present most of the time but aggravated by sudden motion. Vertigo may be produced by organic central-nervous-system lesions. Such lesions are usually associated conspicuously with other clinical evidence of intracranial disorder, cerebellopontile-angle tumor is a classic example. Vertigo may be the symptom of a toxic condition. Evidence for this statement is in the occurrence of vertigo in septic patients after treatment with certain drugs such as the antibiotic streptomycin. It is often a manifestation of a nervous depression. There may be a large psychic factor in typical labyrinthine hydrops although it is probably the effect and not the cause of this syndrome. A vascular accident within the otic labyrinth may be the cause of an explosive attack of vertigo with a roaring noise in one ear, nausea, vomiting and unilateral deafness. All symptoms except the hearing impairment spontaneously disappear. Vertigo is occasionally seen in hypertensive disease. After splanchnicectomy in a series of 37 patients, most of the patients showed a marked decrease in hypertension and a disappearance of the associated vertigo. Symptoms of headache, dizziness, tinnitus and nervous irritability aggravated by fatigue and emotion are evidence of hypertensive disease and warrant the determination of the blood pressure at varying intervals.

#### OTITIS MEDIA

##### *Allergic Otitis*

In a series of 222 patients with manifest chronic otitis media, Koch<sup>15</sup> found that in 41 the secretion

were examined before and after therapy. Of the 81 patients studied, 42 showed a high-tone loss alone. Eleven patients showed a low-tone as well as a high-tone loss. The high-tone losses ranged from 30 to 100 decibels in the frequencies of 2896, 4096 and 8192. The authors believe that these were due to acoustic trauma. Many patients with appreciable high-tone loss gave a history of shell bursts nearby. The 15 patients examined before streptomycin therapy showed similar high-tone losses. Caloric tests after streptomycin therapy revealed a normal response in 65 patients. There was delay in one or both sides in 13 patients. Three patients showed absence of nystagmus after irrigation for five minutes with ice water. Two of these had a persistently negative and one a persistently positive Romberg sign. Two of these patients later showed recovery of the vestibular response.

### *Vertigo*

McNally<sup>10</sup> defines vertigo as a consciousness of discord in the postural mechanism. The maintenance of this mechanism is the main function of the labyrinth. Vertigo may be ocular, central or labyrinthine in cause. These origins are differentiated by the history, description of the vertigo and associated signs and symptoms. In labyrinthine vertigo there may be evidence of disease of the cochlear mechanism, such as deafness and tinnitus. Positional nystagmus may be present. Nystagmus is normally associated with labyrinthine stimulation. In some cases spontaneous nystagmus may occur only when the head is in a certain position. This type of nystagmus is known as positional, and the utricle is probably responsible for it. The presence of positional nystagmus aids in diagnosing pseudo-Ménière's disease. After removal of a cerebral hemisphere in a rabbit, any labyrinthine stimulation that produced a nystagmus toward the side of the brain lesion elicited a greater reaction than a stimulus that produced a nystagmus in the opposite direction. This phenomenon is called directional preponderance and may be of utricular origin. It has been said to occur only in temporal-lobe lesions, in man. The utricle may be concerned in reflex adaptation of posture to the field of gravity. Its function, however, cannot be the steady holding of posture. It helps to break up an existing postural debt and to impose a physiologically more suitable one.

According to Lindsay,<sup>11</sup> vertigo arising from disease of the central nervous system, such as encephalitis, abscess, tumor or multiple sclerosis, is the result of direct involvement of the vestibular nuclei or pathways or of pressure. The vertigo following head injury with concussion is probably central in origin if unaccompanied by auditory disturbance. As a toxic manifestation in the course of some respiratory and gastrointestinal infections, vertigo occurs frequently but without deafness or

tinnitus. It may also occur in cerebral arteriosclerosis and hypertension, as well as in hypotension and during the menopause. The localization is indefinite, but the absence of auditory symptoms suggests that it is central, and the pathologic disturbance is mild and reversible. When deafness and tinnitus occur with vertigo the lesion can be localized in the peripheral labyrinth or eighth nerve. In the past the most frequent cause has been a labyrinthitis from the extension of meningitis or inflammatory disease in the temporal bone. A disturbance of the peripheral labyrinth may occur from several other causes, such as nonsuppurative otitis media, virus diseases and, rarely, extrinsic allergy. The sudden onset of tinnitus, deafness and vertigo in a patient with a previously healthy ear leaves a profound and permanent impairment of function. Should this occur in middle life or later it is considered to be due to a vascular accident in the labyrinth. Similar episodes sometimes occur before middle age, and it may be impossible to differentiate these from an acute toxic process. A toxic disturbance affects auditory function primarily. However, it may not impair vestibular function. Precise pathological information in this type of labyrinthine lesion is not available. A fibroserous labyrinthitis may occur in the late stages of leukemia and is thought to be the result of hemorrhage in the labyrinth. The clinical condition known as Ménière's disease, which is characterized by recurring attacks of vertigo with fluctuating tinnitus and deafness, is now known to be associated with hydrops of the labyrinth. This type of hydrops is distinguishable from that which sometimes occurs in inflammatory disease of the inner ear, since in the former there are no inflammatory changes in the perilymphatic spaces and degeneration of the peripheral cochlear neuron is usually absent. The etiology is not known.

### *Ménière's Disease*

Cawthorne<sup>12</sup> reported a study on a series of 424 patients with Ménière's disease. Excluded were all patients who gave a history of otitis media or in whom an inflammatory process within the labyrinth was suspected, those in whom attacks were induced by sudden head movements, those with dizziness due to cardiovascular disease and those with anxiety neuroses. The general picture of the disease followed the usual pattern of periodic bouts of paroxysmal vertigo accompanied by nausea and vomiting. Some degree of nerve deafness with tinnitus was present and was always more noticeable on one side. No other signs of central-nervous-system disease were evident. The attacks varied greatly in all respects even in the same patient. The attacks tended to occur in groups, usually several within a short period followed by long intervals of freedom. Physical activity did not appear to influence the onset. Many attacks occurred at

procedure. Repeated treatment with external roentgen or radon seeds is effective and leaves only a small residual thickening or some superfluous tissue which may be excised later. Dermoid cysts occurred about the orbit, the floor of the mouth and the nose, in that order of frequency. In the floor of the mouth the cyst may be located above or below the myelohyoid muscle and tends to be spherical. The wall is thick, and where it can be readily palpated, the cyst has a doughy feel. Complete surgical removal is advisable. Thyroglossal cysts are lined by stratified or ciliated epithelium. Treatment consists of the removal of the cyst or cystic tract in the interval between infections. Branchial cysts may be present in the lateral aspect of the pharynx in the region of the posterior pillar, below the tonsils and in the hypopharynx at the base of the tongue. The cyst opening may be further enlarged when suspension laryngoscopy is used and the cystic tract can be destroyed with surgical diathermy using a protected point.

## LARYNX

### Laryngotracheitis

From 1926 to and including the months of January and February, 1945, 549 patients with laryngotracheobronchitis were admitted to the Hospital for Sick Children Toronto.<sup>19</sup> Over these years a steady increase in the number of admissions of patients with this disease was noted and the seriousness of the illness in individual patients was in inverse proportion to the number admitted in any year. In 1928, of 8 children admitted 6 died (a mortality of 75 per cent), whereas in 1944 the mortality was 9.2 per cent for 55 cases. The disease was particularly prevalent in children under the age of two years, 69 per cent of the patients being in this age group, whereas only 5 per cent were over six years of age. Over 70 per cent of the patients were admitted from November to April, the peak months were February and March. Organisms most frequently encountered were *Streptococcus haemolyticus*, *Staphylococcus aureus* and the pneumococcus, *Haemophilus influenzae* was seldom found. Many of the infections apparently were primarily due to a virus, and recognition of this was made by the lack of response to antibiotics, normal leukocyte count or leukopenia failure to grow pathogenic bacteria from culture material taken from the site of the disease and a fairly typical clinical course. Superficial destruction of the mucosa was noted most often in *Staph aureus* and *Sir haemolyticus* infections, and pseudomembranous inflammation was found most commonly in *Staph aureus* infections. Regarding prophylaxis, it was the opinion of these authors that antibiotics should be used in every case of simple croup for if they are given early enough the serious manifestations of bacterial infection will be prevented. If patients have virus infection the antibiotics will have little

curative effect, but secondary infection is prevented and the incidence of serious postoperative complications reduced. Early tracheotomy is the operation of choice and intubation is recommended only as a temporary expedient to relieve obstruction. Bronchoscopic removal of secretion is frequently resorted to. The principal causes of death are failure to relieve obstruction, overwhelming toxemia, postoperative infection, pneumothorax and mediastinal emphysema. The mortality has been gradually reduced for the past twenty years. This has been most striking in the tracheotomized patients, in whom a reduction in mortality from 80 to 55 per cent was accomplished.

### Inflamed Laryngitis

In children laryngeal infection caused by *H. influenzae* (Type B)<sup>21</sup> is rapidly progressive, and unless the disease is properly recognized and properly treated death from toxemia and asphyxiation results. The clinical features of this rapidly developing infection are characterized by an abrupt onset. The child becomes fretful and if old enough, complains of a sore throat and difficulty in swallowing. Respiratory distress with inspiratory retraction of the sternum and soft tissues, cyanosis, hoarseness and a croupy cough develop in extremely rapid progression. Patients are frequently limp and in shock, as shown by their ashen pallor. Children particularly those under the age of two are sometimes moribund within eight to twelve hours of onset. The temperature ranges from 100 to 104°F. The oropharynx is usually intensely red and edematous. Characteristically, the epiglottis and glottis are swollen and fiery red. No membrane is present, but exudate may or may not be present. The white-cell count is elevated to 15 000 or more with the differential count showing 80 or 90 per cent neutrophils. The diagnosis can be confirmed by the recovery of *H. influenzae* (Type B) in cultures from the nasopharynx, oropharynx, larynx, or blood. Catarrhal laryngitis and spasmodic croup present little difficulty in differential diagnosis since in neither condition is the toxicity so marked, the respiratory embarrassment so severe, or the symptoms so rapidly progressive. Although diphtheria and *H. influenzae* (Type B) laryngitis may resemble each other in their later stages, the onset is more insidious in diphtheria than in the former, and a typical membrane is usually present in the oropharynx or larynx from which diphtheria bacilli can be cultured. The three cardinal therapeutic measures in this type of laryngitis are tracheotomy for relief of respiratory obstruction, administration of sulfadiazine and Type B *H. influenzae* rabbit antiserum — both specific agents against this organism, and given together, more effective than either alone and parenteral administration of fluids to combat or prevent shock. There should be no hesitancy in performing trache-

from the ear contained many eosinophils. This group was classified as eosinophilic chronic otitis media. The other patients were classified as of the aneosinophilic type. The macroscopic appearance of the mucosa of the middle ear was strikingly different in the two types. It was slightly or moderately swollen in the aneosinophilic cases. In eosinophilic chronic otitis media on the other hand, the mucous membrane was always edematous and usually pale, with cyanotic areas similar in appearance to the mucous membrane of the nose in vasomotor rhinitis. The secretion was so viscid that often it had to be removed with forceps. Histologically the mucous membrane of the ear in the aneosinophilic cases showed chronic inflammation with round-cell infiltration dominated by lymphocytes and plasma cells. In the eosinophilic group the secretion showed clumps of eosinophilic leukocytes when stained and examined under the microscope. In the aneosinophilic group the microscopical picture of the secretion was wholly dominated by neutrophilic leukocytes interspersed with lymphocytes and monocytes. Healing of the ear was considerably longer in patients with eosinophilic otitis media, and associated allergic nasal symptoms were also more frequent in these patients. Bacteriologic investigation showed that the staphylococci were the commonest organisms in both eosinophilic and aneosinophilic otitis. *Proteus vulgaris* and coliform bacteria were especially common in aneosinophilic otitis. Twenty-seven patients with eosinophilic otitis were successfully treated by elimination of suspected allergins or desensitization, or both.

### SINUSES

#### Frontal Sinus

In acute fulminating frontal sinusitis early trephining is important to prevent extension of infection beyond the confines of the sinus. Good-year<sup>16</sup> uses a curved incision below the eyebrow and after incision of the periosteum an opening is made in the bone with a nail trephine almost at right angles to the sagittal plane of the nose, medial to the suprafrontal notch and just posterior to the medial orbital ridge. The cavity may be irrigated with warm saline solution to which penicillin has been added. A drain may be placed in the wound and removed in forty-eight hours. In acute frontal sinusitis when the size of the nasal chamber permits, the anterior ethmoid cells are opened, and those around the frontal ostium removed. The curet then enters the frontal sinus and allows evacuation of pus. This intranasal approach may also be used in chronic frontal-sinus infection. The depth and width of the affected sinus, as shown by roentgenograms, are important in deciding on the intranasal approach. When failure has occurred an external procedure becomes necessary. The Jansen-Lynch operation with the

use of a self-retaining gold tube is advised in all osteomas of the frontoethmoid area when suppuration is present. This tube may be left in place for life.

#### Subdural Empyema

Subdural empyema<sup>17</sup> may follow the initial attack of frontal sinusitis, or it may occur during an acute exacerbation of chronic frontal-sinus disease. In most cases infection is probably conveyed by way of perforating veins that extend from the frontal-sinus mucosa to the dura. The course of the disease is frequently short, and the period of survival may be only a few days. Headache, stiff neck, somnolence, Jacksonian convulsions and hemiparesis in a patient with frontal-sinus disease strongly suggest subdural abscess. Drainage is best accomplished through enlarged burr holes in the frontal, parietal and temporal regions, so arranged that thorough irrigation of the subdural cavity can be carried out. Drains are maintained in the subdural space for four to six days after operation. Death occurred in two of three patients with subdural infection secondary to frontal sinusitis within two weeks of the onset of cerebral symptoms, despite the use of antibiotics and supportive measures. The third patient recovered completely after early drainage.

### MOUTH AND PHARYNX

#### Congenital Cysts

According to New,<sup>18</sup> congenital cysts of the tongue, floor of the mouth, pharynx and larynx are rare and are difficult to diagnose and to remove completely. Repeated exacerbations due to infection may occur, and at such a time the cyst may rupture. After the discharge of the cyst contents, little can be found to account for the patient's symptoms. Uninfected cysts may cause no other symptoms than those due to increase in size. Ranula should designate only the thin-walled, epithelium-lined cyst, which is sometimes of a bluish tinge, fluctuates but does not pit on pressure and is soft and easily compressible. The cysts may be present at birth or may appear shortly afterward. Unless interference with breathing or eating is produced, immediate removal is not necessary. Complete surgical removal is the treatment of choice. Larger cysts may be treated by incision and destruction of the lining membrane with superficial surgical diathermy.

Cystic hygroma is a multilocular cyst usually found in the floor of the mouth or in the submental or submaxillary region. It is thin walled, has an endothelial lining and is usually filled with clear lymph. It is caused by obstruction or lack of development of afferent lymph vessels. Microscopically, cystic hygroma and lymphangioma cannot be distinguished, and the reaction of each to radium therapy is identical. Surgical removal is satisfactory if the patient can stand the operative

of age and 65 per cent were more than sixty-nine years of age. Of patients who were operated on and who could be traced, 73.5 per cent survived five or more years without recurrence of the growth. Of the laryngectomized patients, 60.2 per cent lived five or more years after operation. Of the patients who underwent thyrotomy, 83.6 per cent lived five or more years after operation. Of the patients treated by surgical diathermy or the insertion of radon seeds under suspension laryngoscopy, 91.7 per cent lived five or more years after operation. Of the patients who were treated by irradiation, 69 per cent lived five or more years after operation, 46 per cent of these patients underwent preliminary tracheotomy. The lower survival rate associated with laryngectomy is to be expected because all malignant lesions treated by this method were large, some had extralaryngeal extensions at the time of operation and some eventually showed metastases. The high rate of survival of patients treated by diathermy or the implantation of radon seeds under suspension laryngoscopy can be attributed to the facts that these patients were selected carefully and that the lesions were of low grade. The low survival rate of patients treated by irradiation is to be expected, since practically all the patients had inoperable lesions, the majority of which were considered completely hopeless when the patient was first examined.

## REFERENCES

- 1 Moorhead R L. Fenestration for otosclerosis: report of 123 cases. *Arch. Otolaryng.* 45:49-60 1947
- 2 Lindsay J R. Fenestration operation: observations on evaluation of hearing tests. *Laryngoscope* 57:367-380 1947
- 3 MacLaren W R. and Chaney A L. Evaluation of some factors in development of occupational deafness. *Indust. Med.* 16:109-115 1947
- 4 Clayton-Jones E. Rubella as cause of congenital deafness in England. *Lancet* 1:56-61 1947
- 5 Goodhill V. Educational treatment of pre-school deaf child. *Laryngoscope* 57:555-563 1947
- 6 de Raadt, O L. E. Initial oto-neurologic disturbance in pellagra. *Acta oto-laryng.* 35:231-250 1947
- 7 Lewis D K. Acoustic neuroma associated with keratitis. *Ann. Otol. Rhin. & Laryng.* 56:194-205 1947
- 8 Von Leden H. and Horton B T. Auditory nerve in multiple sclerosis. *Proc. Staff Meet. Mayo Clin.* 22:279-280 1947
- 9 Fowler E. P. Jr. and Seligman E. Otic complications of streptomycin therapy: preliminary report. *J. A. M. A.* 133:87-91 1947
- 10 McNally W J. Physiology of vestibular mechanism in relation to vertigo. *Ann. Otol. Rhin. & Laryng.* 56:514-533 1947
- 11 Lindsay J R. Pathology of vertigo arising from peripheral vestibular apparatus. *Ann. Otol. Rhin. & Laryng.* 56:541-556 1947
- 12 Cawthorne T. Meniere's disease. *Ann. Otol. Rhin. & Laryng.* 56:18-38 1947
- 13 Williams H L. Diagnosis and treatment of endolymphatic hydrops (Meniere's disease). *J. Iowa M. Soc.* 37:1-6 1947
- 14 Furstenberg A C. Sinusitis: symposium on vertigo. *Ann. Otol., Rhin. & Laryng.* 56:576-582 1947
- 15 Koch H H. Allergic investigations of chronic otitis. *Acta oto-laryng.* (supp.) 62:1-201 1947
- 16 Goodyear H. M. Surgery on frontal sinus. *Laryngoscope* 57:340-353 1947
- 17 Anderson F M. Subdural empyema secondary to frontal sinusitis: review of clinical features and report of three cases. *Ann. Otol. Rhin. & Laryng.* 56:5-17 1947
- 18 New G B. Congenital cysts of tongue, floor of mouth, pharynx and larynx. *Arch. Otolaryng.* 45:145-158 1947
- 19 Morgan E A. and Wishart, D E. S. Laryngo-tracheobronchitis (statistical review of 549 cases). *Canad. M. A. J.* 56:8-15 1947
- 20 Davis H V. Obstructive laryngitis in children caused by *Haemophilus influenzae* bacillus type B. *J. Kansas M. Soc.* 48:105-103 1947
- 21 Priest R. E. Boies L. R. and Goltz, N F. Tracheotomy in bulbar poliomyelitis. *Ann. Otol. Rhin. & Laryng.* 56:250-263 1947
- 22 Figg F A. Etiology and treatment of cicatricial stenosis of larynx and trachea. *South. M. J.* 40:17-26 1947
- 23 New G B. Figg F A. Havens F Z. and Ench J B. Carcinoma of larynx: methods and results of treatment. *Surg. Gynec. & Obst.* 85:623-629 1947

otomy in children showing respiratory obstruction due to laryngeal edema with associated cyanosis and toxicity. Death results from a combination of mechanical obstruction to respiration and shock caused by the overwhelming infection, in addition to the anoxia produced by the respiratory obstruction.

### *Tracheotomy in Bulbar Poliomyelitis*

Tracheotomy is a useful and often life-saving procedure in bulbar poliomyelitis.<sup>21</sup> In the epidemic in Minneapolis in 1946, 400 patients had the bulbar type of poliomyelitis. In this group tracheotomy was performed on 75 patients, of whom 29 survived. On the adult neurologic service at the University of Minnesota Hospital tracheotomy was performed on all patients with early bulbar symptoms, when the disease was progressing rapidly, when the respiratory or circulatory centers were involved or when severe toxic or mental changes were noted. At the Minneapolis General Hospital and the University Hospital Pediatric Service tracheotomy was performed on the following indications: respiratory distress as evidenced by recurrent cyanosis, coarse rales in the chest and laryngeal stridor, excitement and unmanageability causing the patient to resist pharyngeal aspiration, stupor sufficient to make the patient oblivious of the accumulation of secretions in his airway, inability to cough effectively, pharyngeal pooling of mucus, and vocal-cord paralysis or intralaryngeal hypesthesia demonstrable by laryngoscopy.

Tracheotomy gives the best chance for survival when performed before cyanosis occurs. Cyanosis can be detected clinically only when far advanced, by which time anoxia has done irreversible damage to a central nervous system already markedly damaged by the virus. Combativeness, confusion, disorientation, irrationality and coma can be symptoms of early anoxia as well as of polioencephalitis. Failure to recognize the cause of these symptoms may misdirect therapy. The use of a respirator in the presence of both bulbar and spinal-cord lesions may suck the pharyngeal secretions into the lower respiratory tract. Tracheotomy permits aspiration of this secretion from the trachea and bronchi. Sedatives must be used with great caution. Priest et al.<sup>21</sup> felt that tracheotomy has an important place in the treatment of bulbar poliomyelitis and cited 17 cases in which the operation was believed to be the vital factor in successful treatment.

### *Stenosis*

In a series of 42 patients treated by Figg<sup>22</sup> for cicatricial stenosis of the larynx, fracture of the cartilages and previous removal of tumors were the most frequent causes of the stenosis. Less frequent causes were acute infection, self-inflicted and accidental severing of the trachea and the use

of the nasal feeding tubes. In 27 patients the stenosis was treated by opening of the larynx and, when necessary, the trachea and by excision of the scar tissue. A core of air-foam sponge rubber covered with a moderately thin skin graft removed from a nonhair-bearing area was then placed in the larynx or trachea and immobilized by transfixing with two silver alloy wires threaded on a long needle and passed directly through the skin, underlying soft tissues and thyroid cartilage, or between the tracheal rings. The rubber mold was removed at the end of ten days. Usually, the grafts took perfectly. Subsequent dilatation depended on how much cartilage was destroyed by the process that primarily induced the stenosis. If there was no appreciable destruction of cartilage and the stenosing scar was completely excised before the skin graft was applied, dilatation as a rule was not required for more than two or three weeks at most. Return of vocal function depends on the extent of loss of soft tissue and is unpredictable. When extensive destruction has occurred and the vocal cords, ventricular bands and arytenoid cartilages are not recognizable, the likelihood of restoration of voice is remote and the advisability of an attempt at surgical correction questionable. If the sphincteric action of the superior laryngeal orifice is lost, postoperative difficulty is encountered because of the tendency for food and fluid to gravitate into the trachea and lungs. In a patient with this condition after operation it became necessary to reproduce the stenosis because of difficulty in eating and drinking. Of the 27 patients treated by skin grafting, 24 had an ample lumen after operation and subsequent dilatation, and in 22 of these the tracheotomy opening has been closed. Of 10 patients treated by continuous dilatation and incision of the scar, decannulation was carried out in 8, who were free from symptoms at the time of the report. The remaining 2 still require a tracheotomy opening. Two patients treated by repeated incision of a cicatricial diaphragm without continuous dilatation had, at the time of the report, a free airway.

### *Carcinoma*

From the Mayo Clinic<sup>23</sup> a series of 568 patients treated for carcinoma of the larynx from 1934 to 1943, inclusive, was reported. Four hundred and forty-six of these were treated by surgical measures, and 122 were treated by irradiation. Of those patients who underwent operation, 213 were treated by laryngectomy, 184 by thyrotomy, and 49 by suspension laryngoscopy in which surgical diathermy was employed to destroy the growth or in which radon seeds were inserted into the growth. Of the 446 patients who underwent operation, 90.4 per cent were male and 9.6 per cent were female, 80.9 per cent were between the ages of forty-five and sixty-nine years, 12.6 per cent were less than four years

for better understanding and the promotion of world peace.

The House of Delegates also received reports on and discussed the correlation and extension of voluntary prepayment medical care plans, streamlining the procedure of the House, revision of the constitution and by-laws, increasing the Fellowship dues and subscription to the *Journal* to \$12.00 annually, creation of several new sections in the scientific body, approval of the Red Cross blood program, improvement of rural medical service and other matters relating to medical care.

The annual session of the Association will be held in Chicago later this month. Your delegate expects to be present, and will be pleased to bring before the House anything that the House of Delegates may wish presented there.

Dr Sycamore moved that the report of the Delegate to the American Medical Association be accepted.

This motion was duly seconded and was carried.

The report of the Committee on Medical Education and Hospitals was then presented, as follows:

The Speakers' Bureau has been somewhat rejuvenated since the resumption of more normal programs after the war. The membership of the Society was circularized last fall, and twenty-seven men indicated their willingness to be so listed. These lists are being classified by fields and sent to county-society secretaries.

The American Medical Association is now entering this activity with particular emphasis on speakers for lay audiences, and state and national lists will be combined for this purpose. The American Medical Association will keep the Chairman of the Committee informed whenever some prominent figure of the national association might be in this section, so that his services can be made available if desired. In this connection it might be advisable for county-society secretaries to inform the Chairman of the Committee whenever special speakers for lay audiences are sought.

The Hill-Burton Act, providing federal aid for hospital construction, is to operate in connection with the hospital plan of each state as approved by the United States Public Health Service. The New Hampshire plan has now been approved and will soon start operation, the first year of which will have terminated on June 30, 1949. This situation was rather thoroughly covered in the last annual report of the Committee.

The one urgent matter at this time is the enlisting of the active support of the officers of the Society in stimulating the interest of our membership in the New England Postgraduate Medical Assembly. A tremendous amount of work has been done by the Massachusetts membership of its Executive Committee, and the financial risk—a real one in the early days—was entirely assumed by the Massachusetts Medical Society.

The New Hampshire Medical Society, like several other state societies in this region, is not of sufficient membership or financial resources to conduct a state postgraduate assembly of its own. The New England Postgraduate Assembly is a logical solution. It has been a progressively successful venture—last year a splendid program was presented most efficiently—with excellent speakers and a wide range of subjects over the field of the general practice of medicine. Of the 591 members of the New Hampshire Medical Society, less than 30 registered at the Assembly last year. This is a rather pitiful participation from the standpoint of evidence of interest, when it is recollected that 65 per cent of our members are within two hours of Boston. This Committee doubts the extent of its function in stimulating a more real interest in New Hampshire registrations at the Assembly but suggests that the senior officers of the Society bring the matter before one of the general sessions at the annual meeting.

JOHN P. BOWLER, *Chairman*  
JAMES W. JAMESON  
SAMUEL M. BROOKS

Dr Sycamore moved that the Committee on Scientific Work be instructed to recommend procedures for stimulating the interest of the members of the New Hampshire Medical Society in the New England Postgraduate Assembly, and that the Secretary be instructed to carry out such recommendations as may be feasible.

This motion was duly seconded and was carried.

Dr Dye then stated that Dr Parker had requested that the Committee on Industrial Health be made twelve members instead of three. It was necessary that the recommendation be brought before the meeting, to amend the by-laws, and that this matter be laid on the table for one day.

This motion was duly seconded and was carried.

Dr Dye then moved that the meeting be adjourned until the following morning at nine o'clock.

This motion was duly seconded and was carried.

Whereupon, the first meeting of the House of Delegates was adjourned at 10:45 p.m.

The House of Delegates reconvened at Wentworth-by-the-Sea, Newcastle, on June 2, 1948, at 9:00 a.m., with Speaker McIlvor presiding.

The President, *ex-officio*

The Vice-President, *ex-officio*

The Secretary-Treasurer, *ex-officio*

Nathan Brody, Laconia

Reginald F. DeWitt, Plymouth

W. J. Paul Dye, Wolfeboro

Francis J. C. Dube, Center Ossipee

Walter H. Lacey, Keene

Marjorie A. Parsons, Colebrook

Francis M. Appleton, Gorham

Leslie K. Sycamore, Hanover

Leslie E. McKinlay, North Haverhill

Everett C. Campbell, Woodsville

Reginald K. House, Hanover

Joseph N. Friberg, Manchester

Norman W. Crisp, Nashua

Claire G. Cayward, New Ipswich

Daniel J. Sullivan, Nashua

Andrew L. MacMillan, Concord

Francis Brown Henniker

L. Whitaker, Portsmouth (alternate for John W. Blaisdell)

Donald W. Leonard, Exeter

Fred Fernald, Nottingham

A. E. Barcomb (alternate for Daniel F. McCooley)

Edna Walck, Dover

B. Read Lewin, Claremont

The speaker declared a quorum present and asked whether the members had any names to present for life memberships.

Dr MacMillan, for Merrimack County, presented the name of W. H. Mitchell.

Dr Walck, for Strafford County, presented the names of Anna C. Rudd, of Durham, and E. M. Abbott, of Rochester.

The Secretary, when it had been explained that Dr Abbott had not been a member for a continuous fifteen years, stated that the by-laws would have to be amended to authorize life membership for him.

Dr Parsons suggested that, since Dr Abbott was disabled, the by-laws be changed so that anyone who is totally disabled would be eligible.

Dr Dye observed that such a change could be laid on the table and voted on the following day.

## NEW HAMPSHIRE MEDICAL SOCIETY

### PROCEEDINGS OF THE ONE HUNDRED AND FIFTY-SEVENTH ANNIVERSARY

House of Delegates, June 1, 2 and 3, 1948 (Concluded)

The report of the Committee on Public Health was presented

The Committee devoted its attention during the past year to the proper public-health coverage for the State

It is evident through the casual perusal of town reports that the matter of public health receives little or no attention. The smaller towns appropriate five or ten dollars a year as salary for their public-health officials, and expect them to make all sanitary inspections, to correct unsanitary conditions satisfactorily and to post cases of communicable disease. Often, they select as health officer one who has no training whatsoever, and because of the low salary or pay offered, he performs his duties reluctantly, unsatisfactorily and haphazardly. In some towns the physician serves as the community health officer, but has only the time to list the communicable diseases required by law. Even in the larger towns and cities, the health departments, if they can be called such, are undermanned, and an adequate public-health program is not possible.

In some cities more money is expended for the care of cemeteries and for parks and trees than for the health departments. One city, for example, expended \$7000 for the health of its people, \$17,000 for parks and shade trees, and \$39,000 for the care of the dead.

The counties have no health setup whatsoever, and the maintenance of public-health standards for the State resolves in most part upon the State health department. It is generally conceded that with the staff available, the State health department does an excellent job. It is also generally conceded that only the surface can be scratched so far as the entire State is concerned. A much more extensive health organization is needed adequately to protect the health of the people, as well as to educate them in public-health matters. The small beginning made by the Dental Division of the State Department of Health is to be commended.

There are two solutions to the problem at hand. The first is to improve the qualifications of the local health officials, but this seems an impossible task inasmuch as the pay involved is insufficient. The second solution, and by far the more feasible one, is the establishment by the State Department of Health, through proper legislation and adequate appropriations, of regional headquarters by county lines or by geographic areas, so that all the State may be adequately covered.

The opposition to this organization is twofold. The first is the reduction of authority of the towns, and the second the increase of the burden of the taxpayers. It seems that the same situation is present in this case as in that of the State Police, whose duty it is to safeguard the people of the State, in conjunction with local authorities.

The additional expense of this expansion would in part be borne by the federal Government, which would partially offset the budget increases. One such subdivision has been operated in the Exeter area for the past six years, and the results have been gratifying.

This state-wide organization meets the approval of health authorities, and it would mean no radical change in the setup of the State Department of Health.

The immediate expansion of the regional headquarters does not require expensive personnel, and in some areas not even a medical director would be necessary. Properly trained sanitary inspectors, and possibly a sanitary engineer, could adequately run the work for the present.

State nurses, who are now located in various sections, would therefore have local headquarters in place of makeshift ones, which are now used in some areas. These headquarters would serve as local distribution centers for serums, laboratory supplies, public-health literature and

other health information. They not only would expedite the work of the Health Department but also would definitely decrease health hazards, and improve the general health of the communities. An active educational program could be adequately promulgated through societies, schools and special courses.

It is the belief of the Committee that active steps should be taken by the New Hampshire Medical Society to foster this program in the next legislative session. It will be necessary to show clearly and concisely to the various members of the legislature that such a need is evident, and that the increased appropriations for its development will be money well invested with handsome returns in the form of better health to all the people of the State. It is suggested that the Committee on Public Health be given instructions, that the health expansion program may become actual in due time.

DONALD G. BARTON, Chairman  
HARRY W. SAVAGE  
HERMANN N. SANDER

Dr. Sycamore, for the Committee on Officers' Reports, moved that the Society go on record as deploring the inadequacy of public-health measures throughout the state, and that the Committee on Public Health be authorized to appear before the Legislature to present the needs in this field.

This motion was duly seconded and was carried.

Dr. Deering G. Smith, delegate to the American Medical Association, presented the following report:

The first interim session of the American Medical Association was held in Cleveland in January. This included the meeting of the House of Delegates, and a scientific program for general practitioners, which was attended by over 3000 enthusiastic physicians.

Your delegate served as chairman of the Reference Committee on Reports of Officers, and later was appointed a member of an interim committee to study the question of intern placements. Many more internships are available than there are physicians desiring them, which makes their distribution a serious problem to many hospitals. Others matters being studied by special committees are the nursing situation and the practice of medicine by hospitals.

The importance of the general practitioner was stressed in the "Grass Roots Conference," where his problems were discussed, and by the presentation of the General Practitioner's Award, for rendering exceptional service to his community, to Dr. Archer C. Sudan, of Colorado.

The question of what the American Medical Association is doing to improve medical care and to combat state medicine is often heard. The answer is given in an excellent report of the Board of Trustees, showing the progress that has been made toward the accomplishment of the objectives of the "Ten Point National Health Program of the American Medical Association." This report is printed on pages 261-266 of the *Journal of the American Medical Association* of January 24, 1948, and is worthy of attention.

The Council on National Emergency Medical Service has become active, and it is hoped that with the co-operation of the federal authorities and the various state committees like our own, definite plans may be made for handling emergencies.

A report was given concerning the formation of the world medical association. Forty-eight nations are represented in the association, which is indirectly a medium.

It is planned for the coming year that the Committee will prepare and distribute informative literature relative to industrial health problems. This material will be prepared in co-operation with the Division of Industrial Hygiene, State Health Department, and the Committee on Industrial Health, New Hampshire Manufacturers' Association

DAVID W PARKER, *Chairman*

Dr Sycamore moved that the recommendations of the Committee on Industrial Health be approved

This motion was duly seconded and was carried

Dr Dye stated that on the previous night it had been voted to amend the by-laws to change the membership of the Committee on Industrial Health from three to twelve members. It was laid on the table until this morning. He therefore, moved that the by-laws be changed to read "twelve members"

This motion was duly seconded and was carried

President Hunter then stated that he had had a letter from Dr Howard B Sprague, of Boston, asking if the New Hampshire Medical Society would contribute money for the New England Branch of the American Heart Association. He had replied that of course, nothing could be done, until this meeting of the House of Delegates

The Speaker asked for discussion on this matter

Dr Dye replied that he considered the project worth while but doubted whether the Society could afford to establish a precedent of giving contributions to different worthy causes. Therefore, he moved that the Secretary write to Dr Sprague and say that the Society is heartily in sympathy with the American Heart Association cause and will do anything that it can in the way of individual contributions to help out but that as a State Society it had a precedent of not making contributions

This motion was duly seconded and was carried

The Secretary suggested that the President answer the letter of Dr Sprague

Dr Brown then observed that Merrimack County Society had voted at its last meeting to assume the responsibility for a hospital bill of a former member of the Society who was in financial straits, he asked whether there was any fund to take care of anything like this, such as reimbursing the county society

Dr MacMillan stated that Merrimack County was not agreed regarding this matter, he had been asked to present the same question, and his opinion was that such a step was ill advised

The Speaker remarked that he agreed with Dr MacMillan

The second meeting of the House of Delegates adjourned at 9 45 a m

The House of Delegates reconvened at Wentworth-by-the-Sea, Newcastle, on June 3, 1948, at 9 15 a m, with Vice-Speaker Dube presiding

The following members answered the roll call

- Nathan Brody, Laconia
- W J Paul Dye, Wolfeboro
- Francis J C Dube, Center Ossipee
- Walter H Lacey, Keene (alternate)
- Marjorie A Parsons, Colebrook
- Francis M Appleton, Gorham
- Leslie K Sycamore, Hanover
- Reginald K House, Hanover
- Joseph N Friborg, Manchester
- Andrew L MacMillan, Concord
- Francis Brown, Henniker
- Fred Fernald, Nottingham
- A E Barcomb (alternate)
- B Read Lewin, Claremont

The Speaker declared a quorum present

President Hunter nominated Dr George C Wilkins and Dr George Dwinell in place of the delegates from Hillsborough County not present

The Committee on Nominations presented its report, and the balloting took place for the office of president and vice-president, as follows

PRESIDENT

Clarence E Dunbar, M D, of Manchester

VICE-PRESIDENT

John P Bowler, M D, of Hanover

COUNCILOR FOR BELKNAP COUNTY FOR FIVE YEARS

Chester L Smart, M D, of Laconia

COUNCILOR FOR GRAFTON COUNTY FOR FIVE YEARS

Arthur W Burnham, M D, of Lebanon

TRUSTEE FOR TWO YEARS

James W Jameson, M D, of Concord

TRUSTEE FOR THREE YEARS

George C Wilkins, M D, of Manchester

SPEAKER OF THE HOUSE OF DELEGATES

Francis J C Dube, M D, of Center Ossipee

VICE-SPEAKER OF THE HOUSE OF DELEGATES

B Read Lewin, M D, of Claremont

NECROLOGIST

Ralph W Tuttle, M D, of Wolfeboro

DELEGATE TO THE AMERICAN MEDICAL ASSOCIATION FOR 1948-50

Deering G Smith, M D, of Nashua

ALTERNATE DELEGATE TO THE AMERICAN MEDICAL ASSOCIATION FOR 1948-50

Howard P Sawyer, M D, of Brookfield

STANDING COMMITTEES

*Advisory Committee on Jurisprudence* Chester L Smart, Belknap County, W J Paul Dye, Carroll County, Robert W Holmes, Cheshire County, Arthur W Burnham, Grafton County, David W Parker, Hillsborough County, Robert J Graves, Merrimack County, Lawrence R Hazzard, Rockingham County, Jeremiah J Morin, Strafford County, B Read Lewin, Sullivan County, Carleton R Metcalf, Concord, *Chairman*

*Amendments to Constitution and By-Laws* W J Paul Dye, Wolfeboro, Loren F Richards, Nashua, Joseph E Larochelle, Berlin

*Child Health* Thomas B Walker, Portsmouth, Ursula G Sanders, Concord, Marion Fairfield, Nashua

*Control of Cancer* George C Wilkins, Manchester, Ralph E Miller, Hanover, George F Dwinell, Manchester, Walter H Lacey, Keene, Albert Oppenheimer, Laconia

*Council of New England Medical Societies* Carleton R Metcalf, Concord, Clarence E Dunbar, Manchester, Ralph W Tuttle, Wolfeboro

The President, *ex-officio*  
The Vice-President, *ex-officio*  
The Secretary-Treasurer *ex-officio*

Dr Brody moved that the word "continuous" be removed from the by-laws

Dr Friberg seconded the motion

The Speaker then requested all those in favor of amending Section 5 of the by-laws to read "Any physician who has been a member of this Society for fifteen years is eligible for life membership" to signify assent by raising the right hand

There were seventeen hands raised for the motion, and fourteen against the motion, which was declared to be carried

Dr Parsons, for Coos County, presented the names of John M Blodgett, R E Webb, Edward R B McGee, L B Marcou and A C Rondinella.

Dr Dye moved that all the names be accepted for life membership, except Dr Abbott, who would be voted upon on the following day

This motion was duly seconded and was carried

The Report of the Committee on Industrial Health was then presented, as follows

The Committee has not accomplished all it desired during the past year, but it is believed that the ground-work has been laid for greater effort in industrial medicine during the coming years

It is desired to point out at the beginning of this report that, among a large number of industrial officials in New Hampshire, and to a certain extent among the physicians, an apathy exists to industrial medical service. The importance of the problem of preventive medicine in industry received tremendous stimulus during the war, and today in practically every state, more and more emphasis and effort is being directed to meet these problems. Medical societies, nurses' groups, industrial organizations, Government health organizations, insurance companies and others are working together in an effort to reduce to a minimum, sickness and injuries that cause absenteeism from work and great economic losses to both the employer and the employees. It is a well known fact that the provision of good preventive medical programs, with adequate medical care of injuries and potential illnesses, will keep industrial absenteeism at a minimum.

New Hampshire is an industrial state and ranks fourth of all states in the percentage of workers gainfully employed in industrial plants. In 1938 the State Health Department conducted a survey of all plants for the purpose of determining health conditions in the plants, and the medical and nursing services provided for the employees.

The results of this survey showed that the health-service provisions available for workers were much lower than in other states and areas. Although this condition has improved to some extent during recent years, particularly in the number of nurses employed by plants, there is still a great need for improvement.

Early in the year a meeting of the Committee was held with the director of the Division of Industrial Hygiene, New Hampshire State Department of Health in Concord, at which objectives were drawn up that would enhance close co-operation of the New Hampshire Medical Society and the State Department of Health in the conduct of an industrial health program. The following objectives were unanimously approved at this meeting:

The Committee on Industrial Health, New Hampshire Medical Society, and the Division of Industrial Hygiene, New Hampshire State Department of Health, will work in close co-operation with each other. Policies, procedures and methods of the program will be discussed jointly by both organizations.

The Committee on Industrial Health approves the present health activities of the Division of Industrial Hygiene. These activities include engineering and chemical studies for the purpose of evaluating potential health hazards from dusts, gases, fumes, mists, vapors and other substances to which workers are exposed at the

various operations in industrial plants, investigations of reported occupational diseases for the purpose of assisting industry in the prevention of additional cases, the conduct of health evaluation surveys in small industrial plants, the study of the silicosis problem in view of prevention, and the promotion of health education among industrial workers.

The Committee voted to have the Chairman invite the New Hampshire Manufacturers Association to appoint a committee on industrial health, which would work in conjunction with our committee. This invitation was forwarded to the president of the New Hampshire Manufacturers Association, and a reply was received that such a committee would be appointed. After much delay notification was received on April 29, 1948, that a committee had been appointed. Members of this committee are Charles S Parsons, of the Chicopee Manufacturing Company, Manchester, Eustace Cummings, of E Cummings Leather Company, Incorporated, Lebanon and C Henry O'Neil, of the Nashua Gummed and Coated Paper Company, Nashua.

At this meeting, the following resolutions were adopted by the Committee and are submitted to the Society for its consideration and approval:

That the New Hampshire Medical Society urge all members to report known occupational diseases to the New Hampshire State Department of Health as provided under Chapter 132, Section 1-5, of the New Hampshire State Public Law. The reporting of these diseases is particularly important in view of the Workmen's Compensation Law as passed by the last legislature for the compensation of occupational diseases. It is understood by the Committee that no compensation will be paid for occupational diseases until official reports have been made by the attending physician.

That the Society include in its future scientific programs a symposium on industrial health, or invite a nationally known speaker to present a subject of interest to the general practitioners on industrial health. In view of the large variety of new chemicals and other substances being used in the industrial plants in New Hampshire, it is believed that the medical profession should be familiar with the toxicity and action of such materials to recognize early symptoms of absorption among industrial employees. The State Health Department has available a 70-mm mobile x-ray unit, and through the co-operation of the physicians and industrial officials, screening x-ray films can be made available to the industrial workers.

That the Society urge industry to make provisions for employing handicapped persons, provided that they are not hazardous to themselves and fellow employees, and are able to perform assigned duties satisfactorily.

That members of the Society co-operate with the Division of Industrial Hygiene, New Hampshire State Department of Health, in the conduct of health evaluation surveys among industrial employees.

These surveys consist essentially of an evaluation of the health of the employees in various types of industry in the State. The surveys include chest x-ray films, dental examinations, eye tests, hearing tests, examination of the urine for albumin and sugar and special tests if the employees are exposed to toxic materials. The results of these tests are entirely confidential between the individual employee, the employee's physician and the New Hampshire State Department of Health. If defects are found, the employee is requested to see his own physician for further study.

The Committee recommends that industrial plants employing 500 or more persons employ a full-time nurse with adequate industrial training, who will work under the supervision of a physician. Smaller plants should combine to employ a nurse who will divide her services between the individual plants. The physician and nurse should spend regular hours at the plant. In addition, the plants should provide medical dispensaries with adequate facilities and equipment.

For the activities and achievements of the committee to be increased, it is requested that the membership of the committee be increased to twelve members, to include physicians who are actively engaged in industrial medicine and who reside in the industrial cities of this State.

Dr Sycamore then observed that the matter of the telegram from the California Medical Association regarding Governor Warren had been referred to the Committee on Officers' Reports, which recommended the following resolution

*Whereas*, Governor Earl Warren of California has announced his candidacy for the Republican nomination for President of the United States, and

*Whereas*, Governor Warren has advocated a state system of compulsory sickness insurance in California and is alleged to advocate the inclusion in the Republican platform of a plank favoring national compulsory sickness insurance, and

*Whereas*, the New Hampshire Medical Society is opposed to any form of national compulsory sickness insurance,

*Therefore, be it resolved* That the New Hampshire Medical Society is opposed to the nomination of Governor Warren for either the Presidency or Vice-Presidency of the United States

*And be it further resolved* That the New Hampshire Medical Society is opposed to the inclusion in the Republican Platform of any plank favoring national compulsory sickness insurance,

*And be it further resolved* That a copy of this resolution be sent to the New Hampshire representatives in Congress and to the members of the New Hampshire delegation to the Republican National Convention

Dr Sycamore moved the adoption of this resolution

This motion was duly seconded and was carried  
The Secretary then spoke as follows

I am a little discouraged about our New Hampshire Society, which looks as if it were dying from old age. We have 160 people out for this meeting we had 222 last year, and ten years ago we used to draw 300. Whether it is the location of the meeting, the cost of the meeting or the program, I do not know, but the men do not come. It seems to me that we have got to put our finger on the sore spot, if we can, and see why our meetings do not attract more people.

This morning before the meeting, it was mentioned that we could have a meeting at Hanover, so that there could be some clinical cases to see. Dr Sycamore thought they could handle the crowd all right, there, after the middle of June. And, of course, we also spoke about going up into the mountains another year. I do not know whether we can settle on it this morning, if it cannot be settled here, it ought to be delegated to the officers or to somebody who could go over the situation. But, for one, I should certainly like to get any ideas on the subject that will buck the thing up.

Another suggestion that was made was to have a one-day meeting, similar to the meeting of the New Hampshire Surgical Club, and not try to stay overnight anywhere, and have it at some place like Manchester or Concord, and perhaps put on a clinical show in addition to the papers.

If any of you have any ideas on what is wrong with the New Hampshire Medical Society, I should like to hear them.

Dr George C Wilkins stated that if the meetings were held in Manchester or Concord, there would be a larger attendance, but, unfortunately, there were insufficient accommodations in both cities which was one of the reasons why Newcastle had been selected.

He believed that the meetings, when held at a summer hotel, kept away a certain number of people, on account of the expense involved. Another thing was the distance required to travel for a certain

number of people who live in the upper part of the State.

The Secretary observed that for several years, the afternoon programs had been made up of speakers from outside New Hampshire. However, this year, a good many New Hampshire men had been on for brief papers in the afternoon. This matter of the type of program preferred should be settled.

Dr Brody remarked that the largest concentration of medical men was apparently in Nashua, Manchester and Concord — probably close to 150 men — and that if the meetings could be held near those cities, the attendance might be better. He suggested a one-day meeting in one of those cities.

The Secretary replied that the meeting would then be similar to those of the New Hampshire Surgical Club meetings.

Dr Brown asked what the attendance was at those meetings.

The Secretary answered that during the war a great many of the men were away, and the meetings were rather poorly attended.

Dr Brown then asked what percentage of the people attending the meeting attended the scientific sessions.

The Secretary stated that 116 doctors had been registered on the previous day, he did not know how many were present at the afternoon session. He guessed that about half the members went to the scientific sessions.

Dr Dunbar stated that if the meetings were held near the center of the population, the problem of finding accommodations would come up. He suggested that arrangements be made at some of the overnight camps.

Dr MacMillan did not think that it would be wise to go back to the one-day meeting, which he considered to be the poorest meetings the Society had ever had. He suggested that the lack of attendance be overlooked and the meetings made as good as possible, so as to interest more members.

The Secretary asked whether the House of Delegates favored having New Hampshire men on the afternoon program or trying to get men from the urban centers outside the State.

Dr House believed that it was more stimulating to have men from outside the State. If somebody came in from outside, he might give the members a little something else to think about.

The Secretary replied that last year the obstetrician-in-chief at Johns Hopkins University School of Medicine had spoken to an audience of twenty-three.

The Speaker asked how many members were in favor of continuing the two-day sessions.

Almost all hands were raised.

He then asked how many were in favor of returning to Newcastle next year, late in June, when it would be warmer.

Nine delegates raised their hands.

*Industrial Health* David W Parker, Manchester, Henry Almond, Berlin, Robert J Graves, Concord, Charles F Keeley, Claremont, Robert W Holmes, Keene, John Samuel Wheeler, Concord, Daniel F McCooley, Dover, John C Eekels, Laconia, Robert Flanders, Manchester, John H Kennard, Manchester, Timothy Francis Roek, Nashua, Charles I Umpa, Nashua

*Maternity and Infancy* Robert O Blood, Concord, Benjamin P Burpee, Manchester, Frederick S Gray, Portsmouth

*Medical Economics* Leslie K Sycamore, Hanover, Francis J C Dube, Center Ossipee, Joseph N Friborg, Manchester

*Medical Education and Hospitals* John P Bowler, Hanover, James W Jameson, Concord, Howard P Sawyer, Brookfield

*Mental Hygiene* Arthur B Howard, Concord, Edward S Morris, Laconia, Simon Stone, Manchester

*National Emergency Medical Service* Daniel J Sullivan, Nashua, Joseph M McCarthy, Concord, Clarence E Dunbar, Manchester, Bernard J Manning, Dover, John C Eekels, Laconia

*Public Health* Donald G Barton, Concord, Harry W Savage, Lebanon, Hermann N Sander, Manchester

*Public Relations* Clarence E Dunbar, Manchester (president), John P Bowler, Hanover (vice-president), Carleton R Metcalf, Concord, (Secretary-Treasurer), Francis Brown, Henniker, Joseph N Friborg, Manchester

*Publications* Carleton R Metcalf, Concord, Samuel J King, Rochester, Lester R Whitaker, Portsmouth

*Rural Health* William F Putnam, Lyme, William P Clough, Jr, New London, Samuel Feiner, Ashland

*Scientific Work* Carleton R Metcalf, Concord, Robert R Rix, Manchester, Sven Gundersen, Hanover

*Tuberculosis* Robert B Kerr, Manchester, Frank G Seldon, Manchester, John D Spring, Nashua

Dr Dye then moved that the amendment to Section 5 of the by-laws, voted upon at the meeting of the previous day, be approved and that the Article concerning life membership be changed, striking out the word "continuous" on page 19, Section 5, Chapter I, so that the section would read

Any physician who has been a member of this Society for a term of fifteen years and is either not less than sixty-five years of age or totally disabled, on the request of his county society, may be made a life member by a majority of the votes of the House of Delegates. Life members shall have the same rights and privileges as other members of the Society, but shall not be required to pay dues

This motion was duly seconded and was carried by the majority required

Dr Sycamore then stated that the New Hampshire members of the Board of Physicians Service were subject to the approval of the House of Delegates, and he moved that these members be approved

This motion was duly seconded and was carried

The financial report of the Trustees was then presented, as follows

JANUARY 1-DECEMBER 31, 1947

#### GENERAL FUND

##### Receipts

Balance on hand Jan 1	\$2,633 68
Nashua Trust, Interest	10 72

Portsmouth Trust and Guarantee, Interest	23 45
New Hampshire Savings, Interest	15 50
United States Series G Bonds, Interest	81 25
Total receipts	\$2,764 60
Cash balance Dec. 31	\$2,764 60
United States Series G Bonds	5,000 00
Total fund	\$7,764 60

#### BARTLETT FUND

##### Receipts

Balance on hand Jan 1	\$2,190 94
Portsmouth Savings, Interest	43 81
United States Series G Bonds, Interest	25 00
Cash balance Dec. 31	\$2,259 75
United States Series G Bonds	2,000 00
Total fund	\$4,259 75

#### PRAY FUND

##### Receipts

Balance on hand Jan 1	\$350 19
Strafford Savings, Interest	6 64
United States Series G Bond, Interest	12 50
Total receipts	\$369 33
Expenditures	
Essay prize	50 00
Cash balance Dec 31	319 33
United States Series G Bonds	1,000 00
Total fund	\$1,319 33

#### BURNHAM FUND

##### Receipts

Balance on hand Jan 1	\$1,157 11
New Hampshire Savings, Interest	22 20
United States Series G Bond, Interest	12 50
Total receipts	\$1,191 81
Expenditures	
Essay prize	100 00
Cash balance Dec 31	\$1,091 81
United States Series G Bonds	1,000 00
Total fund	\$2,091 81

#### BENEVOLENCE FUND

##### Receipts

Balance on hand Jan 1	\$3,643 59
New Hampshire Savings, Interest	74 51
United States Series G Bonds, Interest	37 50
Dr C R Metcalf	140 00
Total receipts	\$3,895 60
United States Series G Bonds	3,000 00
Total fund	\$6,895 60

Signed,

HOWARD N KINGSFORD  
GEO C WILKINS

Audited and found correct, May 14, 1948

(Signed) DAVID C RENNIE, Auditor

Dr Sycamore then observed that the matter of the telegram from the California Medical Association regarding Governor Warren had been referred to the Committee on Officers' Reports, which recommended the following resolution

*Whereas*, Governor Earl Warren of California has announced his candidacy for the Republican nomination for President of the United States, and

*Whereas*, Governor Warren has advocated a state system of compulsory sickness insurance in California and is alleged to advocate the inclusion in the Republican platform of a plank favoring national compulsory sickness insurance, and

*Whereas*, the New Hampshire Medical Society is opposed to any form of national compulsory sickness insurance,

*Therefore, be it resolved* That the New Hampshire Medical Society is opposed to the nomination of Governor Warren for either the Presidency or Vice-Presidency of the United States

*And be it further resolved* That the New Hampshire Medical Society is opposed to the inclusion in the Republican Platform of any plank favoring national compulsory sickness insurance

*And be it further resolved* That a copy of this resolution be sent to the New Hampshire representatives in Congress and to the members of the New Hampshire delegation to the Republican National Convention

Dr Sycamore moved the adoption of this resolution

This motion was duly seconded and was carried  
The Secretary then spoke as follows

I am a little discouraged about our New Hampshire Society, which looks as if it were dying from old age. We have 160 people out for this meeting, we had 222 last year, and ten years ago we used to draw 300. Whether it is the location of the meeting, the cost of the meeting or the program, I do not know, but the men do not come. It seems to me that we have got to put our finger on the sore spot, if we can, and see why our meetings do not attract more people.

This morning before the meeting, it was mentioned that we could have a meeting at Hanover, so that there could be some clinical cases to see. Dr Sycamore thought they could handle the crowd all right, there, after the middle of June. And, of course, we also spoke about going up into the mountains another year. I do not know whether we can settle on it this morning, if it cannot be settled here, it ought to be delegated to the officers or to somebody who could go over the situation. But, for one, I should certainly like to get any ideas on the subject that will buck the thing up.

Another suggestion that was made was to have a one-day meeting, similar to the meeting of the New Hampshire Surgical Club, and not try to stay overnight anywhere, and have it at some place like Manchester or Concord, and perhaps put on a clinical show in addition to the papers.

If any of you have any ideas on what is wrong with the New Hampshire Medical Society, I should like to hear them.

Dr George C Wilkins stated that if the meetings were held in Manchester or Concord, there would be a larger attendance, but, unfortunately, there were insufficient accommodations in both cities which was one of the reasons why Newcastle had been selected.

He believed that the meetings, when held at a summer hotel, kept away a certain number of people, on account of the expense involved. Another thing was the distance required to travel for a certain

number of people who live in the upper part of the State.

The Secretary observed that for several years, the afternoon programs had been made up of speakers from outside New Hampshire. However, this year, a good many New Hampshire men had been on for brief papers in the afternoon. This matter of the type of program preferred should be settled.

Dr Brody remarked that the largest concentration of medical men was apparently in Nashua, Manchester and Concord — probably close to 150 men — and that if the meetings could be held near those cities, the attendance might be better. He suggested a one-day meeting in one of those cities.

The Secretary replied that the meeting would then be similar to those of the New Hampshire Surgical Club meetings.

Dr Brown asked what the attendance was at those meetings.

The Secretary answered that during the war a great many of the men were away, and the meetings were rather poorly attended.

Dr Brown then asked what percentage of the people attending the meeting attended the scientific sessions.

The Secretary stated that 116 doctors had been registered on the previous day, he did not know how many were present at the afternoon session. He guessed that about half the members went to the scientific sessions.

Dr Dunbar stated that if the meetings were held near the center of the population, the problem of finding accommodations would come up. He suggested that arrangements be made at some of the overnight camps.

Dr MacMillan did not think that it would be wise to go back to the one-day meeting, which he considered to be the poorest meetings the Society had ever had. He suggested that the lack of attendance be overlooked and the meetings made as good as possible, so as to interest more members.

The Secretary asked whether the House of Delegates favored having New Hampshire men on the afternoon program or trying to get men from the urban centers outside the State.

Dr House believed that it was more stimulating to have men from outside the State. If somebody came in from outside, he might give the members a little something else to think about.

The Secretary replied that last year, the obstetrician-in-chief at Johns Hopkins University School of Medicine had spoken to an audience of twenty-three.

The Speaker asked how many members were in favor of continuing the two-day sessions.

Almost all hands were raised.

He then asked how many were in favor of returning to Newcastle next year, late in June, when it would be warmer.

Nine delegates raised their hands.

In reply to the question how many were in favor of going somewhere else, several delegates raised hands, and to the question how many would be in favor of having during the afternoon sessions out-of-state speakers of international or national fame there was no response

Unanimous approval was expressed of the idea of having a program at the afternoon sessions with New Hampshire men, such as those at the present session, as well as out-of-state men

A member asked what the opinion was about using the first evening for papers, and leaving the afternoon free for enjoying golf or whatever the members wished to do

Fifteen delegates raised hands

The Speaker asked how many were in favor of having formal dress at the banquet

No hands were raised

The Secretary stated that the idea of using the first evening for scientific sessions was original but that some members might complain unless there was something for them to do in the afternoon

After further discussion Dr Sycamore moved that the time and place of the next meeting be left to the officers of the Society, taking into consideration the foregoing discussion

This motion was duly seconded and was carried

Dr Dye then moved that Dr Abbott, of Rochester, be made a life member

This motion was duly seconded and was carried

Dr Friberg moved that the Rockingham County Committee be thanked for the work in preparing the program

This motion was duly seconded and was carried

Speaker Dube then declared the meeting adjourned

Whereupon, the third meeting of the House of Delegates was adjourned at 10 15 a m

## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

TRACY B MALLORY, M D, *Editor*

BENJAMIN CASTLEMAN, M D, *Associate Editor*

EDITH E PARRIS, *Assistant Editor*

### CASE 34481

#### PRESENTATION OF CASE

A forty-one-year-old woman was admitted to the hospital from a chest clinic because of a lesion in the left chest

The patient was well until three months before admission, when she contracted an upper respiratory infection with coryza, hoarseness and a cough productive of half a cup of brownish-gray sputum a day. The cough and sputum production subsided, but hoarseness continued, and increasing dyspnea, rapid breathing, occasional "choking" spells and wheezing respiration followed. There had been a 15-pound weight loss in four months, despite an excellent appetite, and progressive weakness. The latter was intermittent, accompanied by profuse sweating and a feeling of imminent blackout. For three weeks she had soreness in the left chest. When she was eighteen, she had a spot on the right lung, which cleared after a year of bed rest. Eleven years before admission a right nephrostomy for renal cal-

culi was performed. Three years before entry a total hysterectomy and right salpingo-oophorectomy were performed at this hospital for vaginal bleeding. The pathological diagnosis was tubal pregnancy. Two years before entry a neighbor, with whom she had had contact, developed tuberculosis. For that reason a chest x-ray film was taken at that time. It was reported to be normal.

Physical examination revealed a woman who appeared chronically ill. The fingernails showed moderate clubbing. There were tenderness on pressure over the left chest, anteriorly and posteriorly, and dullness over the left base posteriorly, with decreased left diaphragmatic excursion.

The blood pressure was 140 systolic, 90 diastolic. Examination of the blood demonstrated a hemoglobin of 12.5 gm and a white-cell count of 8400. The urine specific gravity was 1.020, no albumin or significant formed elements were found. The non-protein nitrogen was 16 mg, and the total protein 7.5 gm per 100 cc.

X-ray examination of the chest demonstrated a well circumscribed area of increased density at the apex of the left lower lobe, measuring about 8 by 8 by 10 cm (Fig 1). There was no degeneration within it. The remainder of the lung parenchyma was clear. Intravenous and retrograde pyelography showed a deformity of the calyces and pelvis on the right, with dilatation of the superior and inferior calyces. The left kidney pelvis was normal. Both kidney shadows were of normal size.

A bronchoscopy demonstrated no abnormalities. A smear taken from the dorsal division of the left upper-lobe bronchus was negative for tumor cells. In smears taken from the left-lower-lobe bronchus a few acid-fast bacilli were found. Needle aspiration of the chest lesion was unsuccessful. During the first

ten hospital days the patient's course was not remarkable. She was afebrile. On the eleventh hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR MERRILL SOSMAN \* I think it is fair, inasmuch as the patient was admitted because of an x-ray finding from a chest clinic, to start with the films and then work back to the history, physical examination and laboratory findings.

We can see in this film that this is the chest of a young woman, "young" being comparative — any-

amination two years before admission following exposure to a patient with tuberculosis. If that is reliable, it certainly would rule out both the congenital group of tumors and the benign tumors. If it was a tumor, it would have had to be malignant to reach this size in two years. Do we know where the x-ray examination was done?

DR TRACY B MALLORY It was done in one of the state sanatoriums.

DR SOSMAN Then it should be reliable. One other thing that we should note in evaluating the shadow is whether or not it was movable with the

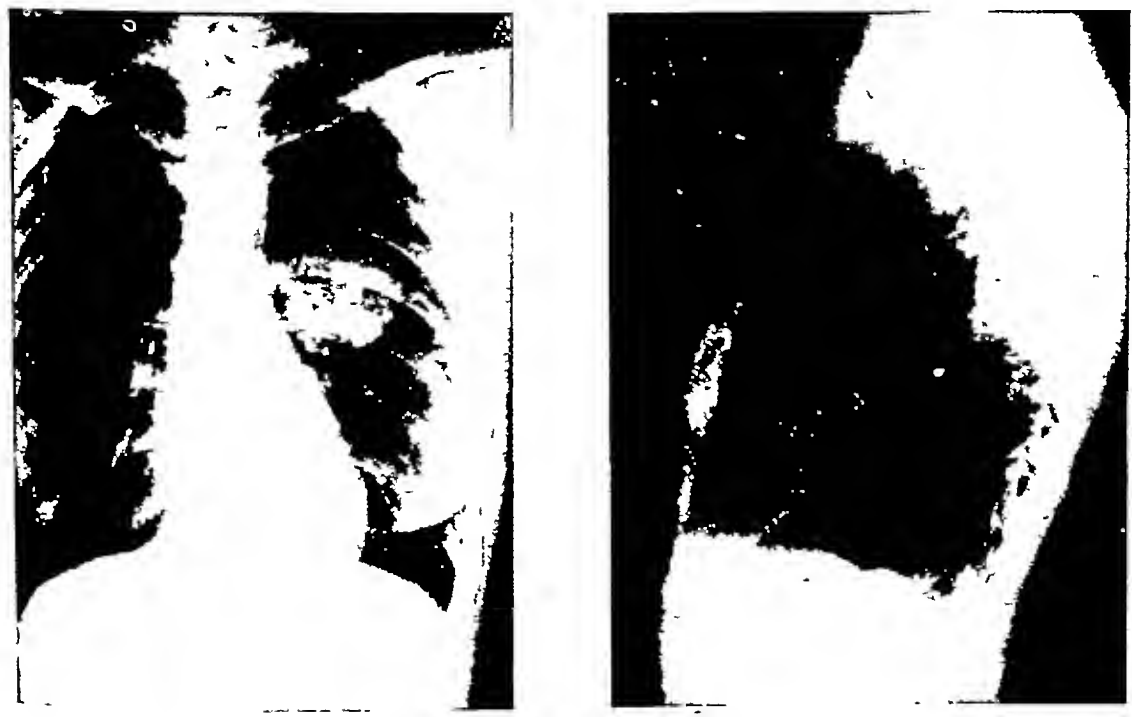


FIGURE 1

one below one's own age is young and anyone above it is old. She has a single lesion in the left midchest, measuring 8 cm in diameter and not very sharply outlined. In the lateral view, lying well back posteriorly in the chest, the shadow is shaped a good deal like a gumdrop, the flat part being against the posterior chest wall and the anterior surface being sharply rounded or convex. The other findings in the chest appear perfectly normal. The heart is not displaced, the diaphragm is in normal position, the ribs are intact. The trachea appears normal, and all the visible bones appear normal.

Our problem then is to try to find out the nature of this circular mass in the left chest posteriorly, which is in the approximate region of the apex of the lower lobe. Going back to the history we find a great many "red herrings" dragged across the trail. The history says that she had a negative x-ray ex-

amination two years before admission following exposure to a patient with tuberculosis. If that is reliable, it certainly would rule out both the congenital group of tumors and the benign tumors. If it was a tumor, it would have had to be malignant to reach this size in two years. Do we know where the x-ray examination was done?

DR JOSEPH HANELIN No. I am not familiar with the case.

DR SOSMAN It might make a difference if it were attached to the chest wall or free in the lung and moved up with cough or expiration. The one thing brought up more than anything else in the history is the story of tuberculosis. She is said to have had "a spot on the right lung" at the age of eighteen. There is no evidence of that at present. She had contact with a patient who was known to have tuberculosis, and this was the cause of her x-ray examination two years previously. Most important of all is the finding of acid-fast bacilli in smears taken from the left-lower-lobe bronchus. If that is reliable, which it certainly should be, we are forced to make a diagnosis of tuberculosis some-

\*Pathologist Peter Bent Brigham Hospital

In reply to the question how many were in favor of going somewhere else, several delegates raised hands, and to the question how many would be in favor of having during the afternoon sessions out-of-state speakers of international or national fame there was no response

Unanimous approval was expressed of the idea of having a program at the afternoon sessions with New Hampshire men, such as those at the present session, as well as out-of-state men

A member asked what the opinion was about using the first evening for papers, and leaving the afternoon free for enjoying golf or whatever the members wished to do

Fifteen delegates raised hands

The Speaker asked how many were in favor of having formal dress at the banquet

No hands were raised

The Secretary stated that the idea of using the first evening for scientific sessions was original but that some members might complain unless there was something for them to do in the afternoon

After further discussion Dr Sycamore moved that the time and place of the next meeting be left to the officers of the Society, taking into consideration the foregoing discussion

This motion was duly seconded and was carried

Dr Dye then moved that Dr Abbott, of Rochester, be made a life member

This motion was duly seconded and was carried

Dr Friberg moved that the Rockingham County Committee be thanked for the work in preparing the program

This motion was duly seconded and was carried

Speaker Dube then declared the meeting adjourned

Whereupon, the third meeting of the House of Delegates was adjourned at 10 15 a m

## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

TRACY B MALLORY, M D, *Editor*

BENJAMIN CASTLEMAN, M D, *Associate Editor*

EDITH E PARRIS, *Assistant Editor*

### CASE 34481

#### PRESENTATION OF CASE

A forty-one-year-old woman was admitted to the hospital from a chest clinic because of a lesion in the left chest

The patient was well until three months before admission, when she contracted an upper respiratory infection with coryza, hoarseness and a cough productive of half a cup of brownish-gray sputum a day. The cough and sputum production subsided, but hoarseness continued, and increasing dyspnea, rapid breathing, occasional "choking" spells and wheezing respiration followed. There had been a 15-pound weight loss in four months, despite an excellent appetite, and progressive weakness. The latter was intermittent, accompanied by profuse sweating and a feeling of imminent blackout. For three weeks she had soreness in the left chest. When she was eighteen, she had a spot on the right lung, which cleared after a year of bed rest. Eleven years before admission a right nephrostomy for renal cal-

culi was performed. Three years before entry a total hysterectomy and right salpingo-oophorectomy were performed at this hospital for vaginal bleeding. The pathological diagnosis was tubal pregnancy. Two years before entry a neighbor, with whom she had had contact, developed tuberculosis. For that reason a chest x-ray film was taken at that time. It was reported to be normal.

Physical examination revealed a woman who appeared chronically ill. The fingernails showed moderate clubbing. There were tenderness on pressure over the left chest, anteriorly and posteriorly, and dullness over the left base posteriorly, with decreased left diaphragmatic excursion.

The blood pressure was 140 systolic, 90 diastolic.

Examination of the blood demonstrated a hemoglobin of 12.5 gm and a white-cell count of 8400. The urine specific gravity was 1.020, no albumin or significant formed elements were found. The non-protein nitrogen was 16 mg, and the total protein 7.5 gm per 100 cc.

X-ray examination of the chest demonstrated a well circumscribed area of increased density at the apex of the left lower lobe, measuring about 8 by 8 by 10 cm (Fig 1). There was no degeneration within it. The remainder of the lung parenchyma was clear. Intravenous and retrograde pyelography showed a deformity of the calyces and pelvis on the right, with dilatation of the superior and inferior calyces. The left kidney pelvis was normal. Both kidney shadows were of normal size.

A bronchoscopy demonstrated no abnormalities. A smear taken from the dorsal division of the left upper-lobe bronchus was negative for tumor cells. In smears taken from the left-lower-lobe bronchus a few acid-fast bacilli were found. Needle aspiration of the chest lesion was unsuccessful. During the first

ten hospital days the patient's course was not remarkable. She was afebrile. On the eleventh hospital day an operation was performed.

### DIFFERENTIAL DIAGNOSIS

DR MERRILL SOSMAN \*I think it is fair, inasmuch as the patient was admitted because of an x-ray finding from a chest clinic, to start with the films and then work back to the history, physical examination and laboratory findings.

We can see in this film that this is the chest of a young woman, "young" being comparative — any-

amination two years before admission following exposure to a patient with tuberculosis. If that is reliable, it certainly would rule out both the congenital group of tumors and the benign tumors. If it was a tumor, it would have had to be malignant to reach this size in two years. Do we know where the x-ray examination was done?

DR TRACY B. MALLORY It was done in one of the state sanatoriums.

DR SOSMAN Then it should be reliable. One other thing that we should note in evaluating the shadow is whether or not it was movable with the



FIGURE 1

one below one's own age is young and anyone above it is old. She has a single lesion in the left midchest, measuring 8 cm in diameter and not very sharply outlined. In the lateral view, lying well back posteriorly in the chest, the shadow is shaped a good deal like a gumdrop, the flat part being against the posterior chest wall and the anterior surface being sharply rounded or convex. The other findings in the chest appear perfectly normal. The heart is not displaced, the diaphragm is in normal position, the ribs are intact. The trachea appears normal, and all the visible bones appear normal.

Our problem then is to try to find out the nature of this circular mass in the left chest posteriorly, which is in the approximate region of the apex of the lower lobe. Going back to the history we find a great many "red herrings" dragged across the trail. The history says that she had a negative x-ray ex-

amination two years before admission following exposure to a patient with tuberculosis. If that is reliable, it certainly would rule out both the congenital group of tumors and the benign tumors. If it was a tumor, it would have had to be malignant to reach this size in two years. Do we know where the x-ray examination was done?

DR JOSEPH HANELIN No. I am not familiar with the case.

DR SOSMAN It might make a difference if it were attached to the chest wall or free in the lung and moved up with cough or expiration. The one thing brought up more than anything else in the history is the story of tuberculosis. She is said to have had "a spot on the right lung" at the age of eighteen. There is no evidence of that at present. She had contact with a patient who was known to have tuberculosis, and this was the cause of her x-ray examination two years previously. Most important of all is the finding of acid-fast bacilli in smears taken from the left-lower-lobe bronchus. If that is reliable, which it certainly should be, we are forced to make a diagnosis of tuberculosis some-

\*Radiologist, Peter Bent Brigham Hospital

where in the respiratory tract and presumably in the left lower lobe because that is where the smears were obtained. Were there any sputum examinations made? I did not notice anything about that in the report.

DR LAMAR SOUTTER The sputum was negative for acid-fast organisms.

DR SOSMAN So this is an isolated finding on bronchoscopic examination. We must make a diagnosis of pulmonary tuberculosis — postulating the ulcerating tracheobronchial type of tuberculosis — and then try to decide whether this shadow that we see can also be explained on the basis of pulmonary tuberculosis. It is a very rare type of shadow to be produced by tuberculosis in my experience. It is peripheral, which tuberculosis usually is, but it is round and smooth and homogeneous in density, and there is no evidence of cavity or any calcification in it. One of the most important things against it, I think, is the statement that she was afebrile. So we have to consider strongly the possibility that this was a separate lesion and not due to the presumed tuberculosis. Another suggestion in the history is the operation on the kidney some years before admission, and we have here a series of renal studies, both intravenous and retrograde pyelograms, all of which show a definite deformity of the right renal pelvis, which I think can readily be seen. It is quite possible, in fact quite probable, that this deformity is merely the result of previous operation and not of any intrinsic disease in the kidney at present. We notice that there is dilatation of the superior and inferior calyces, with a rather contracted central portion of the pelvis. The opposite renal pelvis on the left fills well except on one small film, where there is a suggestion of a negative shadow in the renal pelvis. It does not persist so I think we can disregard that.

The hysterectomy and salpingo-oophorectomy are readily explained by the tubal pregnancy and had nothing to do with the mass in the chest, particularly in this interval of time — three years.

Going back to the physical examination we note clubbing of the fingers. How can we tie that up with the mass that we find described in the history and at physical examination? Clubbing in my experience is most common in congenital heart disease. This patient had no murmurs or signs of heart disease. When patients have clubbing from heart disease they usually have murmurs, cyanosis and polycythemia due to the long-continued shunt of blood. The second most common cause of clubbing is primary tumor of the lung, which is nearly always malignant. I took care of a patient who had marked clubbing with a Pancoast type of tumor. Chronic infection of the lung is a third cause of clubbing of the fingers in my experience, and this, of course, can be a tuberculoma or a tuberculous area at the apex of the lower lobe. But, in my limited experi-

ence, clubbing in tuberculosis is usually found only in the far-advanced case with cavitation and secondary infection. I would expect it to be quite rare in a lesion of such short duration as this. A fourth cause of clubbing is polyposis of the intestine, which is very rare indeed. There is no gastrointestinal examination here so we cannot consider that.

That about covers my discussion except to say that I cannot explain the dyspnea, the rapid breathing, the choking spells and wheezing respirations noted earlier in the history. The hoarseness continued, and it is quite possible that it was due to tuberculosis of the larynx. This would tie up both things on one foundation. But I presume that the larynx was inspected at the time of bronchoscopy.

DR EDWARD B. BENEDICT That is right.

DR SOSMAN And nothing abnormal was seen.

DR BENEDICT The bronchoscopy was negative.

DR SOSMAN If there was enough tuberculosis to cause hoarseness, there should have been something visible on the vocal cords, either thickening or reddening.

So, to sum up this short and very easy case, I may say we are forced to make a diagnosis of pulmonary tuberculosis because of the positive sputum. I would like to tie up the chest lesion with tuberculosis also and call it tuberculoma. If so, one ought to see a large area of consolidation or perhaps atelectasis due to the tuberculosis of the ulcerating tracheobronchial type. But I suspect that there was a separate primary tumor of the lung in addition. Regarding the type of tumor, it is pure speculation in my experience to try to guess the kind of tumor a given patient has unless it has some of the characteristic findings, which this patient did not have. If we want to play poker, which I think is legal in this type of exercise, we may guess that it was nonmalignant because it was located opposite the seventh rib, and yet the ribs resected were the fifth and sixth, leaving the seventh rib intact, which puzzles me a little bit. If it were a malignant tumor invading the chest wall, I would assume that a good surgeon would excise the whole area including the seventh rib. Is that legal?

DR MALLORY It is done. Does anyone want to ask any questions?

DR SOSMAN I would gladly accept any suggestions or help.

DR BENEDICT I do not believe we know what Dr Sosman's diagnosis is. Is it a benign tumor of the lung?

DR SOSMAN No, I think the development of this tumor in two years is against a benign tumor of the lung. My diagnosis, which is based particularly on the acid-fast bacilli that were found, is pulmonary tuberculosis and probably a tuberculous lesion in the apex of the left lower lobe. I would put carcinoma second because of the rapid growth in two years.

## CLINICAL DIAGNOSIS

Carcinoma of lung (before acid-fast organisms were found)

## DR SOSMAN'S DIAGNOSIS

Pulmonary tuberculosis (from bronchoscopic washings)

Tuberculoma?

Carcinoma of lung, apex of left lower lobe?

## ANATOMICAL DIAGNOSIS

*Epidermoid carcinoma of lung, left lower lobe*

## PATHOLOGICAL DISCUSSION

DR SOUTTER I operated on this woman. We made a tentative preoperative diagnosis of bronchiogenic carcinoma. This was before the report of the bronchoscopic smears were received on the ward. The incision was made through the bed of the fifth rib to enable us to get above where the tumor was adherent to the chest wall. The tumor was adherent over the sixth rib. If one looks at the postoperative film, one sees the area of absent rib where the tumor was adherent. The appearance of the tumor suggested malignancy. It protruded from the lung tissue and seemed to invade the chest wall. We did a left lower lobectomy, going extrapleurally, and afterward resected that part of the chest wall to which the tumor had been adherent.

DR SOSMAN That is rather surprising because the sixth rib is at the upper edge of the shadow. The center of the tumor is opposite the seventh rib posteriorly.

DR SOUTTER The tumor was adherent to the chest wall at its apex and not at its center.

DR MALLORY The lobe that was resected showed a large spherical area of epidermoid carcinoma near the apex. We searched very carefully and were not able to find any trace of tuberculosis. I have no explanation for the acid-fast bacilli. I would hate to suggest the bronchoscope.

DR BENEDICT Of course it is possible there was tuberculosis in the other lobe that we knew nothing about. I was as surprised as anyone when tubercle bacilli were found. There must have been a mistake somewhere.

DR MALLORY We must remember that acid-fast bacilli do not always mean tuberculosis although in the sputum the chance of anything else is so slight that we feel safe in neglecting any other possibility. But we have no real knowledge that they were tubercle bacilli.

DR ALLEN G. BRAILEY Where did the tumor arise?

DR MALLORY From one of the secondary bronchi running to the apex of the lower lobe. It was completely occluded and surrounded by tumor, and the bronchus leading still higher up was com-

pressed by the mass. The regional lymph nodes were normal. Tumor cells were found in the parietal pleura after it was resected.

DR BENEDICT The bronchoscopy was negative as you know, but I would like to point out that in that area bronchoscopy probably would be negative for carcinoma. We would not be able to reach a tumor in the apex of the left lower lobe. In a series of 309 cases of proved carcinoma that were bronchoscoped by me in this hospital, there were positive biopsies in 61 per cent. Gibbon and his associates\* in Pennsylvania have had positive cytologic studies from bronchoscopic washings in 89 per cent of 105 cases studied. Our figures are not so good on bronchoscopic washings, nor have we done as many. I would say carcinoma was definitely not ruled out at this examination. We have had a few cases with both tuberculosis and carcinoma.

A PHYSICIAN Was a Papanicolaou stain done?

DR MALLORY Yes, and it was negative.

\*Gibbon J. H., Jr., Clerf L. H., Herbut P. A., and DeTurck J. J. Diagnosis and operability of bronchiogenic carcinoma. *J. Thoracic Surg.* 47:419-427, 1948.

## CASE 34482

## PRESENTATION OF CASE

A sixty-five-year-old woman was admitted to the hospital because of pain in the right side of the face and ptosis of the right eyelid.

About two years before entry the patient began to notice easy fatigability. Eight months before admission, during a routine checkup, she was found to be anemic. She was given liver injections over the following three months and felt improved. Six months before admission the third right upper molar became sensitive to heat, cold and pressure of mastication. A month later the patient began to have a watery discharge from the right nostril, always in the morning and not during the rest of the day. Three months before entry the nasal discharge, still limited to the right nostril, became bloody. The pain increased in severity and spread to the right temporal region. Except for some dried blood in the right nostril an ear, nose and throat specialist could not find any abnormality. Six weeks before admission roentgenograms of the sinuses were reported to be normal. The pain continued to increase, became almost constant and required codeine for relief. It was characterized by a dull, dead ache spreading up from the right maxilla to the temporal region, behind and into the eye, rarely crossing over a little to the left eye. Occasionally the ache was interrupted by shooting pains in the same regions. About ten days before entry the right upper eyelid began to droop. This was followed by diplopia and, three days later, by complete ptosis.

There had not been any weight loss, and appetite was good. There was no history of earache, dis-

charge from the ear, tinnitus, dizziness, nor of unsteadiness, awkwardness or weakness of the arms or legs. Five days before admission a spinal puncture showed an initial pressure equivalent to 65 mm of water, on jugular compression to 110 mm, and on final pressure to 60 mm, a total protein of 23 mg per 100 cc, a negative test for globulin, 1 neutrophil and chloride of 737 mg per 100 cc.

Physical examination showed complete ptosis of the right eyelid, lateral deviation of the eye and almost complete ophthalmoplegia. The right pupil was dilated and did not react to light or accommodation. Visual acuity, fields and fundi were normal. The left eye was not remarkable. There was no sensory impairment, deviation of the jaw, facial-nerve weakness or impairment of hearing. Speech, palate and tongue were normal. Neurologic examination was otherwise negative. An ear, nose and throat consultant found some bloody mucus on the posterior wall of the right nasopharynx.

The temperature, pulse and respirations were normal. The blood pressure was 120 systolic, 80 diastolic.

The hemoglobin was 13.6 gm, and the white-cell count 10,400, with 74 per cent neutrophils. The urine was negative for Bence-Jones protein. The nonprotein nitrogen was 28 mg, the total protein 6.36 gm, the albumin 4.38 gm, the globulin 1.98 gm, the phosphorus 4.1 mg, and the calcium 10.1 mg per 100 cc. The blood Hinton test was negative.

Roentgenograms of the skull and sinuses revealed a calvarium of normal contour but rather diffusely vascular. There was increased density in the region of the sphenoid sinuses on the right, and the outline of the floor of the sella turcica was not clearly seen. There appeared to be some calcification in one or both internal carotid arteries near the sella. The bone partitions of the ethmoid sinuses were somewhat hazy.

In the hospital the patient continued to complain of pain. There were no changes in her general or neurologic status. On the eighth hospital day an operation was performed.

#### DIFFERENTIAL DIAGNOSIS

DR. DAVID G. COGAN: The combination of pain in the face and ptosis suggests rupture of an intracranial aneurysm, but there is no history of hemicranial headaches to go with this diagnosis, and the onset was apparently not sudden. The pain in the tooth may have been a local affair, but the fact that it was right-sided, as was the pain in the face, and chronologically related to the rest of the history, requires that we assume that it had some correlative significance, it may well have been a paresthesia from central involvement of the right fifth nerve. Similarly, the bleeding from the nose and serous discharge may have been a local affair, but the fact that it was unilateral and on the same side as the rest of the patient's symptoms requires

that we consider its most serious implication and assume it to have been an ulcerative process with rhinorrhea from a cerebrospinal fistula. I do not know why the discharge should have been most evident in the morning. The negative findings on physical examination of the nose and the negative x-ray findings do not rule out carcinoma of the nasopharynx. We have recently seen a patient with symptoms almost identical to those presented by this patient in whom carcinoma of the nasopharynx was ultimately found, but in the stage comparable to that of this patient no abnormality was found on examination of the nasopharynx or on x-ray examination.

The pain in this patient was more or less continuous and progressive. There was evidently preferential involvement of the second division of the trigeminal nerve. This, together with third-nerve paralysis, points to a lesion behind the superior orbital fissure and lateral to the sella turcica. Pain is not characteristic of benign lesions in this region and, therefore, suggests a malignant tumor extending from the nose into the subarachnoid space.

The spinal-fluid findings were noncontributory, the only thing of interest being the low cerebrospinal-fluid pressure. A reasonable explanation for this would be the cerebrospinal fistula, and it would be interesting to know whether prolonged jugular compression caused an increase in the rhinorrhea. The only noteworthy feature about the third-nerve paralysis is that the pupil was dilated. Lesions immediately behind the superior orbital fissure frequently do not cause enlarged pupils, presumably owing to coincident involvement of the sympathetic pathways. The lesion in this case might be thought, therefore, to have been nearer the cavernous sinus than the superior orbital fissure. It is also noteworthy that the optic nerve was not involved as so frequently happens with the tumors extending from the sphenoidal region. The x-ray films taken after admission showed an increased density in the sphenoid sinuses on the right with obscuration of the floor of the sella turcica. Dr. MacMillan, radiologist at the Massachusetts Eye and Ear Infirmary, tells me that this is compatible with a tumor extending from the sphenoidal region up through the sella turcica. The x-ray finding of calcification in the carotid arteries is not infrequent in people of this age group.

In summary, the patient was a sixty-five-year-old woman whose outstanding symptoms were severe pain in the right trigeminal region and paralysis of the right third nerve. This suggests a lesion lateral to the sella turcica on the right side. The rhinorrhea and x-ray findings are compatible with a tumor connecting the nasopharynx and cranial cavity. It seems to me that the only reasonable diagnosis is an erosive tumor extending either from the nasopharynx or primarily from the sphenoid sinus up into the cranial cavity. The presence of pain and erosiveness points to malignant tumor.

The two predominant types of cancer found in this region are lymphosarcoma and carcinoma. The lymphosarcomas are less apt to cause pain but are more apt to be diffuse, less circumscribed and less erosive. Also, they are frequently characterized by auditory symptoms unlike those produced by carcinoma. This patient therefore appears to have had a carcinoma. On the basis of frequency, I would suggest a diagnosis of transitional-cell carcinoma of the sphenoid, with fistula connecting the cranial cavity and nasopharynx.

DR TRACY B. MALLORY: Are there any questions that you would like to ask Dr. Cogan, or any other suggestions? Perhaps we should see the x-ray films.

DR JAMES J. McCORT: The soft-tissue mass overlying the sphenoid sinus can be seen in this region, causing some density of the sphenoid sinus. The posterior wall of the sphenoid sinus appears to be missing. It is probably eroded. On this film the floor of the sella turcica is eroded, with no local identification. There are a few flecks of calcification lying apparently over the sella turcica, which as the protocol says may be in the carotid arteries. There is no curved linear distribution of the calcification, which might indicate aneurysm.

DR COGAN: Are you able to differentiate a metastatic and a primary lesion?

DR McCORT: Not here, since we do not have a complete skull series.

DR CHARLES I. JOHNSON: I would like to take issue with Dr. Cogan on the fact that the nose and throat specialist was not able to find a carcinoma in the nasopharynx. This was not a nasopharyngeal tumor, it was a sphenoid tumor. With the aid of a nasopharyngoscope a streak of bloody mucus could be seen coming from the ostium of the sphenoid and joining the posterior ethmoid region. There are four ways of examining the nasopharynx by roentgenograph, mirror, finger and nasopharyngoscope. None of these ways, except x-ray examination and nasopharyngoscope, would have helped in this case. If blood had not been coming out at that instant, the nasopharyngoscope would not have helped. All one would have is the x-ray film. In the presence of suggestive x-ray findings, exploration should be done.

DR COGAN: The reason I was discounting the negative x-ray examination is that the other patient to whom I referred as having identical symptoms, and who was subsequently found to have a transitional carcinoma of the nasopharynx, also had negative findings in the nose and a negative x-ray examination.

DR JOHNSON: How long before the tumor was found was the examination done?

DR COGAN: He was seen by a nose and throat specialist, not by Dr. Johnson, because of recurrent nosebleeds and septal deviation. He had a high blood pressure. Examination of the nasopharynx was negative. He came into the Emergency Ward

two months later with a severe epistaxis and was again examined by a nose and throat specialist and the nasopharyngeal tumor was found.

DR JOHNSON: It means that the patient probably did not have a really good examination the first time.

DR COGAN: I assumed that the tumor could not be found.

## CLINICAL DIAGNOSIS

Transitional cell carcinoma

## DR COGAN'S DIAGNOSIS

Transitional cell carcinoma of sphenoid sinus

## ANATOMICAL DIAGNOSIS

*Transitional cell carcinoma of sphenoid sinus*

## PATHOLOGICAL DISCUSSION

DR JOHNSON: We explored the sphenoid sinus under local anesthesia and took off a good deal of the posterior part of the middle turbinate and removed the anterior face of the sphenoid sinus—removing a mucocele—and then found a large piece of tumor tissue. The superior wall of the sphenoid was gone, according to instrumentation—that is, according to the sensation one gets from instrumentation. We had to be a little careful because we thought there had been a cerebrospinal leak previously. I do not call this a nasopharyngeal tumor, it was a sphenoid tumor, and I do not see how one can possibly miss a nasopharyngeal carcinoma if all four methods of examination are resorted to.

DR CHARLES S. KUBIK: I have nothing to add to what is in the record. The ocular palsies localize the lesion with great precision, as Dr. Cogan has indicated. In this case it is interesting that although there had been a good deal of pain, there apparently was not enough involvement of the fifth nerve to cause sensory impairment.

DR MALLORY: The biopsy, as Dr. Johnson said, showed transitional-cell carcinoma, undoubtedly primary in the sphenoid. I believe you saw the patient in reference to treatment, Dr. Taylor.

DR GRANTLEY W. TAYLOR: My participation in this case was insignificant. The question arose whether or not we could relieve the symptoms. We have had a moderate amount of experience with these tumors. Some are responsive to irradiation—so much so that all symptoms are relieved to a considerable degree. Therefore, we started x-ray therapy, and the results were fairly good. The patient began to get significant relief from symptoms as soon as the treatment was started while she was in the hospital. She had less pain and had some comfort.

DR JOHNSON: I saw her yesterday. She is more comfortable. The ptosis is complete. Everything else is as it was except that she is more comfortable.

# The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established 1828

Official Organ of

THE MASSACHUSETTS MEDICAL SOCIETY  
and  
THE NEW HAMPSHIRE MEDICAL SOCIETY

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND  
PUBLISHED WEEKLY UNDER THE JURISDICTION OF THE  
COMMITTEE ON PUBLICATIONS

James P. O'Hare, M.D. Richard M. Smith, M.D., Chairman  
Oliver Cope, M.D. Conrad Westelhof, M.D.  
John Fallon, M.D.

Joseph Garland, M.D., Editor

ASSOCIATE EDITORS

Thomas H. Lanman, M.D. Donald Munro, M.D.

Henry Jackson, Jr., M.D.

Clara D. Davies, Executive Editor

Robert O'Leary, Assistant Editor

EDITORIAL BOARD

C. Guy Lane, M.D.	Maxwell Finland, M.D.
Henry R. Viets, M.D.	James M. Faulkner, M.D.
Robert M. Green, M.D.	Carroll B. Larson, M.D.
Dwight O'Hara, M.D.	Francis D. Moore, M.D.
Fletcher H. Colby, M.D.	C. Stuart Welch, M.D.
Robert L. Goodale, M.D.	Vernon P. Williams, M.D.
Chester M. Jones, M.D.	Benjamin Castleman, M.D.
Harvey R. Morrison, M.D.	Hugh R. Leavell, M.D.

SUBSCRIPTION TERMS: \$7.00 per year in advance, postage paid for the United States (medical students, \$4.00 per year); Canada, \$8.00 per year (Boston funds); \$9.50 per year for all foreign countries belonging to the Postal Union.

MATERIAL should be received not later than noon on Thursday three weeks before date of publication.

THE JOURNAL does not hold itself responsible for statements made by any contributor.

COMMUNICATIONS including those concerning classified advertising but not those regarding other advertising should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts. Telephone KE 6-2094.

NEW ENGLAND ADVERTISING REPRESENTATIVE (except for classified advertising): Edwin B. Tyler, 89 State Street, Boston, Massachusetts. Telephone LA 3-5516.

## VOX POPULI

THE shouting and the tumult have died away, many of the captains and not a few others have departed. If enough hearts are still humble America has weathered another of her periodic domestic crises, established by her inviolate constitution, and has again emerged as the most democratic nation of any consequence in the world.

This same world of mankind nearly half a century ago entered one of its great revolutionary cycles. Two world wars have been incidents in that cycle and persons of prominence, however important they may have seemed as good or evil influences, have been in many ways little more than symbols of the times in which they have lived. The significant forces have been not emperors or presi-

dents or politicians, not dictators or the champions of democracies, but dissatisfaction with their lot in life, and a great desire to change it, of vast segments of the population. Leaders are but levers that help to put the mass in motion and sometimes try to stop it. Once the reaction has started it usually goes on until its temporary destiny is fulfilled.

America's recent pilgrimage to the polls has shown that in the present instance the voice of the people is not that of the turtle. Patience with slow reforms and half measures is gone. All the countries of the world have turned more or less sharply to the left, and it is inevitable that America should also at least incline in that direction. And where else has government of the people, for the people and by the people a better chance of succeeding?

New experiences will come to this country within the next few years. Labor will have a larger share in government than ever before. Medicine will have to find improved methods of bringing its benefits to all the people if it is still to control its own destiny and escape the sloughs of despond into which it has fallen elsewhere.

The duty of every citizen now is to make a temperate democracy the most successful and the most desirable form of government on earth.

## THE MONTH BEFORE CHRISTMAS

THE Christmas Seal Campaign annually calls attention to a widely prevalent disease that, in spite of notable progress in control, accounts for a disheartening number of deaths, many of them avoidable. This year, from November 22 to Christmas Day, the National Tuberculosis Association again conducts its appeal for contributions to a program designed to prevent and control—and eventually to eradicate—tuberculosis. Throughout the land men and women are asked to give what may be regarded as a Christmas present to humanity: the money that provides the sole financial support of the national, state and local associations in their year-round work of control through education, case finding, rehabilitation and medical research.

There is some ground for comfort (but none for complacency) in the fact that since 1904, when the first nationwide, organized campaign against the disease was inaugurated, tuberculosis has declined from first to seventh place among the leading causes of death in the United States. This disease, whose cause is known and for which methods of control and cure are available still accounts for more deaths than any other disease among people from fifteen to forty-four years of age and still kills 50 000 Americans, including more than 1500 children, each year. A recent increase in the number of new cases in New York City and elsewhere\* re-emphasizes the need for constant alertness to the threat of more widespread infection. Careful estimates of 500,000 active cases in the United States are attended by the warning that only half of them are known to health authorities, the remainder of the patients presumably unaware of their infection and receiving no treatment, provide a reservoir from which the disease is easily spread. Education is thus of primary importance, for if people are made conscious of tuberculosis and its cause and means of prevention, they will more readily take action to protect themselves and their neighbors. The National Tuberculosis Association and more than three thousand affiliated organizations, in co-operation with the United States Public Health Service state and local health departments, physicians and nurses, work ceaselessly to persuade every person fifteen years of age and over to have regular x-ray examinations of the chest. In thousands of communities the tuberculosis associations and the local health authorities provide mass x-ray services large groups are examined quickly and at low cost, and in many sections the service is free. This program is based on a sound principle of preventive medicine: no complete control is possible until the unknown cases, which provide the source of infection, are recognized and the patients treated.

No endeavor to alleviate suffering remains unsupported by Americans. Each year, on the eve of the season of rejoicing and good will among men, their generous response to this appeal represents the conviction that man, in many ways, is his

brother's keeper. As a symbol of a united effort of relief and protection for the unfortunate, the Christmas Seal has fulfilled its office justifying the sentiment expressed in the lofty phrases of a great poet and divine of the sixteenth and seventeenth centuries: "Any man's death diminishes me because I am involved in Mankind."

## PENICILLIN FOR PROPHYLAXIS

THE prophylactic use of penicillin is receiving an increasing degree of attention. The drug is almost universally employed before and after tooth extractions or other dental manipulations particularly in patients who are considered to be susceptible to bacterial endocarditis.<sup>1</sup> By the same token, penicillin is given liberally in the treatment or prevention of mild respiratory infections in patients who have had rheumatic fever<sup>2</sup> or in whom subacute bacterial endocarditis has been arrested or cured by penicillin therapy.<sup>3</sup> The administration of penicillin during severe influenza-virus infections or in certain cases of extensive viral pneumonia may also prove useful in preventing the occurrence or spread of bacterial complications. Penicillin has also been used both with and without influenza-virus vaccine in the prophylaxis of upper respiratory infections.<sup>4, 5</sup>

The use of penicillin in the prophylaxis of venereal infections is an obvious corollary to its use in the treatment of these diseases. It is well to bear in mind that although relatively small doses of penicillin are adequate in the prevention of syphilitic infection in the rabbit,<sup>6-8</sup> the use of penicillin in the small doses that are effective in the treatment of simple gonococcal urethritis has been followed, in a number of reported cases, by the development of syphilis from what probably was the same exposure.<sup>9</sup>

A preliminary trial of the use of penicillin tablets for the prevention of gonorrhea<sup>10</sup> has nevertheless yielded encouraging results from the point of view of reducing the incidence of this infection. In the controlled but brief study thus far recorded there has been no evidence of sensitization to penicillin, no apparent development of penicillin-fast strains of gonococci and no recognized instance of suppressed syphilitic infection. Further reports of

\*Editorial: Increase in tuberculosis. *New Eng. J. Med.* 239:796, 1948.

this and other studies will, of course, be awaited with interest

Some observations have already been made also on the administration of oral penicillin instead of sulfonamides for the prevention of recurrences in cases of rheumatic fever<sup>2, 11</sup> It is too soon to evaluate the results in these cases The potential complications of the widespread use of penicillin and particularly the potentialities of producing and disseminating resistant strains by continuous prophylaxis with this antibiotic are as yet unknown The report<sup>11</sup> of the discovery of highly resistant strains of streptococci in children after they had received penicillin prophylactically by mouth for some time is rather disturbing The data in this regard, however, are inadequate for proper evaluation and require confirmation, particularly in view of the fact that these resistant strains have subsequently been eliminated from the same patients by the use of larger oral doses of penicillin and also because the development of resistant strains of hemolytic streptococci has not yet been encountered during treatment of active infections by any other observers

#### REFERENCES

- 1 Glaser R J, Dankner A, Mathes S B and Harford C G Effect of penicillin on bacteremia following dental extraction *Am J Med* 4 55 65 1948
- 2 Malner M M, and Amsterdam S D Oral penicillin in prophylaxis of recurrent rheumatic fever *J Pediat* 31 658-661 1947
- 3 Tumulty P A and Harvey A McG Experiences in management of subacute bacterial endocarditis treated with penicillin *Am J Med* 4 37 54 1948
- 4 Lapin J H Prophylaxis of upper respiratory infections in children by oral penicillin and influenza virus vaccine inoculation *Arch Pediat* 64 121-131 1947
- 5 *Idem* Prophylaxis of upper respiratory infections in children treated with oral penicillin *J Pediat* 32 119 124 1948
- 6 Eagle H, Magnuson H J, and Fleischman R Relation of size of inoculum and age of infection to curative dose of penicillin in experimental syphilis with particular reference to feasibility of its prophylactic use *J Exper Med* 85 423-440 1947
- 7 Rake G, Dunham W B and Donovan R Evaluation of antibiotics by prevention of experimental syphilis *J Infect Dis* 81 122-129 1947
- 8 Eagle H and Fleischman R Relative antisiphilic activity of penicillins F, G, K and X and of bacitracin based on amounts required to abort early syphilitic infections in rabbits *J Bact* 55 341 346 1948
- 9 Meade M and Finland M Penicillin in treatment of gonococcal infections: analysis of results reported in literature through 1945 *Am J Syph Gonorr & Ven Dis* 30 586-609 1946
- 10 Eagle H, et al Prevention of gonorrhea with penicillin tablets: preliminary report *Pub Health Rep* 63 1411 1415 1948
- 11 Milzer, A, Kohn K H and MacLean H Oral prophylaxis of rheumatic fever with penicillin resistant hemolytic streptococci *J A M A* 136 536-538 1948

#### ROSTER OF PHYSICIANS

ACCORDING to the Bureau of Medical Economic Research of the American Medical Association, there were approximately 199,755 living physicians in the United States on June 1, 1948 The Bureau for over a year has been developing a punch-card system of tabulating physicians, and hopes to have the roster completed early in 1949

The most populous state so far as physicians is

concerned is New York, with 30,970 Nevada, with 198 has the fewest Massachusetts stands sixth in line with 9102, of whom approximately two thirds are fellows of the Massachusetts Medical Society

The 3000 who are not fellow members should be our grave concern Those who are eligible for fellowship should be urged to apply Those who are not now eligible but are capable of becoming so should be encouraged to improve their standing in the profession and should be given all possible assistance in making the effort

Fourth-year students in approved medical schools are reminded of the *Journal's* prize essay competition on preventive medicine

For further information see *The New England Journal of Medicine*, September 30, 1948, p 525, or write to the editor

#### MASSACHUSETTS MEDICAL SOCIETY

##### DEATHS

BARNES — Henry Barnes, M.D., of New Bedford, died on May 29 He was in his seventy-first year

Dr Barnes received his degree from Columbia University College of Physicians and Surgeons in 1903 He was chief of staff at Acushnet Hospital and a fellow of the American Medical Association

GLASSMAN — Nathan B. Glassman, M.D., of Boston, died on June 8 He was in his fifty-ninth year

Dr Glassman received his degree from College of Physicians and Surgeons, Boston, in 1916 He was a fellow of the American Medical Association

His widow, a son and a daughter survive

MAILEY — H. Douglas Mailey, M.D., formerly of Andover, died on October 14 He was in his thirty-fourth year

Dr Mailey received his degree from Boston University School of Medicine in 1942 He was formerly radiologist at the Lahey Clinic

His widow, a son, a daughter, his father and two sisters survive

#### MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

##### PREMARITAL AND PRENATAL BLOOD TESTS

Hospital administrators and laboratory directors are informed that it has been brought to the attention of the Department that laboratories not approved for performing premarital and prenatal blood tests have been accepting specimens from physicians to be examined for this purpose They are requested to call to the attention of laboratory personnel that this practice is contrary to law If a laboratory does not appear among those in the following list, physicians should be told that all specimens should go to a laboratory that has approval for doing these tests

LOCATION	LABORATORY
Boston	Boston Dispensary Boston Health Department Commonwealth Clinical Laboratory Learr Laboratory Massachusetts General Hospital Massachusetts Memorial Hospitals (Genitoinfectious Disease Clinic) State Wassermann Laboratory
Brockton	Brockton Health Department
Brookline	Sias Laboratory (Brooks Hospital)
Clinton	Clinton Hospital
Fall River	Union Hospital
Fitchburg	Burbank Hospital
Great Barrington	Fairview Hospital
Holvoke	Holvoke Hospital Providence Hospital
Lowell	Lowell General Hospital
Montague City	Farren Memorial Hospital
New Bedford	Clinical Laboratory St. Luke's Hospital
Newton	Newton-Wellesley Hospital
North Adams	North Adams Hospital
Pittsfield	St. Luke's Hospital House of Mercy Hospital
Salem	Salem Hospital
Springfield	Mercy Hospital
Tewksbury	State Infirmary and Hospital
Westfield	Noble Hospital
Worcester	St. Vincent Hospital Worcester City Hospital Worcester Health Department

Attention is called to the fact that laboratories that have approval for doing rapid blood Hinton tests for transfusions only are not recognized as qualified to perform premarital and prenatal blood tests.

If a laboratory wishes to be added to the attached list, it should seek approval of the Department for a diagnostic serologic test for syphilis.

#### CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

The December schedule for Consultation Clinics for Crippled Children in Massachusetts under the provisions of the Social Security Act follows:

CLINIC	DATE	CLINIC CONSULTANT
Haverhill	December 1	William T. Green
Lowell	December 3	Albert H. Brewster
Salem	December 6	Paul W. Hugenberger
Brockton	December 9	George W. Van Gorder
Greenfield	December 13	Charles L. Sturdevant
Gardner	December 14	Carter R. Rowe
Pittsfield	December 15	Frank A. Slowick
Worcester	December 17	John W. O'Meara
Springfield	December 21	Garry de N. Hough, Jr.
Hyannis	December 23	Paul L. Norton
Fall River	December 27	David S. Grice

Physicians referring new patients to clinics should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

#### MISCELLANY

##### MASSACHUSETTS DEPARTMENT OF EDUCATION, DIVISION OF VOCATIONAL REHABILITATION

Handicapped persons can be helped by the Division of Vocational Rehabilitation, Massachusetts Department of Education, 200 Newbury Street, Boston. The aim of this division is to improve 'the physical, mental, social, vocational and economic usefulness' of all handicapped persons who are over sixteen years of age and who have a mental or physical disability that is a substantial employment handicap. This division may furnish to eligible clients counseling, guidance training in occupations, refresher training and placement.

The medical or surgical treatment for physical or mental handicaps that are static and may be removed or appreciably alleviated within a reasonable period may be purchased by this division. These services are available to those in economic need and are paid on a fee-for-service basis to physicians, surgeons, psychiatrists and other medical agencies of the patient's choice.

For example, through this division crippled persons may be furnished appliances or taught sedentary trades or both. Cardiac patients may learn lighter trades. Newly ruptured persons may have surgical care. Amputees may be provided with artificial limbs.

It is hoped that the recent increase in the all-inclusive per-diem allowance by this division to hospitals servicing its clients will increase the number of co-operating hospitals, making the services more readily available. The all-inclusive per-diem allowance has been increased to \$10 as of October 1, 1948, in hospitals whose per-diem costs per patient are \$10 or over.

The division will be pleased to furnish further information to patients, physicians, hospitals or other agencies concerning this program of vocational rehabilitation and physical restoration.

#### CORRESPONDENCE

##### DEPRIVATION OF LICENSES

*To the Editor:* At the meeting of the Board of Registration in Medicine held October 21, it was voted to suspend for six months the registration of Dr. Glenn F. Muntz, 30 Huntington Avenue, Boston, and to revoke the registration of Dr. R. Reyes Garcia, 1562 Main Street, Springfield.

GEORGE L. SCHATZ, M.D. *Secretary*  
Board of Registration in Medicine

State House  
Boston

#### BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

*History of the Medical Society of the County of Westchester, 1797-1947. A compilation from the available minutes of the Society and various contemporary sources during the years for which the minutes were lost.* 12°, cloth, 193 pp. New York: Medical Society of the County of Westchester, 1947. \$2.50.

This history of a county medical society of New York has been compiled by the current historian, Dr. Laurence D. Redway, from the available minutes of the Society and contemporary sources. The Society was founded in 1797 and has had a continuous existence until the present time. The text is concluded with two short historical sketches of the Department of Public Welfare of the County, and of the Westchester Nursing Association. The book is privately printed. The lack of an index detracts from its reference value.

*The Care and Management of Laboratory Animals Handbook of the Universities Federation for Animal Welfare With an appendix on statistical analysis* By Aastair N Woden, M A (Cantab), B Sc (Lond), M R C V S, A R I C, Milford Professor and director of research in animal health, University College of Wales, Aberystwyth With a foreword by Professor T Dalling, M A, M R C V S, F R S E, director, Veterinary Laboratory, Ministry of Agriculture and Fisheries, Welbridge, Surrey 8<sup>o</sup>, cloth, 376 pp, with 70 illustrations—Baltimore Williams and Wilkins Company, 1947 \$8 50

This handbook, the composite work of a number of experts in animal husbandry, has been produced under the sponsorship of the Universities Federation for Animal Welfare, London The first three chapters deal with law and practice and the laboratory rights of the animal, the animal laboratory, its construction and maintenance, and the pests of the animal house and their control The following chapters are devoted to the care and handling of animals used in laboratory work and their diseases Separate chapters are given to 19 different small animals, birds, amphibia and fresh-water fish An appendix comprises a technical conspectus of the elements of statistical analysis A selected list of references is appended to each chapter Indexes of subjects and authors are appended to the text The volume is well published in every way This exceptional handbook has long been needed and is an essential reference work It should be in all libraries, general and medical, and in all laboratories where animals are kept for research, control and production purposes Likewise, it should prove valuable to all persons handling small animals

*Manual for Laboratory Work in Mammalian Physiology* By Fred E D'Amour and Frank R Blood 8<sup>o</sup>, paper 162 pp, with 207 illustrations Chicago University of Chicago Press, 1948 \$2 75

This manual is based on a group of fifty experiments in which the rat is used exclusively It is hoped that the use of this convenient animal will greatly simplify the problem of laboratory animal supply The materials and equipment and procedure for each experiment are simply described and illustrated The use of anesthesia in the experiments is stressed The binding is the ring-type The text is well printed The manual should prove valuable to students in physiology

*Neuroanatomy* By Fred A Mettler, A M, M D, Ph D, associate professor of anatomy, College of Physicians and Surgeons, Columbia University Second edition 4<sup>o</sup>, cloth, 536 pp, with 357 illustrations, including 33 in color St Louis The C V Mosby Company, 1948 \$10 00

This second edition of a standard textbook has been revised considerably, and material on the blood supply and venous drainage of the various portions of the neuraxis has been added The volume is well published in every way and is an essential book for all medical libraries and for neurologists and neurosurgeons

## NOTICES

### ANNOUNCEMENTS

Dr William L Davis announces the opening of his office for the general practice of medicine at 262 Beacon Street, Boston

Dr Elliot L Sagall announces the removal of his office for the practice of internal medicine to 371 Commonwealth Avenue, Boston

### MOUNT AUBURN HOSPITAL TUMOR CLINIC

A tumor clinic has been established at Mount Auburn Hospital, 330 Mt Auburn Street, Cambridge The clinics are held on Fridays at 1 30 p m in the Out-Patient Department

The services of the clinic are available to private patients on a consultative basis Patients are seen by appointment only An abstract of the referring physician's findings should accompany the patient

At the clinic an examination will be made calling in the necessary consultants in various specialties After examination a group opinion will be given

A letter stating the results of the examination and the opinion will be sent to the physician The patient will be directed to return to him

The fee for this examination and opinion will be \$10 00

If special examinations, biopsy, laboratory, x-ray, endoscopy and so forth are thought necessary, the referring physician will be notified

Appointments can be made by telephone (TRowbridge 6-5680, Extension 219)

### MASSACHUSETTS GENERAL HOSPITAL RESEARCH COUNCIL

A meeting of the Massachusetts General Hospital Research Council will be held in the Bigelow Amphitheater on Wednesday, December 1, at 4 30 p m

#### PROGRAM

The Effects of Experimental Potassium Deficiency, Lutt I Gardner, Charles D Cook, Helen Berman, Elsie A MacLachlan and Nathan B Talbot (twenty minutes)

Recent Developments in the Study of the Metabolic Functions of the B Vitamins Nathan O Kaplan (twenty minutes)

### NEW ENGLAND HOSPITAL FOR WOMEN AND CHILDREN

The monthly clinical conference and meeting of the staff of the New England Hospital for Women and Children will be held on Thursday, December 2, at 7 15 p m, in the classroom of the Nurses' Residence Dr Harold H Rosenfield will discuss the subject "Some Abnormalities of the Third Stage of Labor Presentation of cases" Dr Mabelle C Hiscock will be chairman

### NEW ENGLAND HEART ASSOCIATION

A meeting of the New England Heart Association will be held at the Massachusetts General Hospital on Monday, December 6, at 8 15 p m, Dr Paul D White presiding

#### PROGRAM

Syphilitic Aortic Regurgitation A follow-up study of 100 cases Drs James H Currens and William R Hill

A Venous Shunt for Marked Mitral Stenosis Drs Edward F Bland and Richard H Sweet

Prognosis in Essential Hypertension Eight-year follow-up of 430 cases Drs Robert S Palmer, Dorothea Loeb-bourrow and Carl Doring

Effect of Skin Resistance in Relation to the Newer Electrocardiographic Leads Dr Hsueh-hwa Wang, Mr Maurice Rappaport and Dr Conger Williams

Physique in the Young Coronary Patient Drs Stanley Garn and Menard M Gertler

The National Heart Institute Dr Paul D White

Interested physicians and medical students are cordially invited to attend

### NEW ENGLAND SOCIETY OF ANESTHESIOLOGISTS

A meeting of The New England Society of Anesthesiologists will be held in the auditorium of Building A, Boston University School of Medicine, 80 East Concord Street, Boston, on Tuesday, December 14, at 8 00 p m The program will include the following reports on medical missions to Europe

Mission to Germany Dr Henry K Beecher

Mission to Poland Dr Meyer Saklad

Physicians and medical students are invited to all meetings

(Notices concluded on page xv)

# NOTICES (Concluded from page 844)

## SOCIETY MEETINGS AND CONFERENCES

### CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, DECEMBER 2

- THURSDAY DECEMBER 2**  
 7:15 p.m. Monthly Clinical Conference and Staff Meeting New England Hospital for Women and Children classroom of Nurses Residence
- FRIDAY DECEMBER 3**  
 9:00 a.m.-12:00 p.m. Combined Medical and Surgical Staff Rounds Peter Bent Brigham Hospital.  
 12:00 p.m. Ray Conference Margaret Jewett Hall, Mt Auburn Hospital Cambridge
- MONDAY DECEMBER 6**  
 12:15-1:15 p.m. Clinicopathological Conference Main Amphitheater Peter Bent Brigham Hospital  
 3:15 p.m. New England Heart Association Massachusetts General Hospital
- TUESDAY DECEMBER 7**  
 12:15-1:15 p.m. Clinicorontgenological Conference Peter Bent Brigham Hospital  
 1:30-2:30 p.m. Pediatric Rounds Brnham Memorial Hospital for Children Massachusetts General Hospital
- WEDNESDAY DECEMBER 8**  
 11:00 a.m.-12:00 p.m. Medical Rounds Amphitheater Children's Hospital  
 12:00 p.m.-1:00 p.m. Clinicopathological Conference (Children's Hospital) Amphitheater Peter Bent Brigham Hospital  
 2:00-3:00 p.m. Combined Clinic by the Medical Surgical and Orthopedic Services. Amphitheater Children's Hospital

\*Open to the medical profession

- OCTOBER 1-MAY 20** Metropolitan State Hospital Page 418 issue of September 9
- NOVEMBER 30** Boston City Hospital House Officers Association Page 762 issue of November 11
- NOVEMBER 17-JANUARY 26** Boston State Hospital Psychiatric Seminar Schedule Page 762, issue of November 11
- NOVEMBER 30** Hampden District Medical Society Page 492 issue of September 23
- DECEMBER 1** New England Dermatological Society Page 800 issue of November 18
- DECEMBER 1** Massachusetts General Hospital Research Council Page 644
- DECEMBER 2** New England Hospital for Women and Children Page 644
- DECEMBER 2** Suffolk Censors Meeting Page 492, issue of September 23
- DECEMBER 4** American Federation for Clinical Research Page 644 issue of October 21
- DECEMBER 4-9** American Academy of Dermatology and Syphilology Page 725 issue of November 4
- DECEMBER 6** New England Heart Association Page 844
- DECEMBER 6-8** American Academy of Allergy Fifth Annual Meeting Clifton-Haddon Hall Hotel Atlantic City New Jersey
- DECEMBER 7-9** Southern Surgical Association Annual Meeting Page 543 issue of April 8.
- DECEMBER 9** Recent Advances in Thoracic Surgery Dr Joseph P Lynch. Pentucket Association of Physicians. 8:30 p.m. Haverhill
- DECEMBER 9 and 10** New York State Society of Anesthesiologists Page 34 issue of July 1
- DECEMBER 14** New England Society of Anesthesiologists Page 844
- FEBRUARY 4 1949** American Board of Obstetrics and Gynecology Inc. Page 244 issue of August 5
- MARCH 7-9 1949** American Academy of General Practice Page 728 issue of November 4
- MARCH 28-APRIL 1 1949** American College of Physicians Page 158 issue of July 22
- MAY 16-19, 1949** American Urological Association Baltimore Hotel Los Angeles California
- MAY 26-28 1949** American Gout Association. Hotel Lorraine Madison Wisconsin
- MAY 30-JUNE 5 1949** International Congress on Rheumatic Diseases. Page 800 issue of November 18
- NOVEMBER 11-17 1949** Third Inter American Congress of Radiology Page 158 issue of July 22.

## DISTRICT MEDICAL SOCIETIES

- BAMFIDE**  
 November 30 8:30 p.m. Academy of Medicine Springfield. Caroma of the Breast. Dr. Grantley W. Taylor
- MIDDLESEX EAST**  
 JANUARY 19  
 MARCH 23  
 MAY 11
- SUFFOLK**  
 DECEMBER 2. Suffolk Censors Meeting
- WORCESTER NORTH**  
 DECEMBER 15 Leominster Hospital Leominster  
 FEBRUARY 23 Burbank Hospital Fitchburg  
 APRIL 27 Annual Meeting



*Take a leaf from the book of Doc Wise  
 Whom his patients all praise to the skies  
 He reads every ad  
 In the Journal, begad,  
 And knows all the wherefores and whys*

5

## MEDICAL CORRESPONDENCE COLLEGE

19, WELBECK STREET LONDON W 1, ENGLAND

PROVIDES postal courses of instruction for medical students and practitioners for all medical and dental examinations, including all U S A and Canadian examinations

Special courses for the higher examinations in surgery for the Fellowship examinations

Free guide to medical and dental examinations on application to the Secretary

Please state for which examination you desire preparation Address the Secretary Medical Correspondence College, 19 Welbeck St, London W 1 England

## Xenopus laevis FROG test

**1 day**

## PREGNANCY TEST



Complete reading in twenty four hours, with a positive result often obtained in eight hours

The Xenopus laevis test is well established as a quick, accurate and economical test for pregnancy

New Eng J Med 231 781 1946

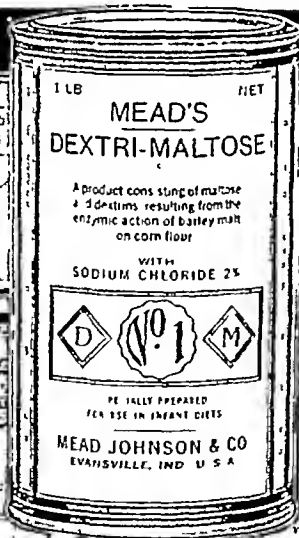
Correctly designed mailing cases for all laboratory tests are promptly furnished on request Results are telephoned to physicians anywhere in New England, followed by a written report

**JAMES QUINN LABORATORY**  
 471 Commonwealth Avenue  
 Boston 15, Mass. Ken. 1356

# BACKGROUND

The use of cow's milk, water and carbohydrate mixtures represents the one system of

infant feeding that consistently, for over three decades, has received universal pediatric



recognition No carbohydrate employed in this system of infant feeding enjoys so rich and enduring a background of authoritative clinical experience as Dextri Maltose

# The New England Journal of Medicine

Copyright 1948 by the Massachusetts Medical Society

Volume 239

DECEMBER 2 1948

Number 23

## NONTUBERCULOUS SPINAL EPIDURAL INFECTIONS\*

A PRICE HEUSNER, M.D.†

BOSTON

**N**ONTUBERCULOUS spinal epidural infections are infrequent disorders that merit periodic reconsideration by the profession at large because of the heavy responsibility accruing to the practitioner who first visits a patient thus afflicted. Final diagnosis and definitive treatment of these infections are now regarded as functions of specialists, but the decisive factor in the outcome of most cases is the celerity with which the first attending physician suspects the probable nature of the ailment and summons expert aid. Thus early diagnosis leading to prompt surgical intervention is regularly rewarded by total recovery. On the other hand, even brief delay of operation can vitiate all subsequent efforts to avert permanent paraplegia or quadriplegia with an attending loss of control over bladder and bowel, an insensible skin predisposed to bedsores and a host of secondary complications inherent in this type of disability. Such crippling effects are traceable to the fact that undrained spinal epidural sepsis can produce irreversible neurologic damage with tragic suddenness, and numerous attempts<sup>1-4</sup> have been made to ensure universal recognition of this dreadful potentiality. Nevertheless, enduring paralyses continue to follow in the wake of these lesions with unnecessary frequency.

It is clearly a matter of general interest to inquire into the factors that seemingly perpetuate these costly delays. Such is the main purpose of this paper, and its conclusions may be anticipated to the extent of declaring that the situation will be rectified only when the entire medical profession becomes sufficiently familiar with the clinical aspects of epidural inflammation to suspect its presence at a preparalytic phase of the disorder. During this remediable stage, the illness is almost routinely mistaken for some more everyday ailment, and in far too many cases the patient reaches the surgeon only after paralysis is complete and all hope for restoration of function has vanished.

The present study will also be of interest to specialists in the field. The literature contains reports on more than 200 cases of spinal epidural sepsis and several excellent review articles,<sup>2-5</sup> but clinical papers have with few exceptions<sup>2,3,6</sup> dealt with one or at most a few cases. No analysis of the clinical features of a relatively large group of cases treated in one clinic is available. Nor has any article attempted either to describe the role or to estimate the value of modern antibacterial agents in a large series of such cases. Information on these matters together with a note on the mechanism of the paralyses is here presented.

### MATERIAL AND CLASSIFICATION

The present report is based upon an analysis of the 20 consecutive cases of nontuberculous spinal epidural infection receiving definitive treatment in this clinic since its organization in 1930.†

It is customary to divide the lesions under consideration into acute spinal epidural abscesses, including metastatic and osteomyelitic, and chronic spinal epidural granulomas. More elaborate nomenclatures have been proposed<sup>5</sup> wherein etiologic pathologic, anatomic and temporal designations are compounded into long, hyphenated names that are both more descriptive and of more prognostic import than those of the above classification. Unfortunately, these are too cumbersome for ordinary usage. The present material is therefore presented under a modification of the customary classification: acute spinal epidural infections, including metastatic and osteomyelitic, and chronic spinal epidural infections, including metastatic and osteomyelitic.

As the names suggest the first variety runs a rapid clinical course while the second develops insidiously. It is important to retain this distinction in clinical tempo if only to stress that surgical urgency increases *pari passu* with the rate of clinical

†During this eighteen year period paraplegic patients with burned-out epidural sepsis have come to this clinic for rehabilitation, but their definitive treatment had been carried out elsewhere and they are not included in this study. Also omitted from consideration here are patients who suffered from tuberculous, syphilitic and coccal epidural infections and a few cases of spinal epidural sepsis all concurrently treated.

\*From the Department of Neurosurgery, Boston City Hospital.

†Instructor in neurology, Harvard Medical School; associate surgeon for neurosurgery, Boston City Hospital.

evolution. If this concept is borne in mind, cases unfolding at a subacute rate will automatically be deemed urgent, and a third major category may thus be safely avoided. As is shown below, prognostic implications probably justify the continued

does not enable one regularly to predict whether abscess or granuloma will be found.

#### ETIOLOGY

It is generally agreed that a spinal epidural infection is traceable to a primary focus of inflam-

TABLE 1 *Etiologic, Pathologic and Clinical Data on Boston City Hospital Series*

SYNDROME	CASE No	AGE	SEX	SITE OF LESION	AXIAL EXTENT IN SEGMENTS	PRIMARY FOCUS	OTHER FOCI AND TRAUMA	BLOOD CULTURE*	CHILL
Acute metastatic	1	16	F	D10-L1	4	Furuncle	0	Negative	Present
	2	64	M	D2	1	Cystotomy wound	0	Not done	Absent
	3	19	M	D9-L1	5	Acne	0	Negative	Absent
	4	13	M	L1-L5	5	None found	Fall on buttocks	Positive	Absent
	5	14	F	D2-D5	4	Infected corn	0	Negative	Absent
	6	57	M	D5-D5	5	Empyema sinus	0	Not done	Absent
	7	64	M	L4	1	None found	Injury to back from lifting	Negative	Absent
	8	14	F	D2-D6	5	None found	Injury to back while skating	Not done	Absent
	9	14	F	D10-L5	7	Pyelitis	0	Positive	Present
	10	29	F	D10-L4	6	Acne	0	Not done	Present
	11	16	M	D6-D10	5	Cellulitis of forearm	Injury to back (football)	Positive	Present
	12	37	M	D3-D7	5	None found	0	Negative	Present
Acute osteomyelitic	13	51	M	D5-D6	2	Caries D9 centrum	0	Negative	Absent
	14	47	F	D5-D9	2	Caries D8 centrum	Sepic nephrectomy	Positive	Absent
	15	36	M	D8-D10	3	Caries D9 laminae	Chronic acne	Positive	Present
	16	51	F	C5-C6	2	Caries C5 and C6 centra	0	Not done	Absent
	17	57	M	C5-D2	5	Caries C5 and C6 centra	0	Negative	Absent
	18	61	M	D7-D9	3	Caries D9 centrum	Cellulitis of toe stump	Positive	Present
Chronic metastatic	19	28	F	D9-D10	2	None found	(?) Grippe	Negative	Absent
Chronic osteomyelitic	20	51	M	C5-C6	2	Caries C5 and C6 centra	0	Not done	Absent

\*In all positive cultures *Staphylococcus aureus* was the organism involved.

recognition of metastatic and osteomyelitic subdivisions within each major category. In the former group, no vertebral osteomyelitis is demonstrable, whereas in the latter, a spinal caries appears to be the reservoir of sepsis from which the

mation located elsewhere in the body either near to or remote from the epidural compartment. In the former case, invasion of this space is thought to occur either by *direct extension* from such a focus as a pre-existing vertebral (or costal) osteomyelitis,

TABLE 1 (Continued)

CASE No	TEMPERATURE °F	SPINAL Ache	ROOT Pain	HEADACHE	STIFF NECK	BLOOD		CEREBROSPINAL FLUID	
						WHITE-CELL COUNT $\times 10^3$	PACK	WHITE CELLS per cu mm	PROTEIN mg/100 cc
1	102.0	Present	Present	Absent	Present	20.0	Present	200	770
2	102.0	Present	Absent	Absent	Absent	9.4	Present	Not done	414
3	101.0	Present	Present	Absent	Absent	14.5	Present	64	1920
4	103.0	Present	Present	Absent	Present	13.0	(Pus)	20	258
5	102.4	Present	Present	Absent	Present	19.0	Present	2	616
6	Normal	Present	Present	Absent	Absent	7.2	Present	—	—
7	101.0	Present	Absent	Absent	Absent	16.0	(Pus)	41	166
8	102.0	Present	Present	Absent	Absent	19.0	Present	—	—
9	103.0	Present	Present	Present	Present	15.5	(Pus)	11	Clot
10	103.0	Present	Present	Present	Present	16.0	Present	720	2000
11	101.0	Present	Absent	Present	Present	24.0	Present	2	167
12	101.0	Present	Absent	Absent	Present	13.6	Present	7	558
13	100.0	Present	Absent	Absent	Absent	15.0	Present	21	570
14	103.0	Present	Present	Absent	Absent	11.4	Present	Not done	Not done
15	103.0	Present	Absent	Absent	Absent	16.4	Present	114	286
16	103.0	Present	Present	Present	Present	11.3	Present	2	1000
17	99.4	Present	Present	Present	Present	17.0	Present	2	111
18	99.4	Present	Present	Absent	Absent	10.7	Present	35	2000
19	Normal	Present	Present	Absent	Absent	6.0	Present	45	800
20	Normal	Present	Present	Absent	Present	10.5	Present	—	—

epidural lesion arises. It is preferable, however, to speak simply of acute and chronic "infections" rather than to imply a fixed correlation between the age of a lesion and its gross pathological appearance. This is because the chronicity of an infection

or by *lymphatic spread* from a paraspinal lesion such as a retropharyngeal abscess or a mediastinal infection. In osteomyelitic cases, the caries, in its turn, may sometimes be traced to a remote reservoir of sepsis such as a chronic acne. In cases in which

a distant focus is the direct source of the epidural lesion, bacteria are believed to reach the normal epidural fat (a *locus minoris resistentiae*) by *hematogenous metastasis* from a furuncle, cellulitis, pyleitis or the like. *Direct inoculation* of the epidural tissues as a result of faulty asepsis during the performance of spinal puncture, or by penetrating wounds of the spine, is said to be another mechanism capable of exciting epidural suppuration but no example has been encountered in this clinic.

It must be admitted that in a few of the presumed metastatic cases, exhaustive searches fail

the appraisal of any puzzling spinal ache or paretic ailment.

Table 1 summarizes the etiologic data on the present material.

The bacteriologic uniformity of these cases is striking. *Staphylococcus aureus* was recovered in pure culture from the epidural space of every patient except 1 (Case 20) in whom no cultures were made. It is generally agreed that this is the most frequent offending organism, but it is also reported<sup>2, 3, 5</sup> that the pneumococcus, streptococcus, *Bacillus pyocyaneus* (*Pseudomonas aeruginosa*), ty-

TABLE 1 (Continued)

CASE No	DIAGNOSIS OF FIRST ATTENDING PHYSICIAN	DURATION OF SPINE ACHES BEFORE OPERATION days	NEUROLOGIC STATUS AT OPERATION	YEAR OF TREATMENT	MEDICAL ADJUNCT	END RESULT
1	Spinal tumor	6	No weakness	1935	None	Complete recovery
2	Spinal infection	5	Paralysis (6 days)	1934	None	Death from pneumonia on 18th postoperative day
3	Acute rheumatoid arthritis	5	Paralysis (24 hr)	1936	None	Complete recovery
4	Meningitis	5	Paralysis (24 hr)	1937	None	Complete recovery
5	No diagnosis ventured	6	Paralysis (48 hr)	1938	None	Survival (with spastic paralysis)
6	Hysteria or ethanolic polyneuritis	24	Paralysis (24 hr)	1938	None	Complete recovery
7	Sacroiliac disease	5	Paralysis (24 hr)	1938	None	Death from uremia and pneumonia on 9th postoperative day
8	Hysteria or cancer of uterus, with metastases	11	Paralysis (3 days)	1941	Sulfathiazole	Survival (with spastic paralysis)
9	Meningitis	8	Weakness only	1945	Sulfadiazine and penicillin	Complete recovery
10	Osteomyelitis of spine	21	Weakness only	1946	Sulfadiazine and penicillin	Complete recovery
11	Meningitis	12	Weakness only	1947	Sulfadiazine and penicillin	Complete recovery
12	Infectious polyneuritis	5	Weakness only	1948	Sulfadiazine and penicillin	Complete recovery
13	Osteomyelitis of spine	41	Paralysis (24 hr)	1938	None	Death from pneumonia and lung abscess on 14th postoperative day
14	Osteomyelitis of spine	14	Paralysis (48 hr)	1942	Sulfadiazine	Death from uremia and pneumonia on 15th postoperative day
15	No diagnosis ventured	5	Paralysis (48 hr)	1944	Sulfadiazine and penicillin	Survival (with spastic paralysis)
16	Cervical neuritis	5	Paralysis (36 hr)	1946	Sulfadiazine and penicillin	Survival arms recovered patient walks with crutches but without braces
17	Spinal tumor	30	Severe weakness	1946	Sulfadiazine and penicillin	Complete recovery
18	Osteomyelitis of spine	38	Severe weakness	1947	Sulfadiazine and penicillin	Survival (only slight neurologic improvement)
19	Spinal tumor	60	Severe weakness	1947	Sulfadiazine and penicillin	Complete recovery
20	Spinal tumor	45	Severe weakness	1943	Sulfathiazole	Complete recovery

to uncover primary foci, and, as might be expected, no remote focus can be found for the vertebral caries in a high percentage of the osteomyelitic cases. Some authors<sup>6</sup> hold that all cases are but complications of a vertebral osteomyelitis that frequently escapes detection only because the search for it is seldom diligent. Others<sup>7</sup> dissent from this contention, and while there is more to be said on this score, I pause over it here merely to emphasize that antecedent infections outside the epidural compartment are of such frequent occurrence (75 per cent of cases in this series) as to be worthy of detailed inquiry in

phoid bacillus and other bacteria are occasionally found. (This discussion does not concern the frequent epidural extensions from tuberculous caries or those sometimes arising from actinomycotic and echinococcal disease.)

Table 1 shows that among the 18 acute cases, antecedent infections outside the epidural space were discovered in 14 (78 per cent). These foci were skin lesions in 7 (39 per cent), vertebral osteomyelitis in 6 (33 per cent) and pyleitis in 1 (6 per cent). The role of cutaneous infections is really greater than the 39 per cent indicates because

lesions of this type were the remote sources for the spinal caries in 2 of the acute osteomyelitic cases (Cases 15 and 18), thus raising the over-all incidence to 50 per cent among acute cases

Among skin infections, acne and furuncles were most frequent. They appeared to be the primary foci for 3 of the acute metastatic (Cases 1, 3 and 10), and the remote focus for the spinal caries in 1 of the acute osteomyelitic cases (Case 15). Of the former group, the most recent pustules had appeared healed for several days prior to the onset of the spinal disease, and blood cultures were sterile in the 2 cases in which they were obtained. In the latter case, however, the acne was active, and *Staph aureus* was recovered from the blood stream as well as from the epidural space.

Infected operative sites, cutaneous in 3 cases and deep in 1, appeared to be the primary foci for 2 acute metastatic lesions and the distant foci for the spinal caries in 2 acute osteomyelitic cases. The 3 cellulitides involved an amputated toe (Case 18), a suprapubic cystotomy wound (Case 2) and a virtually healed empyema sinus (Case 6), the deep operative sepsis was proved by autopsy to be in an apparently healed nephrectomy bed (Case 14). In all these patients the foci were active at the onset of spinal symptoms, and blood cultures were positive for the *Staph aureus* in the only 2 cases (Cases 14 and 18) in which such studies were made.

The remaining cutaneous foci, an infected corn (Case 5) and a traumatic cellulitis of the forearm (Case 11), were found to antecede acute metastatic lesions. Both were suppurating at the onset of the spinal symptoms, and blood culture, omitted in Case 5, yielded the *Staph aureus* in Case 11.

In 1 acute metastatic case (Case 9), a pyelitis was demonstrated by pyelography. *Staph aureus* was found in the urine, the blood stream and the epidural space.

Of the chronic lesions, that in Case 20 was osteomyelitic but without discernible remote focus from which the caries might have arisen. In this case, neither blood nor wound cultures were obtained. The other chronic lesion (Case 19) was without spinal caries or detectable distant focus. The blood culture was sterile on the fifty-fifth day of the illness but might have been otherwise during a bout of "grippe" that antedated spinal symptoms by several days.

Among the 6 acute osteomyelitic cases there were 3 (Cases 13, 16 and 17) in which no remote foci for the caries were found. In none of these was a bacteremia demonstrated after the onset of neurologic symptoms, nor did trauma appear in the histories.

In 4 of 12 acute metastatic cases no primary foci could be discovered, but 3 patients (Cases 4, 7 and 8) had suffered recent, though mild, closed spinal injuries (Table 1) — of the entire series of 20 patients, only 1 other (Case 11) gave a history of trauma.

Blood cultures, made in 3 of these cases, yielded *Staph aureus* only in Case 4.

Sex appeared to play no role in susceptibility to these lesions. On the other hand, a difference of age incidence between the metastatic and the osteomyelitic categories is readily apparent. The average ages at onset were 29.6 and 50.6 years respectively. This difference is more arresting if it is noted that among the 7 osteomyelitic cases, no patient was younger than 36 years, whereas among the 13 metastatic cases there were 7 patients in the teens and 2 in the twenties. Any significance attaching to this difference is not clearly evident, but, taken in conjunction with pathologic, clinical and prognostic dissimilarities yet to be considered, it influences me to retain the distinction between metastatic and osteomyelitic syndromes.

It must be emphasized that the foregoing list does not exhaust the causative possibilities. Indeed, cumulative experience<sup>2-6, 8</sup> indicates that almost any reservoir of sepsis caused by almost any pyogenic organism can occasion the development of an epidural lesion either directly by a hematogenous implant or sequentially by extension from an intermediately excited vertebral caries.

#### PATHOLOGY

Once established in the epidural space, infection spreads axially along the surface of the dural tube. Pus and granulomatous tissue in differing proportions usually accumulate in greatest amounts over the dorsum of this tube and exhibit little tendency to encircle it, although in osteomyelitic cases they occupy one or the other lateral epidural gutter at their site of origin from the bony lesion. Rarely, a lesion of bony origin is confined to the ventral compartment of the spinal canal. It is not entirely clear why the products of inflammation are thus deployed, but two discernible factors may be partially explanatory: the dorsal region is the normal disposition of the epidural fat, which, like adipose tissue elsewhere, offers little resistance to infection, and the ventral surface of the dural tube is moderately adherent to the underlying spinal ligaments, thereby affording a mechanical deterrent to the spread of infection that does not obtain dorsally where the dura lies free from the vertebral arches.

Among the acute cases, the epidural portion of the lesion was always predominantly granulomatous tissue. Usually, the red, friable tissue contained several tiny locules of pus that varied in amount from a mere droplet to 1, or at most, 2 cc. In 1 case (Case 6), however, no macroscopic pus was present, this lesion was thus a true "granuloma."

In 1 of the 2 chronic cases (Case 20), the lesion was a ventrally placed granuloma atop a cervical caries. In the other, a metastatic case (Case 19), the lesion consisted of two contiguous cocoons of granulomatous tissue, each containing about 5 cc of pus. The walls of these cocoons were friable.

and not fibrous, but this lesion was more nearly an "abscess" than that of any other case in the entire series

Table 1 shows the axial extent of all lesions as determined by operative inspection. Among the 12 acute metastatic cases, this varied from 1 to 7 laminae with an average length of 4.3 bony segments. The 6 acute osteomyelitic lesions ranged within the narrower limits of 2 to 5 laminae, but, of more importance, they averaged only 2.8 segments. There is, then, less tendency for the osteomyelitic cases to spread axially within the epidural space. Their extensions beyond this compartment also differ from those of the metastatic cases both as to direction and as to type.

In acute osteomyelitic lesions, extensions beyond the epidural space were confined to ventrally placed sequestra (Case 14), frank pus issuing from an underlying paravertebral abscess (Case 18) and supuration of a lamina (Case 15). The last case was the only 1 of the entire series of 20 patients in which laminar involvement was either suspected at the time of operation or subsequently proved by biopsy or x-ray study. The other acute osteomyelitic cases had disease of the vertebral bodies only. This was detected by preoperative roentgenographic examination in Cases 13, 14 and 18. The preoperative study in Case 17 was reported as uninterpretable, but caries was confirmed by biopsy and by postoperative x-ray examination. In Case 16 the epidural extension provoked neurologic trouble so suddenly (on the third day) as to preclude the preoperative roentgenographic demonstration of caries. Laminar biopsy was likewise nonconfirmatory, but postoperative x-ray study revealed caries of two cervical centra.

In acute metastatic cases, extensions beyond the epidural compartment were of quite a different nature. Pus often burrowed dorsally through the yellow ligaments to dissect along intermuscular planes (Cases 4, 5, 8, 9 and 10) or even to penetrate the lumbodorsal fascia and attain a subcutaneous position (Case 11). In no case was a ventral extension found, nor was caries demonstrated by biopsy or by roentgenographic studies in either the preoperative or the postoperative periods. Admittedly, as some<sup>6</sup> contend, this might have been overlooked, but an intensified search during recent years has failed to establish an osteomyelitic basis for an increased percentage of cases in this clinic. Moreover, there are clinical and prognostic differences yet to be added to those of age incidence and pathology that appear, collectively, to warrant adherence to the old practice of distinguishing between metastatic and osteomyelitic syndromes.

Of more interest, however, is the effect of epidural sepsis upon the underlying neural elements. So tough is the dura that its penetration by bacteria was not achieved in any of the present cases although some of them had woefully belated treatment.

Penetration of the dura is said to occur,<sup>2</sup> but it is so rare that, upon the whole, the paralyzing effects of these lesions are to be accounted for by extradural phenomena.

In most discussions, the paralyses are ascribed either to mechanical compression or to some vaguely defined alteration in the blood supply of the neural tissue. Compression is the most obvious mechanism to invoke because the lesions are space-occupying. This explanation has not been universally accepted, however, because there are those who believe that the neurologic damage inflicted by an acute epidural infection is sometimes out of all proportion to the pressure it exerts. Also, it has been remarked that neural tissue appears less able to withstand the compressive action of inflammatory masses than that of noninflammatory lesions such as spinal tumor and cyst, the changes provoked by the former seem to be more abrupt in onset, more rapid in progression and less readily reversible. It is possible that any such apparent differences in tolerance can be explained away by variations in the amounts of pressure exerted by inflammatory and noninflammatory masses respectively, by dissimilarities in their respective rates of pressure increment or by inequalities in the axial extent (or area) of their application. Nonetheless, many surgeons have felt the need for a mechanism other than simple compression to explain the neurologic features of spinal epidural sepsis.

To meet this need, most authors postulate a blood-circulatory disturbance, but only Browder et al.<sup>6</sup> provide a specific illustration of such a mechanism. They present a specimen from a fatal case in which epidural arterial thromboses are seen in conjunction with myelomalacia. Hassin<sup>7</sup> made a detailed study of another fatal case and concluded that in his patient the fault lay in a stagnation of the spinal fluid although the pathologic picture was otherwise similar to that created by simple compression.

It is obvious that more and critical observations are needed to clarify this issue. It is my impression that the compressive action of these lesions, like that of noninflammatory masses, may harm neural tissue directly, or indirectly either by impairing its intrinsic circulation or through a pressure occlusion of epidural blood vessels, especially veins. A slowing of the blood flow in vessels surrounded by purulence would pave the way for thromboses and permanent neurologic damage. In this way, the action of inflammatory lesions might indeed be found to differ from that of noninflammatory masses.

#### CLINICAL SYNDROMES AND DIFFERENTIAL DIAGNOSES

Spinal epidural sepsis produces clinical syndromes that differ from one another not only in tempo but also in their respective epiphenomena. There is,

however, a basic clinical pattern common to all variants, it consists of the following march of events

Phase I	Spinal ache	
Phase II	Root pain	
Phase III	Weaknesses of	{ voluntary muscles sphincters sensibilities
Phase IV	Paralyses	

In acute cases, the epiphenomena, in the form of signs and symptoms of unrestrained sepsis, may mask this basic pattern, but it is always present and requires only to be considered and inquired into. Also shared by all syndromes is the characteristic total (or but slightly subtotal) subarachnoidal block of the spinal fluid. If the spinal needle does not encounter epidural pus and thereby terminate the procedure at this depth, it finds yellowish spinal fluid showing a high protein content, usually a few white cells, but neither chemical nor bacteriologic evidence of leptomeningitis.

Details of the clinical data in this series of cases are given in Table 1. The broad features of the several syndromes may profitably be summarized around parenthetical comments upon frequent errors in diagnosis.

#### *Acute Metastatic Syndrome*

This illness (an obviously septic disorder) begins with an aching pain at the affected level of the spine. The pain soon becomes more severe and may bring the patient to his doctor within twenty-four hours. At this stage, fever and localized tenderness over the spine may be the only signs, but suspicion should be aroused if the history uncovers an extraspinal focus of chronic infection, recent injury to the spine or a chill (42 per cent of cases). Too often the case is dismissed as one of lumbago, arthritis, grippe or traumatic strain without provision for adequate follow-up care.

In most cases, however, the physician is first consulted on the second or third day of the illness when Phase II of the syndrome begins with root pains radiating from the now exquisitely tender spinal segment. These symptoms are sometimes construed as those of an acute "neuritis" even though the severity of the attending malaise, fever, tachycardia and leukocytosis (average white-cell count 15,600) is clearly inconsistent with this diagnosis. Although palsies are still wanting, the occasionally proffered diagnosis of acute arthritis is untenable because headache (25 per cent of cases), stiffness of the neck (58 per cent of cases) and reflex changes compatible with the anatomic level of the lesion—that is, depression of the deep tendon reflexes if it overles the cauda equina, or heightening of them if over the spinal cord—are sufficiently evident in some combination to direct attention toward the central nervous system and to indicate the need for

diagnostic spinal puncture. *By this procedure the correct diagnosis can and should be made before the end of Phase II of this syndrome.* It must be emphasized that this maneuver is safe only if undertaken by one who is both technically skillful and fully acquainted with the gross pathology of the suspected lesion. Otherwise, infection may inadvertently be carried from the epidural into the subdural or the subarachnoidal space, or both. In proper hands, however, the procedure incurs no risk that is not fully vindicated by the penalties of procrastination. In general, there is no more justification for the diagnosis of this disorder to await the appearance of paralyses than for the diagnosis of brain tumor to await coma.

If still untreated, the disease enters Phase III, in which motor weaknesses, gradually ascending numbness and impaired control over bladder or bowel supervene either concurrently or in any sequence. All the general signs of infection are intensified, the spinal ache becomes excruciating, and nuchal rigidity is apt to be extreme. At this stage, the usual mistakes are those of diagnosing leptomeningitis, poliomyelitis or infectious polyneuritis. The palsies should suffice to exclude meningitis, sensory defects and localized spinal tenderness should exclude poliomyelitis just as the latter finding is entirely out of keeping with polyneuritis. However, all doubt can be dispelled by spinal puncture because none of these diseases cause the block or the spinal-fluid formula characteristic of epidural sepsis.

If further neglected, the illness rapidly enters upon Phase IV, in which complete paralyses are conjoined with toxic prostration and even local tumor, *rubor et calor* if pus has attained a subcutaneous position. Such a state of affairs or even death itself may be reached within as few as six days. Occasionally, transition from Phase II to Phase III is delayed several days or even longer than a week, but passage from the latter to the paralytic stage is always rapid.

#### *Acute Osteomyelitic Syndrome*

As a general rule, this illness (an obviously septic disorder) differs clinically from the metastatic syndrome in only two respects: transition from Phase I to Phase II is delayed several days or even a few weeks—once Phase II is reached, however, the illness progresses with great rapidity, and vertebral caries is usually demonstrable by x-ray examination. Occasionally, the epidural extension from the caries arises very early (as in Case 16), bony changes cannot be shown by preoperative x-ray studies, and the illness appears to be metastatic until biopsy or postoperative roentgenographic examination proves it otherwise.

Differential diagnosis in the most acute cases is as outlined for the metastatic syndrome with one additional consideration. Acute vertebral osteomyelitis, uncomplicated by an epidural extension,

simulates Phase I of the syndrome under discussion. Development of an epidural extension is said to be quite infrequent,<sup>9</sup> but it must be given serious contemplation if root pains appear. A careful neurologic base-line is drawn at once, and the subsequent appearance of reflex alterations, paresthesias, weakness of the limbs or impaired functioning of the bladder calls for diagnostic spinal puncture, which *clarifies the issue immediately*.

Usually, however, the disease unfolds at a slower rate and roentgenographic changes in the spine make it necessary to consider tuberculosis. The epiphenomena of sepsis serve to exclude neoplasia, in most cases they are too intense even for the lesions of Hodgkin's disease. More trouble is afforded by tuberculosis because the staphylococcal lesions may also destroy intervertebral disks (as in Cases 13 and 14) and thus render roentgenographic appraisal of the bony lesion quite uncertain. Of most help in this connection are family history, pre-existing pulmonary symptoms, chest x-ray films and the usually more insidious development of the tuberculous lesions.

### Chronic Syndromes

These illnesses (seemingly nonseptic disorders) differ from the foregoing syndromes not merely in that the march of events is strung out over weeks or months, the epiphenomena of sepsis are entirely lacking. The spinal ache is much less severe than that in acute lesions, and the entire picture of a chronic metastatic case is consistent with the development of a primary spinal tumor. In chronic osteomyelitic cases, however, the bony changes seen on x-ray study necessitate consideration of both tuberculosis and metastatic neoplasia. Final diagnosis may have to await biopsy, which is usually forthcoming before the advent of Phase IV because this disorder is seldom confused with non-surgical ailments.

### Initial Diagnosis

Table 1 lists the diagnoses entertained by the first attending physician in each case of this series. Specific mention should probably be made of the fact that in this clinic diagnostic spinal puncture in suspected cases of spinal epidural sepsis has never excited a leptomeningitis.

### TREATMENT

In 1926, after a review of this entire subject, Dandy<sup>4</sup> summarized the incontrovertible evidence that chronic lesions are curable by surgery.

However, with the evidence then at hand, Dandy could only conjecture regarding the efficacy of operation for acute cases. He emphasized that the only 2 survivors among the 25 cases reported had been surgically drained, whereas the others had been paralyzed within forty-eight hours after the onset of neurologic changes, and had succumbed

within six to thirty days. Neither of the survivors<sup>10, 11</sup> made full neurologic recovery, but Dandy prophesied that results would depend upon the stage of the illness in which operation was undertaken.

During the next several years, sporadic reports of the surgical cure of acute cases began to appear so that by 1934 Slaughter, Fremont-Smith and Munro<sup>1</sup> were able to cite 6 survivors, including several neurologic recoveries to which they added 1 of their own (Case 1, of this series). This case was the first in which diagnosis and treatment were completed during a preparalytic phase of the illness. It typifies the possible but still rarely realized ideal management to which may now be added the adjunct of modern antibacterial agents.

Rare cases of recovery from presumed spinal epidural sepsis without operation were reported<sup>12, 13</sup> more than two decades ago, but the diagnoses in these cases are, in my opinion, open to considerable question.\* The conception of nonoperative management is mentioned only to be condemned, notwithstanding a recent suggestion<sup>16</sup> that penicillin might sometimes obviate the need for surgery. I join Grant<sup>3</sup> in strenuous protest against any idea of surgical temporization with these lesions.

Once the diagnosis is made, laminectomy for drainage of the epidural space becomes a true surgical emergency. Every care, of course, is exercised to preserve the integrity of the dura. The lesion should be cultured, and a gram preparation of an epidural specimen should be made at once for tentative chemotherapeutic guidance. Administration of sulfadiazine and penicillin is begun while the patient is being prepared for operation, and a catheter is fixed in the wound for topical instillation of the penicillin during the immediate postoperative period. After the first forty-eight hours, the wound is dressed daily with scrupulous aseptic technic, care being taken to prevent pocketing or premature closure by gently lavaging penicillin-soaked sponges to the very floor of the incision. Daily wound cultures should be made for immediate detection of any secondary invaders that might require alteration of the topically applied antibacterial agent. Results of the original wound culture may occasionally necessitate a change of all antibacterial agents, but unless an obvious primary focus is known to be other than a *Staph aureus* infection, it is safest to assume at the outset that this is the offending organism.

If the primary focus is active it should be cultured and treated by appropriate means but only after spinal drainage has been instituted.

Since the advent of penicillin and the sulfonamides, I have made delayed closure of these lami-

\*Campbell<sup>14</sup> says that von Leyden and Nonne also have reported non-operative recoveries, but he does not give the specific references. Von Leyden<sup>15</sup> does not mention such a case in his comprehensive monograph on diseases of the spinal cord, and I have been unable to locate Nonne's case. Nonne<sup>16</sup> in reporting a fatal case of otogenic origin does mention having witnessed a recovery, but this patient had had the benefit of surgical drainage. The case is undated, but it must be among the very first of surgical cures.

nectomy wounds to minimize morbidity. This is undertaken only after the patient's temperature, white-cell count and sedimentation rate are returned to normal, and the wound itself has satisfied certain criteria—namely, a full lining of clean granulation tissue, a low population of culturable bacteria and freedom from sinuses that yield pus when deep pressure is applied to the paraspinous musculature. The technical details for closure of these contaminated but noninfected wounds is beyond the scope of this paper. Suffice it to say that there have been no disruptions, and the total morbidity for metastatic cases has been reduced to an average of thirty-five hospital days in the last 3 cases. By contrast, closure of osteomyelitic wounds cannot be undertaken as early because of the more prolonged purulent drainage from the depths of the incision near the bony lesion.

When the wound is healed, patients with metastatic cases enjoying neurologic recovery are ready

folds at a leisurely pace that almost assures the patient of operation before paralysis is complete or neurologic damage irreversible. The advent of modern antibacterial agents has made little change in the outlook because these patients never present the picture of unbridled sepsis.

The prognosis for acute cases has always been quite different, regarding both life and neurologic function. This is shown in Table 2, where the end-results of 158 acute cases are aligned both for comparison by decades, and for contrast with the fate of 44 patients suffering subacute or chronic lesions. Grant<sup>2</sup> attributes the improved results of the past decade to earlier treatment made possible by publications designed to acquaint the medical profession with the urgency of these cases. That early diagnosis is the key to neurologic recovery is borne out by the present series, in which *total recovery was realized in all patients who had no paralysis at the time of operation or who had a paresis of fewer*

TABLE 2 Comparative End Results in 202 Cases by Decade and by Type

TYPE OF CASE	COLLECTED BEFORE 1927*		COLLECTED BEFORE 1937†		COLLECTED AFTER 1937†		BOSTON CITY HOSPITAL SERIES 1930-1948	
	NO. OF CASES	PER CENTAGE	NO. OF CASES	PER CENTAGE	NO. OF CASES	PER CENTAGE	NO. OF CASES	PER CENTAGE
Acute	25		71		44		18	
Deaths	92		60		31		22	
Survivals	8		40		69		78	
Patient paralyzed	8		7		25		28	
Neurologic recovery	0		7		43		50	
Subacute			2		6			
Deaths			100		33			
Survivals			0		67			
Patient paralyzed			0		0			
Neurologic recovery			0		67			
Chronic			15		19		2	
Deaths			20		10		0	
Survivals			80		90		100	
Patient paralyzed			7		10		0	
Neurologic recovery			7		80		100	

\*Series of Dandy.<sup>1</sup>

†Series of Grant.<sup>2</sup>

for discharge and immediate return to work. No support for the spine is necessary even though as many as 7 laminae have been removed, assuming of course that the articular facets were, as is proper, undisturbed by surgery. Convalescence of osteomyelitic cases is more prolonged, and it is advocated that a spinal support be worn until there is x-ray evidence to confirm a clinical impression that the spine is healed and stable.

The extensive program necessary for rehabilitation of patients who are left paraplegic lies outside the present discussion.

PROGNOSIS AND RESULTS

Since the dawn of neurosurgery the prognosis for chronic cases has been good (Table 2). Although frequently operated on under the mistaken diagnosis of spinal tumor, the great majority of these patients have lived to enjoy neurologic recovery. This is understandable because the syndrome un-

than thirty-six hours' duration. By contrast, no patient whose paralysis had been present longer than forty-eight hours made a neurologic recovery, and it was among cases of this type that all deaths occurred.

The present material indicates, however, that the prognosis for life in acute cases has been materially improved since the arrival of penicillin and the sulfonamides (Table 3). Prior to 1939, there were 3 deaths among 8 cases. The patient in Case 7 succumbed on the ninth postoperative day in uremia with pneumonia and would probably be lost even today because of the renal failure. On the other hand, the 2 patients (Cases 2 and 13) who succumbed on the eighteenth and fourteenth postoperative days of pneumonia and pneumonia with lung abscess, respectively, might have fared better had potent antibacterial preparations been available. Since 1939, the single death among 10 patients was the patient in Case 14, who died in

uremia with pneumonia and a persistent bacteremia on the thirteenth postoperative day. Concurrently, however, penicillin and sulfadiazine were probably responsible for the survivals in Cases 15 and 18—patients who suffered septic complications analogous to those proving fatal in Cases 2 and 13.

One further point concerning prognosis is worthy of note. I have maintained a distinction between metastatic and osteomyelitic cases on the grounds of dissimilarities of age incidence, pathogenesis, pathology and clinical features. Equally apparent are wide differences in their respective end results (Table 4).

### SUMMARY AND CONCLUSIONS

Nontuberculous spinal epidural infections are infrequent disorders that usually occur in patients who harbor a focus of chronic infection somewhere outside the epidural space. Among such foci, acne, furunculosis, cellulitis, vertebral caries and old

TABLE 3 *Effect of Penicillin and Sulfonamides upon Mortality in Acute Cases at the Boston City Hospital*

PERIOD	TOTAL CASES	DEATHS	SURVIVALS
Before 1939	8	57%	61
After 1939	10	10	90

operative sites (sometimes apparently healed) are the most frequent. The symptomatology regularly unfolds in 4 steps:

- Phase I Spinal ache
- Phase II Root pain
- Phase III Weaknesses of  $\left\{ \begin{array}{l} \text{voluntary muscle} \\ \text{sphincters} \\ \text{sensibilities} \end{array} \right.$
- Phase IV Paralysis

When this syndrome develops over the course of weeks or months and is unattended by the signs or symptoms of infection, the case is designated "chronic." When it is compressed into a few days or a week of illness that is further marked by chills, fever, malaise, headache, stiff neck and leukocytosis, it is designated "acute." In either event, properly executed spinal puncture during (or after) Phase II establishes the diagnosis by yielding either epidural pus or a subarachnoidal block with yellowish spinal fluid that exhibits an elevated protein content, usually a few white cells, but neither chemical nor bacteriologic evidence of leptomeningitis.

Treatment is primarily surgical and consists of immediate laminectomy for drainage of the epidural space. Penicillin and the sulfonamides are valuable adjuncts.

Total recovery depends upon early diagnosis and prompt surgical intervention. If operation is done before paralysis is established, the outlook is good. After forty-eight hours of paralysis, operation may save life but the neurologic damage is probably irreparable. Prognosis for life is further dependent upon the curability of the primary focus and any

TABLE 4 *Comparative End Results of Acute Metastatic and Osteomyelitic Cases at the Boston City Hospital*

OUTCOME	METASTATIC CASES		OSTEOMYELITIC CASES	
	NO	PERCENTAGE	NO	PERCENTAGE
Deaths	12	17	6	53
Survivals		83		67
Paralysis paralyzed		17		50
Neurologic recovery		67		17

additional septic complications. If the former is an osteomyelitis the outlook is more guarded than otherwise.

Delay in diagnosing epidural sepsis is more often attributable to a failure to give it consideration than to any other cause. Fear of performing diagnostic spinal puncture in questionable cases is seldom a factor in delayed recognition of the disease, nor should it be. This procedure is of crucial importance to early diagnosis, and in proper hands its performance is infinitely less risky than its omission.

Bad results are usually traceable to the mistaking of these disorders for more everyday ailments until paralysis is complete and neurologic damage irreversible. Experience shows that the acute infections are almost routinely confused with meningitis, poliomyelitis, infectious polyneuritis, ethanolic polyneuritis, nonspecific monoradicular neuritis, arthritis, uncomplicated osteomyelitis of the spine or even hysteria (Cases 6 and 8).

The etiologic, pathologic, clinical, therapeutic and prognostic aspects of nontuberculous spinal epidural infections are discussed in the light of experience gathered in the definitive treatment of 20 consecutive cases on the Neurosurgical Service of the Boston City Hospital between the years 1930 and 1948. It is hoped that this discussion will enhance the general understanding of these disorders, facilitate their earlier recognition and thus further reduce the incidence of poor therapeutic results.

### REFERENCES

1. Slaughter, R. F., Fremont-Smith, F. and Munro, D. Metastatic spinal epidural abscess: report of case with recovery following operation. *J. A. M. A.* 102:1468-1470, 1934.
2. Mixer, W. J. and Smithwick, R. H. Acute intraspinal epidural abscess. *New Eng. J. Med.* 207:126-131, 1932.
3. Grant, F. C. Epidural spinal abscess. *J. A. M. A.* 128:507-512, 1945.
4. Dandy, W. E. Abscesses and inflammatory tumors in spinal epidural space (so-called pachymeningitis externa). *Arch. Surg.* 13:477-494, 1926.
5. Campbell, M. M. Pyogenic infections within vertebral canal. *Bull. Neurol. Inst.* 6:574-591, 1937.

nectomy wounds to minimize morbidity. This is undertaken only after the patient's temperature, white-cell count and sedimentation rate are returned to normal, and the wound itself has satisfied certain criteria—namely, a full lining of clean granulation tissue, a low population of culturable bacteria and freedom from sinuses that yield pus when deep pressure is applied to the paraspinous musculature. The technical details for closure of these contaminated but noninfected wounds is beyond the scope of this paper. Suffice it to say that there have been no disruptions, and the total morbidity for metastatic cases has been reduced to an average of thirty-five hospital days in the last 3 cases. By contrast, closure of osteomyelitic wounds cannot be undertaken as early because of the more prolonged purulent drainage from the depths of the incision near the bony lesion.

When the wound is healed, patients with metastatic cases enjoying neurologic recovery are ready

fold at a leisurely pace that almost assures the patient of operation before paralysis is complete or neurologic damage irreversible. The advent of modern antibacterial agents has made little change in the outlook because these patients never present the picture of unbridled sepsis.

The prognosis for acute cases has always been quite different, regarding both life and neurologic function. This is shown in Table 2, where the end-results of 158 acute cases are aligned both for comparison by decades, and for contrast with the fate of 44 patients suffering subacute or chronic lesions. Grant<sup>2</sup> attributes the improved results of the past decade to earlier treatment made possible by publications designed to acquaint the medical profession with the urgency of these cases. That early diagnosis is the key to neurologic recovery is borne out by the present series, in which *total recovery was realized in all patients who had no paralysis at the time of operation or who had a paresis of fewer*

TABLE 2 Comparative End Results in 202 Cases by Decade and by Type

TYPE OF CASE	COLLECTED BEFORE 1927*		COLLECTED BEFORE 1937†		COLLECTED AFTER 1937†		BOSTON CITY HOSPITAL SERIES 1930-1948	
	NO OF CASES	PER CENTAGE	NO OF CASES	PER CENTAGE	NO OF CASES	PER CENTAGE	NO OF CASES	PER CENTAGE
Acute	25		71		44		18	
Deaths		92		60		31		22
Survivals		8		40		69		78
Patient paralyzed		8		?		25		18
Neurologic recovery		0		?		43		50
Subacute			2		6			
Deaths				100		33		
Survivals				0		67		
Patient paralyzed				0		0		
Neurologic recovery				0		67		
Chronic			15		19		2	
Deaths				20		10		0
Survivals				80		90		100
Patient paralyzed				?		10		0
Neurologic recovery				?		80		100

\*Series of Dandy.<sup>1</sup>

†Series of Grant.<sup>2</sup>

for discharge and immediate return to work. No support for the spine is necessary even though as many as 7 laminae have been removed, assuming of course that the articular facets were, as is proper, undisturbed by surgery. Convalescence of osteomyelitic cases is more prolonged, and it is advocated that a spinal support be worn until there is x-ray evidence to confirm a clinical impression that the spine is healed and stable.

The extensive program necessary for rehabilitation of patients who are left paraplegic lies outside the present discussion.

#### PROGNOSIS AND RESULTS

Since the dawn of neurosurgery the prognosis for chronic cases has been good (Table 2). Although frequently operated on under the mistaken diagnosis of spinal tumor, the great majority of these patients have lived to enjoy neurologic recovery. This is understandable because the syndrome un-

than thirty-six hours' duration. By contrast, no patient whose paralysis had been present longer than forty-eight hours made a neurologic recovery, and it was among cases of this type that all deaths occurred.

The present material indicates, however, that the prognosis for life in acute cases has been materially improved since the arrival of penicillin and the sulfonamides (Table 3). Prior to 1939, there were 3 deaths among 8 cases. The patient in Case 7 succumbed on the ninth postoperative day in uremia with pneumonia and would probably be lost even today because of the renal failure. On the other hand, the 2 patients (Cases 2 and 13) who succumbed on the eighteenth and fourteenth postoperative days of pneumonia and pneumonia with lung abscess, respectively, might have fared better had potent antibacterial preparations been available. Since 1939, the single death among 10 patients was the patient in Case 14, who died in

uremia with pneumonia and a persistent bacteremia on the thirteenth postoperative day. Concurrently, however, penicillin and sulfadiazine were probably responsible for the survivals in Cases 15 and 18—patients who suffered septic complications analogous to those proving fatal in Cases 2 and 13.

One further point concerning prognosis is worthy of note. I have maintained a distinction between metastatic and osteomyelitic cases on the grounds of dissimilarities of age incidence, pathogenesis, pathology and clinical features. Equally apparent are wide differences in their respective end results (Table 4).

### SUMMARY AND CONCLUSIONS

Nontuberculous spinal epidural infections are infrequent disorders that usually occur in patients who harbor a focus of chronic infection somewhere outside the epidural space. Among such foci, acne, furunculosis, cellulitis, vertebral caries and old

TABLE 3 *Effect of Penicillin and Sulfonamides upon Mortality in Acute Cases at the Boston City Hospital*

PERIOD	TOTAL CASES	DEATHS %	SURVIVALS
Before 1939	8	37	61
After 1939	10	10	90

operative sites (sometimes apparently healed) are the most frequent. The symptomatology regularly unfolds in 4 steps:

- Phase I Spinal ache
- Phase II Root pain
- Phase III Weaknesses of  $\left\{ \begin{array}{l} \text{voluntary muscle} \\ \text{sphincters} \\ \text{sensibilities} \end{array} \right.$
- Phase IV Paralyzes

When this syndrome develops over the course of weeks or months and is unattended by the signs or symptoms of infection, the case is designated "chronic." When it is compressed into a few days or a week of illness that is further marked by chills, fever, malaise, headache, stiff neck and leukocytosis, it is designated "acute." In either event, properly executed spinal puncture during (or after) Phase II establishes the diagnosis by yielding either epidural pus or a subarachnoidal block with yellowish spinal fluid that exhibits an elevated protein content, usually a few white cells, but neither chemical nor bacteriologic evidence of lept meningitis.

Treatment is primarily surgical and consists of immediate laminectomy for drainage of the epidural space. Penicillin and the sulfonamides are valuable adjuncts.

Total recovery depends upon early diagnosis and prompt surgical intervention. If operation is done before paralysis is established, the outlook is good. After forty-eight hours of paralysis, operation may save life but the neurologic damage is probably irreparable. Prognosis for life is further dependent upon the curability of the primary focus and any

TABLE 4 *Comparative End Results of Acute Metastatic and Osteomyelitic Cases at the Boston City Hospital*

OUTCOME	METASTATIC CASES		OSTEOMYELETIC CASES	
	NO.	PERCENTAGE	NO.	PERCENTAGE
Deaths	12	17	6	53
Survivals		83		67
Patient paralyzed		17		50
Neurologic recovery		67		17

additional septic complications. If the former is an osteomyelitis, the outlook is more guarded than otherwise.

Delay in diagnosing epidural sepsis is more often attributable to a failure to give it consideration than to any other cause. Fear of performing diagnostic spinal puncture in questionable cases is seldom a factor in delayed recognition of the disease nor should it be. This procedure is of crucial importance to early diagnosis, and in proper hands its performance is infinitely less risky than its omission.

Bad results are usually traceable to the mistaking of these disorders for more everyday ailments until paralysis is complete and neurologic damage irreversible. Experience shows that the acute infections are almost routinely confused with meningitis, poliomyelitis, infectious polyneuritis, ethanolic polyneuritis, nonspecific monoradicular neuritis, arthritis, uncomplicated osteomyelitis of the spine or even hysteria (Cases 6 and 8).

The etiologic, pathologic, clinical, therapeutic and prognostic aspects of nontuberculous spinal epidural infections are discussed in the light of experience gathered in the definitive treatment of 20 consecutive cases on the Neurosurgical Service of the Boston City Hospital between the years 1930 and 1948. It is hoped that this discussion will enhance the general understanding of these disorders, facilitate their earlier recognition and thus further reduce the incidence of poor therapeutic results.

### REFERENCES

1. Slaughter, R. F., Fremont-Smith, F. and Munro, D. Metastatic spinal epidural abscess: report of case with recovery following operation. *J. A. M. A.* 102:1468-1470, 1934.
2. Mixer, W. J. and Smithwick, R. H. Acute intraspinal epidural abscess. *New Eng. J. Med.* 207:126-131, 1932.
3. Grant, F. C. Epidural spinal abscess. *J. A. M. A.* 128:509-512, 1945.
4. Dandy, W. E. Abscesses and inflammatory tumors in spinal epidural space (so-called pachymeningitis externa). *Arch. Surg.* 13:477-494, 1926.
5. Campbell, M. M. Pyogenic infections within vertebral canal. *Bull. Neurol. Inst.* 6:574-591, 1937.

nectomy wounds to minimize morbidity. This is undertaken only after the patient's temperature, white-cell count and sedimentation rate are returned to normal, and the wound itself has satisfied certain criteria—namely, a full lining of clean granulation tissue, a low population of culturable bacteria and freedom from sinuses that yield pus when deep pressure is applied to the paraspinous musculature. The technical details for closure of these contaminated but noninfected wounds is beyond the scope of this paper. Suffice it to say that there have been no disruptions, and the total morbidity for metastatic cases has been reduced to an average of thirty-five hospital days in the last 3 cases. By contrast, closure of osteomyelitic wounds cannot be undertaken as early because of the more prolonged purulent drainage from the depths of the incision near the bony lesion.

When the wound is healed, patients with metastatic cases enjoying neurologic recovery are ready

folds at a leisurely pace that almost assures the patient of operation before paralysis is complete or neurologic damage irreversible. The advent of modern antibacterial agents has made little change in the outlook because these patients never present the picture of unbridled sepsis.

The prognosis for acute cases has always been quite different, regarding both life and neurologic function. This is shown in Table 2, where the end-results of 158 acute cases are aligned both for comparison by decades, and for contrast with the fate of 44 patients suffering subacute or chronic lesions. Grant<sup>3</sup> attributes the improved results of the past decade to earlier treatment made possible by publications designed to acquaint the medical profession with the urgency of these cases. That early diagnosis is the key to neurologic recovery is borne out by the present series, in which *total recovery was realized in all patients who had no paralysis at the time of operation or who had a paresis of fewer*

TABLE 2 Comparative End Results in 202 Cases by Decade and by Type

TYPE OF CASE	COLLECTED BEFORE 1927*		COLLECTED BEFORE 1937†		COLLECTED AFTER 1937†		BOSTON CITY HOSPITAL SERIES 1930-1948	
	NO. OF CASES	PER-CENTAGE	NO. OF CASES	PER-CENTAGE	NO. OF CASES	PER-CENTAGE	NO. OF CASES	PER-CENTAGE
Acute	25		71		44		18	
Deaths	92		60		31		22	
Survivals	8		40		69		78	
Patient paralyzed	8		?		25		28	
Neurologic recovery	0		?		43		50	
Subacute			2		6			
Deaths				100		33		
Survivals				0		67		
Patient paralyzed				0		0		
Neurologic recovery				0		67		
Chronic			15		19		2	
Deaths				20		10		0
Survivals				80		90		100
Patient paralyzed				?		10		0
Neurologic recovery				?		80		100

\*Series of Dandy.<sup>4</sup>

†Series of Grant.<sup>3</sup>

for discharge and immediate return to work. No support for the spine is necessary even though as many as 7 laminae have been removed, assuming of course that the articular facets were, as is proper, undisturbed by surgery. Convalescence of osteomyelitic cases is more prolonged, and it is advocated that a spinal support be worn until there is x-ray evidence to confirm a clinical impression that the spine is healed and stable.

The extensive program necessary for rehabilitation of patients who are left paraplegic lies outside the present discussion.

### PROGNOSIS AND RESULTS

Since the dawn of neurosurgery the prognosis for chronic cases has been good (Table 2). Although frequently operated on under the mistaken diagnosis of spinal tumor, the great majority of these patients have lived to enjoy neurologic recovery. This is understandable because the syndrome un-

than thirty-six hours' duration. By contrast, no patient whose paralysis had been present longer than forty-eight hours made a neurologic recovery, and it was among cases of this type that all deaths occurred.

The present material indicates, however, that the prognosis for life in acute cases has been materially improved since the arrival of penicillin and the sulfonamides (Table 3). Prior to 1939, there were 3 deaths among 8 cases. The patient in Case 7 succumbed on the ninth postoperative day in uremia with pneumonia and would probably be lost even today because of the renal failure. On the other hand, the 2 patients (Cases 2 and 13) who succumbed on the eighteenth and fourteenth postoperative days of pneumonia and pneumonia with lung abscess, respectively, might have fared better had potent antibacterial preparations been available. Since 1939, the single death among 10 patients was the patient in Case 14, who died in

uremia with pneumonia and a persistent bacteremia on the thirteenth postoperative day. Concurrently, however, penicillin and sulfadiazine were probably responsible for the survivals in Cases 15 and 18—patients who suffered septic complications analogous to those proving fatal in Cases 2 and 13.

One further point concerning prognosis is worthy of note. I have maintained a distinction between metastatic and osteomyelitic cases on the grounds of dissimilarities of age incidence, pathogenesis, pathology and clinical features. Equally apparent are wide differences in their respective end results (Table 4).

### SUMMARY AND CONCLUSIONS

Nontuberculous spinal epidural infections are infrequent disorders that usually occur in patients who harbor a focus of chronic infection somewhere outside the epidural space. Among such foci, acne, furunculosis, cellulitis, vertebral caries and old

TABLE 3 *Effect of Penicillin and Sulfonamides upon Mortality in Acute Cases at the Boston City Hospital*

PERIOD	TOTAL CASES	DEATHS	SURVIVALS
Before 1939	8	6	63
After 1939	10	10	90

operative sites (sometimes apparently healed) are the most frequent. The symptomatology regularly unfolds in 4 steps:

- Phase I Spinal ache
- Phase II Root pain
- Phase III Weaknesses of  $\left\{ \begin{array}{l} \text{voluntary muscle} \\ \text{sphincters} \\ \text{sensibilities} \end{array} \right.$
- Phase IV Paralyzes

When this syndrome develops over the course of weeks or months and is unattended by the signs or symptoms of infection, the case is designated "chronic." When it is compressed into a few days or a week of illness that is further marked by chills, fever, malaise, headache, stiff neck and leukocytosis, it is designated "acute." In either event, properly executed spinal puncture during (or after) Phase II establishes the diagnosis by yielding either epidural pus or a subarachnoidal block with yellowish spinal fluid that exhibits an elevated protein content, usually a few white cells, but neither chemical nor bacteriologic evidence of leptomeningitis.

Treatment is primarily surgical and consists of immediate laminectomy for drainage of the epidural space. Penicillin and the sulfonamides are valuable adjuncts.

Total recovery depends upon early diagnosis and prompt surgical intervention. If operation is done before paralysis is established, the outlook is good. After forty-eight hours of paralysis, operation may save life but the neurologic damage is probably irreparable. Prognosis for life is further dependent upon the curability of the primary focus and any

TABLE 4 *Comparative End Results of Acute Metastatic and Osteomyelitic Cases at the Boston City Hospital*

OUTCOME	METASTATIC CASES		OSTEOMYELITIC CASES	
	NO	PER CENTAGE	NO	PER CENTAGE
Deaths	12	17	6	33
Survivals		83		67
Patient paralyzed		17		50
Neurologic recovery		67		17

additional septic complications. If the former is an osteomyelitis, the outlook is more guarded than otherwise.

Delay in diagnosing epidural sepsis is more often attributable to a failure to give it consideration than to any other cause. Fear of performing diagnostic spinal puncture in questionable cases is seldom a factor in delayed recognition of the disease, nor should it be. This procedure is of crucial importance to early diagnosis, and in proper hands its performance is infinitely less risky than its omission.

Bad results are usually traceable to the mistaking of these disorders for more everyday ailments until paralysis is complete and neurologic damage irreversible. Experience shows that the acute infections are almost routinely confused with meningitis, poliomyelitis, infectious polyneuritis, ethanolic polyneuritis, nonspecific monoradicular neuritis, arthritis, uncomplicated osteomyelitis of the spine or even hysteria (Cases 6 and 8).

The etiologic, pathologic, clinical, therapeutic and prognostic aspects of nontuberculous spinal epidural infections are discussed in the light of experience gathered in the definitive treatment of 20 consecutive cases on the Neurosurgical Service of the Boston City Hospital between the years 1930 and 1948. It is hoped that this discussion will enhance the general understanding of these disorders, facilitate their earlier recognition and thus further reduce the incidence of poor therapeutic results.

### REFERENCES

1. Slaughter R. F., Fremont-Smith, F., and Munro D. Metastatic spinal epidural abscess: report of case with recovery following operation. *J. A. M. A.* 102:1468-1470, 1934.
2. Mixer W. J. and Smithwick R. H. Acute intraspinal epidural abscess. *New Eng. J. Med.* 207:126-131, 1932.
3. Grant, F. C. Epidural spinal abscess. *J. A. M. A.* 128:503-512, 1945.
4. Dandy, W. E. Abscesses and inflammatory tumors in spinal epidural space (so-called pachymeningitis externa). *Arch. Surg.* 13:477-494, 1926.
5. Campbell M. M. Pyogenic infections within vertebral canal. *Bull. Neurol. Inst.* 6:574-591, 1937.

6. Browder, J and Meyers R. Infections of spinal epidural space aspect of vertebral osteomyelitis. *Am J Surg* 37:4 26 1937
7. Hassin, G B. Circumscribed suppurative (nontuberculous) peripachymeningitis: histopathologic study of case. *Arch Neurol & Psychiat* 20 110 129, 1928
8. Stammers, F A R. Spinal epidural suppuration with special reference to osteomyelitis of vertebrae. *Brit J Surg* 26 366-374 1938
9. Turner, P. Acute infective osteomyelitis of spine. *Brit J Surg* 26 71-85 1938
10. Pulvirenti, S. Sopra un caso di spondilite acuta purulenta lombare con sindrome midollare acuta. *Policlin* 28 27-34 1921
11. Taylor, A S and Kennedy F. Case of extrathecal abscess of spinal cord. *Arch Neurol & Psychiat* 9 652 1923
12. Braun, H. Über Epimeningitis spinalis. *Zentralbl f Chir* 49 1274-1276 1922
13. Keimburg, F. Über akute eitrige Perimeningitis. *Med Klin* 20 640-642 1924
14. von Leyden, E and Goldscheider, A. Die Erkrankungen des Rückenmarkes und der Medulla Oblongata. 760 pp. Wien. Holder 1904. Teil II. Pp 77-78
15. Nonne, M. Otogener Rückenmarksabscess. *Ztschr f Hals, Nasen- und Ohrenh* 13 574-579 1926
16. Verbrugghen, A. H. Discussion of Grant.

## PROGRESS IN GROUP PSYCHOTHERAPY

### A Summary of the Literature

WILLIAM B. TERHUNE, M.D.,\* AND JAMES R. DICKENSON, M.D.†

NEW CANAAN, CONNECTICUT

GROUP psychotherapy has aroused much interest in psychiatric and general medical circles. The literature is voluminous and varied, indicating many approaches and as many purposes, with coincident confusion. This report summarizes the recent literature. Medical group psychotherapy was initiated in Boston in 1905 by Dr. Joseph H. Pratt. Psychiatric group therapy has been practiced in the Boston Dispensary since 1930.

Military necessity and a shortage of psychiatric personnel resulted in the employment of this form of treatment by the armed forces in World War II. At the same time its use became expedient in civilian mental hospitals. Results indicate the need for a continuing exploration of group psychotherapy inasmuch as it is a valuable adjunct to individual psychotherapy.

In military group therapy, methods differed depending on the time and place, the facilities, the severity of illness and the therapist. There was, however, a general plan of treatment. Didactic subject matter used was analogous and usually was what the particular psychiatrist would have given patients in individual interviews. Emphasis was laid upon the normalcy of fear, aggression, projection and hostility to authority. Catharsis was employed for the relief of emotional tension and identification with others of similar experiences.

Participation in the group varied from compulsory disciplined attendance to "leaderless groups," in which patients selected their leader from their members and planned their program. The psychiatrist served as teacher-physician until the group attained sufficient knowledge of their problems and mental mechanisms to act more independently and until they had gained sufficient esprit de corps to do so. Activities were limited, but interesting

and useful projects helped group solidarity and hastened recovery. In some cases therapists distinguished between treating individuals *in a group* and *true group psychotherapy*, in which treatment is largely through the interaction of members of the group upon each other. The average period of treatment was from six to eight weeks.

Psychiatrists employing group psychotherapy treated hundreds of thousands of men, usually with only one or two individual interviews. There was little follow-up study, and return to duty terminated treatment. Many reported "cures" were not permanent, and although symptoms were temporarily alleviated, the underlying personality structure remained unchanged. The limited number of psychiatrists made adequate treatment impossible.

Group psychotherapy is being extensively used by the Veterans Administration in both their hospitals and outpatient clinics; it is being employed in some state and a few private mental hospitals. The general opinion to date is that it is not nearly so effective as individual therapy, but that it is a useful adjunct to the latter. It enables a few doctors to give a large number of patients attention that they would not otherwise receive. It helps people, it certainly does not cure them. Group therapy, or therapy carried out in groups, seems to get patients just so far, but fails to take them across the line to a final and permanent recovery.

A review of current literature indicates the following tentative conclusions:

Group psychotherapy can extend aid to a larger number of patients than individual psychotherapy alone.

Over and above the questions of expediency, the shorter period of treatment and lessened expense, group psychotherapy offers in some cases fundamental values not obtainable through individual treatment alone.

\*Associate clinical professor of psychiatry, Yale University School of Medicine; medical director, Silver Hill Foundation for the Treatment of the Psychoneuroses.

†Associate physician, Silver Hill Foundation for the Treatment of the Psychoneuroses.

This method is particularly applicable to psychoneurotics and to patients who, as children, felt rejected by the family group and who have not subsequently adapted themselves to other social groups.

Individual psychotherapy does not always solve the difficulty of the neurotic. The therapeutic group offers an opportunity to practice adaptation in a social milieu.

#### NATURE OF GROUP PSYCHOTHERAPY

Group psychotherapy involves more than an assemblage of persons with similar aims and problems. Nor does leadership of a psychiatrist in itself constitute group psychotherapy. When the therapist directs treatment toward a particular patient among several this is psychotherapy *in a group*. The relation is between therapist and patient, the selected patient benefits by identification with the leader and his support, but not through sharing group interaction. This is in contrast to psychotherapy *through* a group — the true group psychotherapy, here the interaction of the group, the psychologic effect of members upon each other, is the therapeutic agent. There is considerable difference in the technics involved and in the benefits received.

The neurotic person avoids social groups, fears criticism and is afraid to exchange his isolation for social satisfactions of which he cannot be sure. In a well conducted therapeutic group patients gain security through their acceptance by the leader and other members of the group. The therapist often represents the good parent, consistent, understanding and nonpunitive. As the members become used to one another he withdraws, throwing them more and more upon each other, deflecting their dependence from himself to the group. Emphasis is placed upon constructive achievement and emotional maturation. The group becomes a substitute for lack of gratification in early life.

Accessory technics and settings vary with the patients, their ages and their problems. Groups should be small, usually not more than seven or eight members. The room, the therapist and the time of meeting should remain the same, these constant elements affording a sense of security.

#### TYPES OF GROUP PSYCHOTHERAPY

The method employed by the psychotherapist depends directly upon his orientation. The Freudian analytic method, with loosening of repression and the conscious recognition of asocial desires, has as its aim the freeing of energy bound in needless repression. The patient is expected to find his own social outlets. This method is used by Schilder and members of his school. Schilder believes that the patient must gain insight into social and psychosexual adjustment and into premature solutions that were formed in childhood. His outpatient

group therapy makes patients realize that thoughts that they have allowed to isolate them are similar to the thoughts of others. The patients' autobiographies are read and discussed by the group, the patient having the benefit of their interpretation as well as that of the therapist. The objective of treatment is to bring the patient to mature adult development.

At the opposite end of the scale is the inspirational method, which relies to a large extent upon suggestion and the contagion of useful emotions. The patient is urged to control his behavior, to suppress asocial and harmful thoughts, and to find inspiration in religion and life work. This method is utilized by many religious groups and by Alcoholics Anonymous.

Between the analytic and the inspirational types of group therapy is a third, which employs the best elements from each, utilizing both conscious and unconscious mechanisms. Through re-education the patient is helped to understand his problems. A corrective, stabilized life is instituted, and personality reintegration is effected.

#### DYNAMICS

Group psychotherapy offers values not available through individual treatment alone, and has inherent merits dependent upon specific factors.

The family is a social and emotional unit in which the child is dependent and submissive, or else rebellious toward the authority of parents — this is often complicated by sibling rivalry. Primitive instincts must be replaced by social instincts, and in this process of personality development the group affords reassurance not always found in the home. In this group the therapist symbolizes the loving parent who does not retaliate to hostility. Emotional releases are permitted, repressed conflicts with parents and siblings may be acted out, and a new perception of self is gained.

In a psychotherapeutic group there is a fluid, changing relation. Assured of emotional support from their leader and peers, patients may test reality situations in the group without fear of reprisal. Emotional tension is released, and conflicts are resolved, with a lessening of anxiety. Insight is gained by a comparison of personal experience with the experience of others. Rejecting parents meet parents with similar problems. Persons laden with guilt find themselves no longer unique and with no further need to be isolated. Combat veterans discover the normalcy of fear.

To dispel ignorance and correct distorted attitudes, specific information is given through re-educational lectures, with varying degrees of participation by the group. Patients with tuberculosis, peptic ulcers, diabetes, heart disease and even some psychoses respond to this treatment as readily as psychoneurotics do. The force of example, seeing others with the same difficulty making a success,

is encouraging Alcoholics Anonymous employs this psychologic technic, and military groups utilize the presence of combat veterans strong in their desire to return to duty. Because of the contagion of emotion, abreaction is of limited use in a group. It has been successfully employed to remove fear through desensitization and acting out of the situation with the accompanying fears. Aggression may be released, but must be tempered, for emotionally disturbed patients react badly to displays of anger or hostility.

Guilt is dispelled, and feelings of failure lessened through the sharing of common knowledge and the common purpose of the group. Preliminary catharsis aids this function. Group purpose can be contagious, particularly when combined with the spirit of teamplay. All members must have a common goal, as those who do not sabotage the effort of the group. The group, however, must be tolerant toward the members who cannot yet enter into activities wholeheartedly.

Successful adaptation and acceptance within the group give rise to new confidence, loss of sense of inferiority and lessening of self-consciousness. Tolerance toward one's self and others is gained, with better understanding of the needs of others. Once he has attained this tolerance the neurotic learns to forgive himself and others. In the group the necessity for reasonable compromise soon becomes apparent, and such compromises become acceptable to the patient as desired results are obtained.

#### AIMS AND LIMITATIONS OF TREATMENT

Aims and limitations of treatment should be established early. These are dependent upon the training and skill of the therapist, the patient being treated and his problems and his capacities. Careful and accurate diagnosis helps to establish objectives and to indicate results that may reasonably be expected.

Catharsis is palliative and temporary. Supportive treatment—giving sympathy, understanding and some environmental manipulation—is also palliative, and is not designed to cure. Integrative treatment aims at a cure through the approach that all psychoneuroses are the result of unconscious conflict, the objective is recovery, and the therapist is the guide toward a better way of living—a balanced life.

#### THE ROLE OF THE THERAPIST

The psychotherapist must be sensitive to group reactions. In 1940 Schuler commented that the psychiatrist who uses group therapy to gratify his curiosity, feeling of superiority or sexual interests, or to receive admiration, and who is the object of the patient's sex desire is but the target for hatred and criticism in their symbolic expression of early childhood formations. His success as a therapist

depends upon his ability to understand his own tendencies to incomplete experiences and patterns of infantile reaction. Psychiatrists on the whole do not have the personality that intuitively takes to group leadership. Many enter this field of medicine with personality difficulties, conscious or unconscious. These psychiatrists tend to keep their problems secret, and therefore favor an isolated type of treatment. Secrecy of motivation is a fundamental characteristic of a neurosis, and the first step in treatment is to do away with it. In a group the physician is less authoritative, with courage gained from others the patient may challenge the physician and express hostility toward him.

A directive leader who gives a lecture, or who acts as chairman of a seminar, and who more or less controls group reaction can give information and teach the principles of re-education, but he does not contribute to group interaction, the patient identifies himself with the leader and not with the group. Too close or prolonged identification with the leader, undiluted by identification with the group, recreates the parent-child situation, and if therapy is attempted in the group it leads to rivalry among the members.

The permissive leader gradually withdraws from the group and enables the members to *re-learn* new attitudes toward authority and toward the group. He retains his importance only in the early sessions when it is necessary for him to amalgamate the group in a common purpose, this accomplished, he deflects the dependence and identification from himself to the group itself, aiding the patient in his first steps toward the socialization that is one of the prime objectives of group psychotherapy. The leader becomes less and less active in the group, as through group interaction the patient progresses toward mature adult relationships, success therein enables him to attempt with confidence to adjust to outside groups and personal relations that he has hitherto feared. When he has arrived at this point, he has no further need for the leader, and treatment may be considered a success.

#### PERSONNEL OF THE GROUP

The selection of the group is dependent on the aim, the problem of the patient and his age, as well as the training of the therapist, the time available and the setting. Group psychotherapy is designed primarily for psychoneurotics. All psychoneurotics have basic difficulties in relating themselves to others. Analysis and insight do not necessarily solve this difficulty, for the patient is left without psychologic tools, skills, practice in social adaptation or sufficient security to relate to the family in which his patterns of neurotic reaction were laid, or to the ordinary social groups in which he has never been at ease nor felt that he was accepted. As he relives his experiences as a rejected child, he needs guidance and exposure to a therapeutic group in which he can attain success before he ventures

into what are to him threatening social situations in which he feels inadequate

Through satisfying group experiences, emotionally disturbed adolescents and rejecting parents learn to deal with frustration and to find compensations and sublimations. They discover that it is more comfortable and wiser to deal with their own fear, anger and hostility, and that of others, tolerantly and with good humor. As they mature emotionally they learn to fight nobly and effectively, not primitively and unsuccessfully.

Psychopaths and psychotics are usually not treated by group therapy. If this method is to be used, they should not be included in groups made up of psychoneurotics or of patients who are only slightly disturbed.

### FUTURE GOALS

Group psychotherapy is a new type of psychiatric endeavor, experience in this field is limited, and there is much to be learned about it. Just as a very careful choice of the members of the group is required, the psychotherapist must be even more carefully chosen. Unfortunate and harmful reactions stimulated by group psychology must be held to a minimum. There has been little follow-up study, and the literature indicates that results have been too optimistically interpreted. All future reports must be carefully scrutinized. The newly organized society for the study of group psychotherapy will have a great deal to do with the stabilization and standardization of technique and the extension of new knowledge regarding this promising field.

Some of the intrinsic values of group psychotherapy have been demonstrated, and under wise leadership this contribution to mental health may be considerable. One of the outstanding merits of this form of psychotherapy is that it is practical. Small treatment units similar to those for the treatment of medical problems and for behavior problems in children may be set up throughout the country. This can be done for the psychoneurotics in general hospitals, where patients at no great cost can participate daily in group re-education. Group re-education in accordance with the Freudian technique has been given by Lazell at St. Elizabeth's Hospital with considerable success. Paroled psychotics who have recovered from acute episodes in the convalescent period can benefit from group psychotherapy in selected settings. It offers an opportunity to continue treatment on a wider scale outside an institution, to observe progress and to prevent unnecessary psychotic recurrences. It would be of inestimable value to have marital and family clinics where erroneous basic concepts could be eliminated and serious damage to personality prevented. Child-guidance clinics, with concurrent parental education, afford a natural opportunity for the organization of fathers and mothers for group psychotherapy.

### SUMMARY

The original purpose of group psychotherapy was to make treatment available to greater numbers. Its present impetus came in World War II, with extensive use in the armed forces, later in veterans' hospitals and more recently in clinics, psychiatric units and private practice.

The patient finds in the group emotional satisfactions that he was denied in childhood and has not found outside the family. Through discussion he attains a degree of desensitization and comes to realize that he is not different from others. Too close family attachments are diluted, and often he is able to make a transference from one person, upon whom he has been dependent, to a group of equals.

Group psychotherapy is particularly applicable to psychoneurotics, adolescents and rejecting parents.

Treatment is not dependent primarily upon the therapeutic relation between psychiatrist and patient, but upon interaction between members of the group. Some groups rely upon discussion and group interaction alone, but the most effective group therapy combines these with individual interviews and a twenty-four-hour daily program.

The three most widely used methods are the analytic, the inspirational and the re-educational-integration, combining the chief values of the first two methods with a definite teaching of mental-hygiene principles.

In this new form of psychotherapy overenthusiasm of therapists and noncritical evaluation of results may be detrimental to sound practice and good psychiatric technique. Group psychotherapy has demonstrated its value, not merely as a time-saver and a relatively inexpensive method of treatment but also as one that has intrinsic values not found in individual therapy alone. The patient is regarded as a social being, and in the group is given opportunity for discovering and practicing the principles of social adaptation.

### BIBLIOGRAPHY

- Ackerman N. W. Dynamic patterns in group psychotherapy. *Psychiatry* 7:341-348 1944
- Axelrod P. L., Cameron M. S. and Solomon J. C. Experiment in group therapy with shy adolescent girls. *Am. J. Orthopsychiat* 14:616-627 1944
- Cohen R. R. Factors in adjustment to army life: plan for preventive psychiatry by mass psychotherapy. *War Med* 5:53-91 1944
- Group therapy: special section meeting 194" (various authors). *Am. J. Orthopsychiat* 13:648-650 1943
- Klapman J. W. Observation on interrelationship of group and individual psychotherapy. *J. Nerv. & Ment. Dis.* 101:242-246 1945
- Lewney L. G. Group treatment for mothers. *Am. J. Orthopsychiat* 14:589-592 1944
- Paster S. Group psychotherapy for combat neuroses. *Am. J. Orthopsychiat* 15:472-482 1945
- Rome H. P. Military group psychotherapy. *Am. J. Psychiatry* 101:494-497 1945
- Sarlin C. N., and Berenn M. A. Group psychotherapy on modified analytic basis. *J. Nerv. & Ment. Dis.* 104:611-667 1946
- Slavson S. R. Group therapy at Jewish Board of Guardians. *Ment. Hyg.* 28:414-422 1944
- Idem. Some elements in activity group therapy. *Am. J. Orthopsychiat.* 14:578-588 1944
- Thomas G. W. Group psychotherapy: review of recent literature. *Psychosomatic Med* 5:168-180 1943

## LOCAL HEALTH SERVICES IN MASSACHUSETTS

ROBERT E ARCHIBALD, M D , M P H ,\* AUTINO FIORE, M D ,† AND SOLOMON L SKVIRSKY, M D ‡

BOSTON

MASSACHUSETTS has long been recognized as a leader in many phases of public health. However, there has been a considerable lag in the provision of adequate local health facilities, owing in part to the heritage of local autonomy. Our interpretation of adequate facilities is the complete coverage of the state by local health units, conducted by the official governing body of the units and financed wholly or in part with local funds. These units should be staffed with full-time, well trained personnel rendering at least basic health services to all people of the Commonwealth. Until such local health units become a reality, a sound public-health program cannot be administered in an efficient, economic and competent manner. The primary purpose of this paper is to present a critical evaluation of existing official local health facilities in Massachusetts.

## SERVICES

Local health units should provide the six so-called minimum services recommended by Dr Haven Emerson<sup>1</sup> in his report on local health units for the nation. These include the control of communicable diseases, environmental sanitation, hygiene of maternity, infancy and childhood, including the supervision of the school child, public-health laboratory services, health information, and vital statistics. The control of chronic diseases should be added, since this is being regarded more and more as a basic health service. Actually, the activities of any given health department must fit the particular health situation of the community served. Therefore, further extension of services may include accident prevention, dental care, nutrition, mental hygiene, industrial hygiene, medical social service, housing surveys, hospital surveys and construction, and certain medical care programs. One of the most important responsibilities of the administrator of a local health unit is to set up a health program that provides maximum health benefits.

## PERSONNEL

To render necessary health services, a well trained professional staff is essential. Health departments should serve units of population of sufficient size to make possible the full-time employment of personnel. Emerson recommends that a unit serving 50,000 persons should have a staff consist-

ing of a full-time public-health physician, a full-time sanitary engineer, a sanitary inspector, 10 public-health nurses, 1 of whom should be of supervisory grade, and 3 clerical workers. This is considered basic personnel required by health units. Actually, the type and number of personnel employed will depend upon the size of the population served and the scope of the health program planned.

## STATISTICAL DATA

Massachusetts has a total population of 4,493,281 (1945 Census). Its area covers 7838.7 square miles with a density of 573.2 persons per square mile. There are 39 cities and 312 towns, with average populations of 76,577 and 4,829 respectively. Metropolitan Boston, which includes 43 communities, has 2,066,100 inhabitants, or 46 per cent of the total population.

The state is composed of 14 counties (Table 1). Community population is given in Table 2, which shows that 317 communities, representing 90.3 per cent of all the cities and towns, are inhabited by only 33.7 per cent of the total population. On the other hand, 66.3 per cent of the total population resides in only 34 or 9.7 per cent of the 351 communities.

It is evident that the bulk of the population is situated in a few communities, which for the most part should be able to provide necessary funds for adequate local health facilities and services. However, many communities with relatively small populations are economically unable to do so.

## LAWS PERTAINING TO LOCAL HEALTH UNITS

The *General Laws* (Ter Ed.) provide that every town shall elect three members of the board of health for a term of three years, if the town provides such a board; otherwise, the board of selectmen shall act as the board of health.<sup>2</sup>

In each city, the board of health shall consist of three persons appointed by the mayor, except in any city authorized to have a different type of organization by a special legislative act.<sup>3</sup> One member of the board shall be a physician. Also, provisions are made whereby a city or town may create a health department to replace the board of health, and specific procedures for making this change are outlined by law.<sup>2</sup>

It is possible for two or more towns, by vote of each, to form a district for the purpose of employing therein a health officer and necessary assistants and clerks. The law gives specific instructions for

\*Director, Division of Local Health Administration, Massachusetts Department of Public Health.

†Epidemiologist, Division of Local Health Administration, Massachusetts Department of Public Health.

‡Assistant director, Division of Local Health Administration, Massachusetts Department of Public Health.

the formation of a health district, and forbids any city to join such a union.<sup>4</sup>

Any governmental unit, including a city or town, may enter into an agreement with one or more other governmental units to perform jointly any service, activity or undertaking that each contracting unit is authorized by law to perform.<sup>5</sup>

The County of Barnstable is authorized to appoint a county health officer.<sup>6</sup> This is the only

charged primarily with the responsibility of preventing disease dangerous to the public health among the people within their jurisdiction by all reasonable and lawful methods. These methods include the carrying out of specific duties delegated to them by law and the adoption and enforcement of reasonable local rules and regulations.

Scientific advances, especially in the fields of bacteriology and immunology, and the demonstration of what may be accomplished in health promotion by the dissemination of information have greatly expanded the scope of public-health activities during recent years. Traditionally, boards of health have been thought of chiefly as exercising broad police powers through the right to license, to abate nuisances, to condemn unfit dwellings and to order personal or property quarantine. Although environmental sanitation is still very important, recent trends have brought health departments and their personnel more directly

TABLE 1 *Population and Number of Cities and Towns in Each County (Based on 1945 State Census)*

COUNTY	CITIES	TOWNS	POPULATION
Barnstable	0	15	38,216
Berkshire	2	50	127,620
Bristol	4	16	375,619
Dukes	0	7	5,040
Essex	8	26	519,535
Franklin	0	26	51,056
Hampden	4	19	521,757
Hampshire	1	19	74,475
Middlesex	11	43	1,022,331
Nantucket	0	1	2,870
Norfolk	1	27	363,410
Plymouth	1	26	180,518
Suffolk	3	1	860,709
Worcester	4	56	522,607
	39	312	4,493,281

permissive law that allows a county to employ a county health officer.

By law, the school committee appoints school physicians and nurses. However, in cities where the medical inspection prescribed was substantially provided by the board of health on the date of the

TABLE 2 *Distribution of the 351 Communities by Population Groups (Population Figures Based on 1945 State Census)*

POPULATION GROUP	NO OF COMMUNITIES IN GROUP	PER CENTAGE OF COMMUNITIES IN EACH GROUP	TOTAL POPULATION IN EACH GROUP	PERCENTAGE OF POPULATION IN EACH GROUP
Over 500,000	1	0.3	766,386	17.1
100,000-499,999	8	2.3	1,007,396	22.4
50,000-99,999	9	2.6	601,039	13.4
25,000-49,999	16	4.5	601,823	13.4
10,000-24,999	44	12.5	724,789	16.1
5,000-9,999	53	15.1	390,615	8.7
Under 5,000	220	62.7	401,215	8.9
Totals	351		4,493,281	

act (1906), the board of health was allowed to continue the appointment and assignment of school physicians and nurses. In some communities, local boards of health assume responsibility for medical inspection of parochial and private schools.

#### RESPONSIBILITIES OF BOARDS OF HEALTH

Every board of health must organize annually and select one of its members as chairman. They may appoint agents to act for them in cases of emergency, or if they cannot conveniently assemble. This agent will have all the authority of the board and will be directly responsible to it. The board is

TABLE 3 *Classification of Health Officers*

CLASSIFICATION OF HEALTH OFFICERS	NO OF COMMUNITIES	PER CENTAGE OF COMMUNITY IN GROUP	POPULATION OF EACH GROUP	PERCENTAGE OF POPULATION IN EACH GROUP
Full time medical health officers	10	3	1,559,052	34.7
Full time lay health officers	45	13	1,485,887	33.1
Part time medical health officers	38	11	296,928	6.6
Part time lay health officers	145	41	749,407	16.7
No health officer listed	113	32	402,007	8.9
Totals	351		4,493,281	

in contact with individuals or groups of persons by programs in preventive medicine, diagnostic services and follow-up home visits under the direction of the family physician. Thus, a logical and necessary expansion in public-health activities has occurred.

#### LOCAL HEALTH UNITS

Independent local health units are maintained by all of the 351 communities in Massachusetts. Separate boards of health exist in 232 communities, whereas the selectmen act as such in 107 additional towns. Health departments have been established by 9 communities. The public welfare commission assumes the duties of the board in one city, and in another city the board of health and the board of charities are combined. In the town of Nantucket, which is a separate county in itself, the county commissioners also function as the board of health. A physician serves as a member of the board in but 132 communities.

Table 3 shows a grouping of communities based on a classification of health officers.

Except for established health departments all health officers derive their authority from their appointments as agents of the boards of health.

The director of a local health unit should be a full-time, medically trained health officer. Services rendered by a health unit are such that a physician trained and experienced in modern public-health practice is best qualified to serve as a director.

Table 3 reveals the lack of full-time health officers, especially in the many communities with relatively small populations. Only 34.7 per cent of the population is served by health units employing full-time medically trained health officers. The full-time nonmedical health officers, serving 33.1 per cent of the population, have made a remarkable and praiseworthy contribution to the health administration of their communities. They have demonstrated their ability to hold responsible positions in public health, and there will always be a place

TABLE 4 *Public-Health Nurses in Massachusetts according to Employing Agency*

OFFICIAL AGENCY	TOTAL NO OF NURSES	VOLUNTARY AGENCY	TOTAL NO OF NURSES
Massachusetts Department of Public Health	31	Visiting Nurse Association	585
Boards of health	391	Insurance companies	17
School committee	306	Red Cross	10
Other	36	Others	3
	<hr/> 764		<hr/> 615

for the experienced or trained nonmedical health officer. The part-time officers are handicapped by the limitations inherent in such employment, their situation does not encourage efficiency or economy.

#### *Barnstable*

A county health department, authorized by the General Court, was established in Barnstable County in 1926. Independence of the board of health of each town is maintained in that the county health officer acts as agent only for the boards of health that specifically appoint him to do so. Towns preserve their full rights of local control, and some of them employ their own agents, inspectors and nurses. Health regulations of the towns are not uniform. The county health officer is not given adequate authority, and his knowledge and experience cannot be utilized to full advantage. This type of health organization is not sound.

#### *Local District Health Units*

In 1927 legislation was passed to permit the formation of health districts by unions of towns, small communities being allowed to avail themselves of the services of an adequately staffed full-time health department. The significance of that native feeling of local self-sufficiency may be appreciated by the fact that no towns have ever taken the initiative in forming such a union. However, in 1930, under a co-operative arrangement with the Commonwealth Fund, the Massachusetts Department of Public Health began to organize two separate local health units, one of 15 towns in the Southern Berk-

shire area, and another of 14 towns in the Nashoba Valley. A difficult task was accomplished in convincing the boards of health of the need for centralizing their health activities. By 1931, the two units were established. Each unit represented a voluntary grouping of towns, for the purpose of demonstrating the advisability of co-ordinated full-time health services not obtainable by the individual communities.

The director of each unit received his legal status by being appointed agent of the constituent boards of health. The local boards did not lose their identity or relinquish any of their prerogatives. The towns could vote themselves out of the union whenever they so desired. During the years of demonstration, the Commonwealth Fund financed the project with the expectation that the communities would realize the value of such a health district, and would assume complete financial responsibility. This did not materialize in the Berkshire Unit, which ceased to function in 1940 because of insufficient funds. The director of the Nashoba Unit resigned in 1943. War-time manpower shortages made it impossible to fill the vacancy. However, the Nashoba Associated Boards of Health organized a skeleton force and continued its activities on a limited scale.

The law permitting towns to join and form health units has not met with success in Massachusetts. There are two inherent weaknesses in the law. First of all, unions of towns are usually not contained within any established governmental unit and hence are difficult to administer. Secondly, towns may withdraw from the union, thus assuring no stability to it.

A medical director assumed responsibility for the Nashoba Health Unit on July 1, 1948. In conjunction with the Harvard School of Public Health, plans have been made for the development of a public-health field-training center in this unit, which at present is composed of nine towns. It is expected that the reorganized Nashoba Unit will demonstrate to other communities a workable solution of their local health problems.

#### *Nursing Service*

Every community in Massachusetts has some public-health nursing service administered by either official or voluntary agencies or a combination of both. Voluntary agencies are included because of the direct services they render to communities. Table 4 shows the number of nurses employed by each agency. There are approximately 1379 public-health nurses in the Commonwealth exclusive of industrial nurses, whose activities are mainly limited to industry. This would give a ratio of 1 nurse to each group of 3379 residents, if the distribution of nurses were even. However, the larger cities employ the majority of these nurses—for example Boston alone has 276 nurses. Also, 44 of the school nurses are employed part time. Therefore, the

above ratio does not indicate the true nursing facilities

The 1379 nurses in Massachusetts are employed by a total of 452 agencies. There are 97 communities with school nursing service only, and 90 communities with but 1 nurse carrying on generalized nursing services. There are 123 communities with more than 4 nurses whose activities are directed by three different agencies. Only 18 communities have agencies with a full-time nursing supervisor. Thus, although some of the small communities are urgently in need of more complete nursing service, many other communities have three or more agencies employing numerous nurses whose activities are not co-ordinated, whose services often overlap and whose programs actually are at times conflicting. Poor distribution of nurses, multiplicity of employing agencies, lack of adequate nursing supervision and the shortage of properly trained nursing personnel all combine to decrease the efficiency of public-health nursing. In addition, many nurses are employed in specialized programs that limit their nursing activities. The principle of generalized public-health nursing should be adopted for greater nursing benefits and for economy. Also, communities and agencies should in some way pool their nursing resources and work together as one team.

#### *Sanitarians*

The health units of 37 communities employ full-time sanitarians, and 118 employ part-time sanitarians. In 71 communities, the agent or some other employee of the board of health, in addition to his other duties, acts as the sanitary officer. In 110 communities, the services of a sanitary officer are not available, and it is assumed that some member of the board of health acts as sanitarian when the occasion arises. The remaining 15 communities jointly employ four full-time sanitarians. Thus, only 14.6 per cent of the communities have full-time sanitary officers, and 31.3 per cent are without the services of a sanitarian. The 220 towns with a population of 5000 or less can hardly be expected to employ full-time trained sanitarians unless they decide to combine their resources, as was done by the 15 communities mentioned above.

#### *Nutritionists*

There are approximately 30 full-time and 13 part-time nutritionists in the Commonwealth. The Greater Boston area accounts for 25 full-time and 11 part-time nutritionists, and Springfield, Lowell, Lawrence, Beverly, Pittsfield and Framingham account for the remainder. All other communities must depend upon the nutritional services offered by the Department of Public Health or voluntary agencies.

#### CONCLUSIONS

Adequate facilities are not available for the provision of basic health services to all citizens of

Massachusetts. The problem especially concerns many small communities, economically unable to provide these facilities and yet reluctant to form co-operative health units for the purpose of employing a sufficient number of trained personnel.

A duty and responsibility of civil government is to provide its citizens with all benefits conducive to maximum health and well-being. In 1797, the legislature authorized each community to provide a board of health. However, with the many changes that have occurred in all aspects of living, and with the increased medical knowledge, especially in prevention of disease, most local boards are not equipped at present to render modern health services and meet all emergencies. In larger communities, health departments with greatly increased facilities have been established, and progress has been satisfactory. In small communities, expansion has been impossible for economic reasons. Permissive laws have been passed in the hope that these communities would join forces in the battle for health, but to no avail. Since these communities elected to retain their local autonomy, efficient and often necessary health services are lacking because of inadequate facilities.

Local health units, rendering direct services to the people, form the foundation of public health in the nation. Sound public-health programs can be best administered through sound local health departments, covering the entire population. On the basis of existing facilities and laws, such health units are not feasible in this state. Massachusetts needs new laws and increased facilities to keep abreast of public-health progress.

The first and most important step is the enlightenment of the public. Pertinent information must be disseminated to all citizens, whose understanding and active interest are essential in effecting the changes necessary to correct existing inadequacies. We are indeed fortunate to live in a country in which the lawmakers respond favorably to the will of the people. Therefore, those interested in health must carry on a sustained, vigorous and intensive campaign until the ultimate goal has been attained — that is, the provision through local government of a sufficient number of adequately staffed, full-time local health units, so as to make available at least minimum health services to every person in Massachusetts and over every square mile of the Commonwealth.

#### REFERENCES

1. Emerson, H. and Luginbuhl, M. *Local Health Units for the Nation. A report.* 333 pp. New York: Commonwealth Fund, 1945.
2. *General Laws*, Chapter 41, Section 11.
3. *General Laws*, Chapter 111, Section 26, as amended.
4. *General Laws*, Chapter 111, as amended.
5. *General Laws*, Chapter 40, Section 4A.
6. *General Laws*, Acts of 1926, Chapter 133.
7. *General Laws*, Chapter 71, Section 53.

The director of a local health unit should be a full-time, medically trained health officer. Services rendered by a health unit are such that a physician trained and experienced in modern public-health practice is best qualified to serve as a director.

Table 3 reveals the lack of full-time health officers, especially in the many communities with relatively small populations. Only 34.7 per cent of the population is served by health units employing full-time medically trained health officers. The full-time nonmedical health officers, serving 33.1 per cent of the population, have made a remarkable and praiseworthy contribution to the health administration of their communities. They have demonstrated their ability to hold responsible positions in public health, and there will always be a place

TABLE 4 *Public-Health Nurses in Massachusetts according to Employing Agency*

OFFICIAL AGENCY	TOTAL No. of Nurses	VOLUNTARY AGENCY	TOTAL No. of Nurses
Massachusetts Department of Public Health	31	Visiting Nurse Association	585
Boards of health	391	Insurance companies	17
School committee	306	Red Cross	10
Other	36	Others	3
	764		615

for the experienced or trained nonmedical health officer. The part-time officers are handicapped by the limitations inherent in such employment, their situation does not encourage efficiency or economy.

#### *Barnstable*

A county health department, authorized by the General Court, was established in Barnstable County in 1926. Independence of the board of health of each town is maintained in that the county health officer acts as agent only for the boards of health that specifically appoint him to do so. Towns preserve their full rights of local control, and some of them employ their own agents, inspectors and nurses. Health regulations of the towns are not uniform. The county health officer is not given adequate authority, and his knowledge and experience cannot be utilized to full advantage. This type of health organization is not sound.

#### *Local District Health Units*

In 1927 legislation was passed to permit the formation of health districts by unions of towns, small communities being allowed to avail themselves of the services of an adequately staffed full-time health department. The significance of that native feeling of local self-sufficiency may be appreciated by the fact that no towns have ever taken the initiative in forming such a union. However, in 1930, under a co-operative arrangement with the Commonwealth Fund, the Massachusetts Department of Public Health began to organize two separate local health units, one of 15 towns in the Southern Berk-

shire area, and another of 14 towns in the Nashoba Valley. A difficult task was accomplished in convincing the boards of health of the need for centralizing their health activities. By 1931, the two units were established. Each unit represented a voluntary grouping of towns, for the purpose of demonstrating the advisability of co-ordinated full-time health services not obtainable by the individual communities.

The director of each unit received his legal status by being appointed agent of the constituent boards of health. The local boards did not lose their identity or relinquish any of their prerogatives. The towns could vote themselves out of the union whenever they so desired. During the years of demonstration, the Commonwealth Fund financed the project with the expectation that the communities would realize the value of such a health district, and would assume complete financial responsibility. This did not materialize in the Berkshire Unit, which ceased to function in 1940 because of insufficient funds. The director of the Nashoba Unit resigned in 1943. War-time manpower shortages made it impossible to fill the vacancy. However, the Nashoba Associated Boards of Health organized a skeleton force and continued its activities on a limited scale.

The law permitting towns to join and form health units has not met with success in Massachusetts. There are two inherent weaknesses in the law. First of all, unions of towns are usually not contained within any established governmental unit and hence are difficult to administer. Secondly, towns may withdraw from the union, thus assuring no stability to it.

A medical director assumed responsibility for the Nashoba Health Unit on July 1, 1948. In conjunction with the Harvard School of Public Health, plans have been made for the development of a public-health field-training center in this unit, which at present is composed of nine towns. It is expected that the reorganized Nashoba Unit will demonstrate to other communities a workable solution of their local health problems.

#### *Nursing Service*

Every community in Massachusetts has some public-health nursing service administered by either official or voluntary agencies or a combination of both. Voluntary agencies are included because of the direct services they render to communities. Table 4 shows the number of nurses employed by each agency. There are approximately 1379 public-health nurses in the Commonwealth exclusive of industrial nurses, whose activities are mainly limited to industry. This would give a ratio of 1 nurse to each group of 3379 residents, if the distribution of nurses were even. However, the larger cities employ the majority of these nurses—for example Boston alone has 276 nurses. Also, 44 of the school nurses are employed part time. Therefore, the

toses studied, furacin in solution and soluble dressing is an effective bactericidal agent

### SENSITIZING EFFECT

In consideration of the fact that a change in the base was made, the substitution of polyethylene glycol for propylene glycol, 25 volunteers were patch tested with the newer soluble dressing and the new base for irritant properties, ten days later the same volunteers were retested for sensitizing properties. The tests were applied to the skin for forty-eight hours, and reactions were noted at twenty-four, forty-eight, seventy-two and a hundred and twenty hours. The substances were applied under a 2.5-cm-square piece of cotton fabric covered with oiled silk and fixed with adhesive tape. The first application of the dressing and soluble base resulted in no reaction at twenty-four, forty-eight, seventy-two and a hundred and twenty hours. The second application ten days later resulted in no reaction in 24 of the volunteers. One subject developed pruritus and erythema 2 cm square, after twenty-four hours, this subsided in twenty-four hours, with negative findings at seventy-two and one-hundred and twenty hours, and no desquamation at the site of either test. Twelve cases of sensitivity reaction were noted in this group of 203 cases remaining under observation. Reactions were severe local erythematous vesicular and oozing outbreaks often accompanied by generalized eczematoid dermatitis involving the face, neck, trunk and extremities. Examples of reactions and investigations are best shown by the case reports presented below.

### CASE REPORTS

**CASE 1 L C** a 26-year-old man, suffered from an infectious eczematoid dermatitis of both lower legs for 6 months despite treatment with various ointments. On October 31, 1946, he was started on furacin soluble dressing twice daily. One week later he showed considerable improvement, with the lesions drying and less crusting present. On November 19 he reported to the Clinic his local dermatitis worse and accompanied by a generalized papulovesicular eruption. Treatment was suspended, and cornstarch baths were prescribed twice daily. The patient's condition became worse despite soothing applications. On November 26 he was hospitalized with a generalized eczematous dermatitis the face and legs were edematous and covered with oozing and crusted lesions. Under continued bed rest, baths and soothing applications, the dermatitis subsided in 2 weeks. The patient refused patch tests and further investigation.

**CASE 2 J C** a 38-year-old woman had an eczematous dermatitis of 5 years' duration on the right ankle and dorsum of the foot. Examination showed an irregular infiltrated area of eczematous dermatitis 7.6 by 10.2 cm in diameter over the lateral aspect of the right ankle and dorsum of the foot with ulcerated areas covering most of the lesion. Moderate vesicles of the right leg were noted. Serologic examination of the blood was negative. Daily application of furacin soluble dressing with bandaging was instituted on January 22, 1947. It was continued with slow improvement of the dermatitis and healing of the ulcerations until February 13, when the lesions on the foot showed decided increase in erythema and oozing accompanied by a generalized papular and eczematous dermatitis. Treatment was discontinued. Cornstarch baths and soothing applications were prescribed with general clearing of the dermatitis and symptoms in 3 weeks. On March 4 the patient consented to patch testing

with the following combinations of ingredients and results: furacin powder in vaseline (0.2 per cent), negative; carbowax (1540 in vaseline), negative; furacin powder in polyethylene glycol, + + + +, carbowax (4000 in vaseline) negative; furacin base (polyethylene glycol C W 1540 and 4000), negative; furacin and carbowax (1540-4000), negative; furacin soluble dressing (whole product), + +, and polyethylene glycol doubtful.

**CASE 3 A B** a 32-year-old man gave a history of recurrent attacks of infectious eczematoid dermatitis of both legs. On January 17, 1947, he showed vesicular crusted and oozing lesions extending from the midleg to the ankles. The past history indicated a poor response to various topical medication. A patch test with furacin soluble dressing to the left deltoid area was negative at 24, 48 and 72 hours and daily

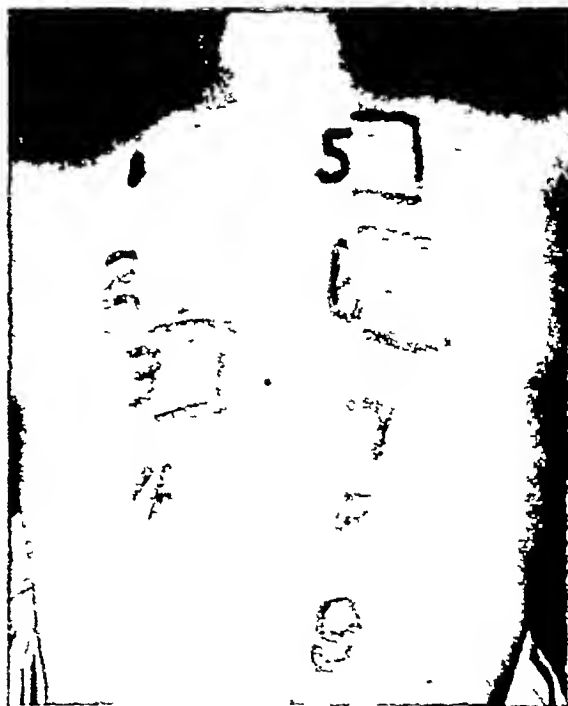


FIGURE 1 Positive Reactions in Case 3 at Sites of Furacin Soluble Dressing (3) Furacin Topical Solution (5) and Furacin Powder in Polyethylene Glycol (6)

applications of the dressing were started on January 20. Two days later the patient complained of increased burning and itching after application. Examination showed increased erythema, vesiculation and serous discharge over the involved areas. The eruption slowly improved under boric acid wet dressings and plain Lassar's paste daily. Four weeks later patch tests were performed with the various combinations of ingredients and results noted as follows: furacin powder in vaseline (0.2 per cent) negative; furacin and carbowax negative; furacin soluble dressing (whole product), +; furacin base (polyethylene glycol C W 1540 and 4000) negative; furacin topical solution + + +; furacin powder in polyethylene glycol + — —; polyethylene glycol doubtful; and carbowax (4000 in vaseline) negative. The reactions to furacin are shown in Figure 1.

**CASE 4 P M**, a 60-year-old man came to the Skin Clinic on February 20, 1947, showing on both legs eczematous lesions of 3 weeks' duration. Prior treatment had consisted of boric acid ointment and Lassar's paste without result. Treatment was instituted with furacin soluble dressing twice daily with gradual improvement and healing of the lesions.

## FURTHER STUDIES IN THE USE OF FURACIN IN DERMATOLOGY\*

JOHN GODWIN DOWNING, M D,† AND F WELLINGTON BRECKER, M D‡

BOSTON

FROM August, 1946, to September 10, 1947, 278 additional cases of dermatoses were treated with furacin (5-nitro-2-furaldehyde semicarbazone) soluble dressing and furacin solution by the Dermatologic Department of the Boston City Hospital. The diseases treated and the results obtained are presented in Table 1. It will be noted that the

contributory factor. However, 5 patients have died while under treatment with furacin compounds. Although in no case was the local medication deemed contributory, one cannot rule out the possibility of toxic effects by absorption. Therefore, it would be of extreme value if further studies were made to prove or disprove that the drug is

TABLE 1 Comparative Results in Diseases Treated

CONDITION	RESULT					TOTAL NO. OF CASES
	EXCELLENT	GOOD	QUESTION- ABLE	NONE	NO FOLLOW UP STUDY	
Group I (diseases due to infections with lower organisms)						
Cellulitis	—	2	—	—	—	2
Infectious eczematoid dermatitis	2	26	7	10	14	59
Ecthyma	—	21	3	2	6	32
Impetigo contagiosa	9	73	3	3	38	126
Sycosis vulgaris	—	4	1	1	3	9
Furuncle	—	—	1	—	4	5
Folliculitis	—	1	1	—	2	4
Group II (diseases due to higher plant or animal parasites)						
Tinea capitis ( <i>Microsporum audouinii</i> )	—	—	—	2	—	2
Group III (diseases due to intoxication)						
Dermatitis venenata	—	—	—	2	—	2
Group IV (diseases due to trauma or physical agents)						
Ulcer (decubitus)	—	3	—	2	2	7
Infection from second degree burn	—	—	—	—	1	1
Group V (diseases due to circulatory disturbances)						
Ulcer hypostaticum	—	14	2	3	2	21
Stasis eczema	—	2	—	1	—	3
Group VI (diseases due to metabolism disturbances)						
Acne vulgaris	—	—	—	1	3	4
Group VII (diseases of uncertain cause with structural reaction alone)						
Neurodermatitis	—	—	—	—	1	1
Totals	11	146	18	27	76	273

results obtained were similar to those in the original report.<sup>¶</sup> Again, the drug showed itself to be effective in the treatment of pyogenic infections—impetigo contagiosa, ecthyma and hypostatic and decubitus ulcers—and of some value in the treatment of infectious eczematoid dermatitides. However, the danger of sensitization in the latter group prohibits its extended use.

Two elderly women died while under treatment with furacin soluble dressing for decubitus ulcers. One died on the thirteenth day of therapy, and the other on the thirtieth day. They were over eighty years of age, and had been bedridden for years after multiple cerebral thromboses. Bronchopneumonia was the diagnosis at discharge in each case. Furacin soluble dressing was not considered as a

absorbed into the general circulation. In all these cases the local destruction of tissue was marked, and large amounts of medication were used.

## BACTERIOLOGY

Cultures of the bacterial flora present in the dermatoses treated were made in 59 cases before the institution of treatment. There were 124 strains of 9 species of organisms isolated. The gram-positive organisms—*Staphylococcus aureus*, *Staph. albus*, *Streptococcus haemolyticus*, *Corynebacterium diphtheriae* and diphtheroids—were found in 85.4 per cent of the total cultures. In the gram-negative group there were 10 cultures of *Pseudomonas aeruginosa*, 4 of *Proteus vulgaris* and 3 of enterococci. One case of pyoderma of the left foot showed a virulent *C. diphtheriae* growth and *Staph. albus*. A repeat culture in one week was negative for *C. diphtheriae*, and *Str. haemolyticus* was cultured. From the response noted in this group of derma-

\*From the Department of Dermatology, Boston City Hospital.

†Professor of dermatology, Tufts College Medical School, professor of dermatology, Boston University School of Medicine, dermatologist in chief, Boston City Hospital and Massachusetts Memorial Hospitals.

‡Assistant dermatologist, St. Francis Hospital, Hartford, Connecticut.

¶Downing J G, Hanson M C and Lamb M. Use of 5-nitro-2-furaldehyde semicarbazone in dermatology. *J A M A* 133:279-30, 1947.

toses studied, furacin in solution and soluble dressing is an effective bactericidal agent

### SENSITIZING EFFECT

In consideration of the fact that a change in the base was made, the substitution of polyethylene glycol for propylene glycol, 25 volunteers were patch tested with the newer soluble dressing and the new base for irritant properties, ten days later the same volunteers were retested for sensitizing properties. The tests were applied to the skin for forty-eight hours, and reactions were noted at twenty-four, forty-eight, seventy-two and a hundred and twenty hours. The substances were applied under a 2.5-cm-square piece of cotton fabric covered with oiled silk and fixed with adhesive tape. The first application of the dressing and soluble base resulted in no reaction at twenty-four, forty-eight, seventy-two and a hundred and twenty hours. The second application ten days later resulted in no reaction in 24 of the volunteers. One subject developed pruritus and erythema, 2 cm square, after twenty-four hours, this subsided in twenty-four hours, with negative findings at seventy-two and one-hundred and twenty hours, and no desquamation at the site of either test. Twelve cases of sensitivity reaction were noted in this group of 203 cases remaining under observation. Reactions were severe local, erythematous vesicular and oozing outbreaks, often accompanied by generalized eczematoid dermatitis involving the face, neck, trunk and extremities. Examples of reactions and investigations are best shown by the case reports presented below.

### CASE REPORTS

**CASE 1 L C**, a 26-year-old man, suffered from an infectious eczematoid dermatitis of both lower legs for 6 months, despite treatment with various ointments. On October 31, 1946, he was started on furacin soluble dressing twice daily. One week later he showed considerable improvement, with the lesions drying and less crusting present. On November 19 he reported to the Clinic, his local dermatitis worse and accompanied by a generalized papulovesicular eruption. Treatment was suspended, and cornstarch baths were prescribed twice daily. The patient's condition became worse despite soothing applications. On November 26 he was hospitalized with a generalized eczematous dermatitis, the face and legs were edematous and covered with oozing and crusted lesions. Under continued bed rest baths and soothing applications, the dermatitis subsided in 2 weeks. The patient refused patch tests and further investigation.

**CASE 2 J C**, a 38-year-old woman had an eczematous dermatitis of 5 years' duration on the right ankle and dorsum of the foot. Examination showed an irregular infiltrated area of eczematous dermatitis 7.6 by 10.2 cm in diameter, over the lateral aspect of the right ankle and dorsum of the foot, with ulcerated areas covering most of the lesion. Moderate vesicles of the right leg were noted. Serologic examination of the blood was negative. Daily application of furacin soluble dressing with bandaging was instituted on January 22, 1947. It was continued with slow improvement of the dermatitis and healing of the ulcerations until February 13, when the lesions on the foot showed decided increase in erythema and oozing, accompanied by a generalized papular and eczematous dermatitis. Treatment was discontinued. Cornstarch baths and soothing applications were prescribed with general clearing of the dermatitis and symptoms in 3 weeks. On March 4 the patient consented to patch testing,

with the following combinations of ingredients and results: furacin powder in vaseline (0.2 per cent), negative; carbowax (1540 in vaseline), negative; furacin powder in polyethylene glycol, ++++, carbowax (4000 in vaseline), negative; furacin base (polyethylene glycol C W 1540 and 4000), negative; furacin and carbowax (1540-4000), negative; furacin soluble dressing (whole product), ++, and polyethylene glycol, doubtful.

**CASE 3 A B**, a 32-year-old man, gave a history of recurrent attacks of infectious eczematoid dermatitis of both legs. On January 17, 1947, he showed vesicular crusted and oozing lesions extending from the midleg to the ankles. The past history indicated a poor response to various topical medication. A patch test with furacin soluble dressing to the left deltoid area was negative at 24, 48 and 72 hours, and daily

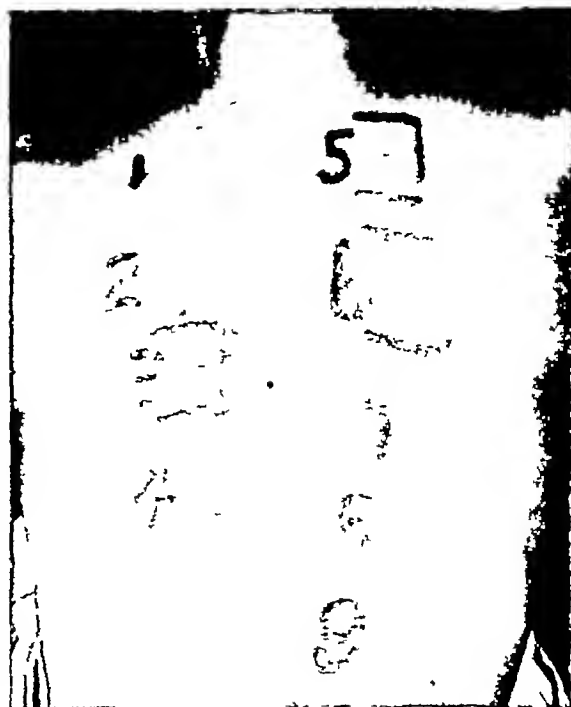


FIGURE 1 Positive Reactions in Case 3 at Sites of Furacin Soluble Dressing (3) Furacin Topical Solution (5) and Furacin Powder in Polyethylene Glycol (6)

applications of the dressing were started on January 20. Two days later the patient complained of increased burning and itching after application. Examination showed increased erythema, vesiculation and serous discharge over the involved areas. The eruption slowly improved under boric acid wet dressings and plain Lassar's paste daily. Four weeks later patch tests were performed with the various combinations of ingredients and results noted as follows: furacin powder in vaseline (0.2 per cent), negative; furacin and carbowax negative; furacin soluble dressing (whole product), +; furacin base (polyethylene glycol C W 1540 and 4000) negative; furacin topical solution, +++; furacin powder in polyethylene glycol, +; polyethylene glycol, doubtful; and carbowax (4000 in vaseline), negative. The reactions to furacin are shown in Figure 1.

**CASE 4 P M**, a 60-year-old man came to the Skin Clinic on February 20, 1947, showing on both legs eczematous lesions of 5 weeks' duration. Prior treatment had consisted of boric acid ointment and Lassar's paste without result. Treatment was instituted with furacin soluble dressings twice daily with gradual improvement and healing of the lesions.

until the 27th day, when sensitivity consisting of increased erythema, vesiculation and serous oozing developed at the sites of application. These lesions subsided in approximately 3 weeks with applications of bland ointments. Patch tests were performed with the following combinations of ingredients and results: furacin soluble dressing (whole product), ++, furacin topical solution, +++, furacin powder in polyethylene glycol, +++++, furacin base (polyethylene glycol C. W. 1540 and 4000), negative, furacin powder (0.2 per cent in C. W. 1540 and 4000), negative, furacin powder in vaseline, negative, carbowax (4000 in vaseline), negative, carbowax (1540 in vaseline), negative, and polyethylene glycol, negative.

The results in these cases strongly suggest that the sensitizing effect of the product is due to a synergistic action between the furacin powder and the polyethylene glycol present in the dressing.

### DISCUSSION

In addition to the cases reported above, the records of 30 patients treated in private practice showed similar results. In this group 2 patients became sensitized. Both were treated for a recurrence of otitis externa, after an apparent cure several months previously with furacin solution. Within forty-eight hours of reapplication of the substance there was marked erythema, vesiculation and oozing of the skin of the auricle and periauricular area. Several other cases of sensitization were seen in the office of one of us (J. G. D.), as well as in various state and federal institutions. These sensitizations were for the most part severe and disabling, necessitating hospitalization for weeks. With this increase in the number of untoward reactions, one becomes very careful and somewhat hesitant about prescribing these compounds, for it is difficult to foresee which patient will become sensitized. It is apparent that the longer the drug is used, the greater is the reaction to sensitivity.

It is believed that the number of these reactions will increase when the drug is used the second time, either for a recurrence of the previous eruption or for another pyogenic dermatosis. It might be noted in the patch tests that the furacin in addition to carbowax caused no reaction. Apparently, some chemical reaction from the combination of the polyethylene glycol and the furacin powder gives the sensitizing factor. Throughout the studies it was apparent that the best results were obtained in the use of the compounds in pyogenic infections

not sensitized — namely, impetigo contagiosa, ecthyma and otitis externa. The success of the compounds as noted by the subsequent cultures show that furacin is an effective agent in reducing infection. We therefore believe that if the element of sensitization were reduced, this drug would be of greater value in the treatment of pyogenic infections of the skin. Case 3 shows the futility of pre-treatment patch tests.

### SUMMARY

Two hundred and seventy-eight additional patients were treated at the Dermatologic Department of the Boston City Hospital with furacin (5-nitro-2-furaldehyde semicarbazone) in a soluble base and in topical solution. Two hundred and forty-five patients were treated with the product in the soluble base, and 33 with the topical solution of the product.

No noticeable difference in effectiveness in the soluble dressing and topical solution was noticed, with the possible exception of ease of application of the different products — that is, the solution was used in infectious eczematoid dermatitis in a group of cases secondary to ear infections with greater facility of application than the soluble base containing the product, whereas the soluble base seemed more satisfactory for use in ecthyma and ulcer cases.

The substitution of polyethylene glycol for propylene glycol in the product caused little or no sensitization of normal skin in a group of 25 volunteers tested.

The effectiveness of the compounds as noted by subsequent cultures showed that furacin is an effective agent in reducing infection.

Sensitization to the drug was noted in 12 out of 203 cases remaining under observation at the hospital, and in 2 out of a group of 30 cases seen in private practice, which makes over 6 per cent sensitization. This percentage is considered too high.

Sensitivity is apparently due to a synergistic action of the furacin powder and the polyethylene glycol on the abnormal skin treated.

With this high rate of sensitization, extreme care in the selection of cases and careful supervision of the patients using these compounds are recommended.

## MEDICAL PROGRESS

## CLINICAL AND PATHOLOGICAL ASPECTS OF ENCEPHALITIS\*

RAYMOND D ADAMS, M D,† AND LOUIS WEINSTEIN, M D ‡

BOSTON

A GREAT deal of confusion appears to exist in the minds of many physicians regarding the criteria necessary for the diagnosis of encephalitis. There is a common tendency on the part of clinicians to designate as encephalitis any disease in which fever and neurologic symptoms are conjoined. In the New England states and probably in many other areas of the United States this diagnosis almost invariably proves to be incorrect at autopsy. The pathologist in such cases usually turns out to be bacterial endocarditis with multiple brain emboli, tuberculosis or torulosis of the meninges, thrombophlebitis of cerebral vessels, tumor, vascular disease or abscess of the brain. Sometimes there are no demonstrable neuropathologic lesions, and by inference a diagnosis of acute "toxic" or confusional psychosis is reached. The purpose of this brief communication is therefore to present, for the use of general practitioners, some of the salient clinical and pathological features of the various types of encephalitis.

At the outset, an exact definition of *encephalitis* is required. As most generally used, this term signifies an inflammatory disease of the brain, if concomitant involvement of the brain and spinal cord exists the condition is specified as *encephalomyelitis*. Unfortunately, however, a few writers apply these names to a large variety of brain diseases of diverse etiology—some infectious and others not—hence such incongruous terms as "traumatic encephalitis" and "toxic encephalitis." The more restricted meaning is the one used in this paper. Meningitis, in the sense of an inflammatory disease confined to the pia-arachnoid membranes and subarachnoid space, is not included in the present discussion.

To obtain clarity of thought on this subject a sound classification of the various forms of encephalitis is essential. Several have been proposed, though none of them are entirely adequate. The following classification, based on etiology, if known, and otherwise on descriptive pathology, is probably the most satisfactory one available at present and

has the sanction of two eminent neuropathologists, Spielmeyer<sup>1</sup> and Greenfield<sup>2</sup>

- Encephalitis due to visible micro-organisms
  - Bacterial infections, such as focal embolic encephalomyelitis
  - Spirochetal infections such as syphilitic meningoencephalitis (general paresis)
  - Fungous infections, such as torula
  - Rickettsial disease, such as typhus
  - Parasitic infections, such as trichinosis, malaria and toxoplasmosis
- Encephalitis due to filterable viruses §
  - Encephalitis lethargica
  - St. Louis encephalitis
  - Equine encephalitis—Eastern, Western and Venezuelan types
  - Poliomyelitis
  - Herpes zoster
  - Mumps meningitis, ? encephalitis
  - Lymphocytic choriomeningitis
  - Infectious mononucleosis—probably of viral etiology
  - Herpes simplex encephalitis
  - Encephalitis with intranuclear inclusion bodies—? herpes simplex
  - Rabies
  - Lymphogranuloma venereum
- Encephalitis of unknown etiology
  - Acute disseminated encephalomyelitis—following exanthems such as measles, vaccination against rabies and cowpox, and serum reactions
  - Acute hemorrhagic encephalitis
    - Acute brain purpura
    - Acute necrotizing hemorrhagic encephalopathy (hemorrhagic leukoencephalitis of Hurst)
  - Encephalitis complicating scarlet fever and rheumatic fever
  - Acute "toxic" encephalopathy

## PATHOLOGY OF ENCEPHALITIS

The neuropathological changes in this heterogeneous group of inflammatory diseases appear, at first glance, to be hopelessly complex. Not only are the diseases varied but also many of them have a predilection for special parts of the nervous sys-

\*From the Neurological Service, Boston City Hospital, the Haynes Memorial and Evans Memorial, Massachusetts Memorial Hospitals, the Department of Neurology, Harvard Medical School, and the Department of Medicine, Boston University School of Medicine.

†Assistant professor of neurology, Harvard Medical School, visiting neurologist and neuropathologist, Boston City Hospital, lecturer in neurology, Tufts College Medical School, neurologist, Joseph H. Pratt Diagnostic Hospital.

‡Assistant professor of medicine, Boston University School of Medicine, physician and chief of service, Haynes Memorial, and assistant member, Evans Memorial, Massachusetts Memorial Hospitals.

§Japanese B, Russian tick borne, looping ill, and Australian X encephalitis are omitted from this classification and discussion because they have not been seen in the United States.

tem However, a survey of the morbid anatomy will show that there are only a limited number of ways in which the nervous system can react and that some pathological changes, common to all neurologic diseases of this type, depend more on special properties of brain tissue than on the causative agent For example, nerve cells can only react by degeneration and death, whatever the disease process, and regeneration does not occur The large amount of fatty material in the sheaths of the myelinated nerve fibers will, if caused to degenerate, excite the formation of phagocytes, both microglial and histiocytic, which form such a prominent feature of all inflammatory diseases Also, microglia will be activated by the selective degeneration of nerve cells and will assume elongated or pleomorphic forms often arranged in clusters or nodules, a process referred to as neuronophagia In some diseases, such as rabies and typhus fever, nodules of microglia, histiocytes and inflammatory cells sometimes known by special names — Babes's nodules in rabies — are present The neuroglial cells or astrocytes undergo hyperplasia in all subacute and chronic diseases and, since there is relatively little fibrous connective tissue in the brain, account for the reparative process — namely, gliosis Another general feature of all types of encephalitis is the infiltration of the perivascular spaces of Virchow-Robin, which have no counterpart in other organs, by lymphocytes, plasma cells or neutrophilic leukocytes, or all three This is especially prominent around the cortical and subependymal vessels The meninges are usually infiltrated with cells of the same type All these changes — that is, nerve-cell degeneration and neuronophagia, myelin destruction and its removal by macrophages, perivascular and meningeal infiltrates of inflammatory cells and ultimate gliosis — may occur in any inflammatory disease of the brain or spinal cord

Each of the different types of encephalitis is distinguished pathologically by the presence of the causative agent in the nervous tissue, the character of the lesion and the distribution of the lesions within the brain, spinal cord and peripheral nerves Demonstration of the causative agent by special stains or by culture is the only means by which a specific diagnosis can be made This is possible in most of the bacterial, fungous, spirochetal and parasitic diseases of the nervous system and in a few of the virus diseases by the occurrence of inclusion bodies In other infections, particularly those due to rickettsias and viruses, the etiologic factor has not been isolated or is so difficult to demonstrate that the diagnosis must depend either on the character and distribution of the lesions or on special serologic tests

The pathological changes in the bacterial, fungous, rickettsial, spirochetal and parasitic infections of the nervous system, with due allowance

for the special anatomic peculiarities of nervous tissue, closely resemble those in other viscera The changes in the brain in such diseases are viewed as part of a generalized infection and are not usually given separate consideration These general pathological findings are quite well known, having been well presented in most textbooks of pathology, and it is not necessary to describe them here

Neurotropic viruses, which comprise a large portion of the encephalitides due to viruses, exert their deleterious effects principally on the nervous system and have the following unique properties they enter the nervous system along nerves and spread by way of neurones from one part to another, they are incorporated into the protoplasm of the nerve cells and form, in some cases, intracytoplasmic or intranuclear inclusion bodies, and they have an affinity for certain groups of neurones

The nervous system reacts to many of the neurotropic virus infections in a fairly uniform manner There is evidence of nerve-cell destruction, proliferation of microglial cells, meningeal and perivascular infiltrates of lymphocytes and gliosis In some of the more strictly neurotropic virus infections, such as poliomyelitis and encephalitis lethargica, neurone damage or destruction is the primary event, and the activation of microglial cells and probably the meningeal, perivascular infiltration are secondary This type of reaction is so characteristic that the pathologist is probably justified in inferring from its presence the existence of a virus The occurrence of this type of pathological reaction is the chief basis for classifying encephalitis lethargica and herpes zoster as virus infections because in neither disease has the organism been isolated In other more acute forms of encephalitis, such as St Louis, equine and Japanese B, however, the brain damage is not limited to the nerve cells These forms have therefore been called pantropic instead of neurotropic In these there are scattered petechial hemorrhages, focal areas of tissue necrosis and microglial proliferation, and lymphocytic and neutrophilic leukocytic infiltrates in the gray matter and to a slight extent the white matter All the proved virus infections of the nervous system are essentially diseases of the gray matter — that is, polioclastic

Although many types of virus disease of the brain conform to the general type of pathological reaction described above, minor differences between them deserve special emphasis

In *encephalitis lethargica* (epidemic or Type A encephalitis), as in most infections of the brain, there are usually no gross changes or, at most, only slight opacity of the arachnoid membrane, congestion of vessels in the meninges, occasionally a few petechial hemorrhages in the gray matter and slight brain swelling There is marked destruction of the nerve cells in the substantia nigra, nuclei

in the hypothalamus, globus pallidus and tegmentum of the pons. Relatively few lesions are seen in the cerebral cortex and cerebellum, medulla and spinal cord. These lesions are of several types. Many nerve cells disappear completely, and others appear altered in several ways — that is, shrunken or chromatolytic. There are nodules of transitional microglial cells and astrocytes and parenchymatous infiltrations of lymphocytes and plasma cells. Lymphocytes and mononuclear leukocytes are also found in the perivascular spaces, chiefly about the veins, in the midbrain, walls of the third ventricle and basal ganglions. Meningeal infiltration is slight. Minute bodies have been demonstrated by toluidine blue and silver stains in the cytoplasm of nerve cells, but a definite opinion regarding their nature has not been expressed. Definite inclusion bodies have not been identified. In subacute cases, inflammatory cells are less numerous, and reparative gliosis more pronounced, in the chronic cases which are the only ones being seen by present-day pathologists, the chief findings are loss of and degeneration of neurones, especially in the substantia nigra, which may be grossly depigmented, and gliosis (von Economo<sup>3</sup>).

In *St. Louis encephalitis* the lesions are fairly uniformly distributed through the cerebral cortex, basal ganglions and brain stem. Occasionally petechial hemorrhages and congestion of blood vessels are noted. There is a mild leptomeningeal infiltration of lymphocytes and other mononuclear cells at the base of the brain, and the perivascular spaces contain similar cells. The nerve-cell injury varies with the severity of the infection, in severe cases swelling and chromatolysis, or shrinkage of cell bodies and finally disappearance of cells occurs. Focal and diffuse infiltrations of lymphocytes and, in acute cases, neutrophilic leukocytes are found. Neuronophagia is prominent. Foci of tissue necrosis, both interstitial and parenchymatous, with microglial proliferation and gliosis in the gray and to a slight extent the adjacent white matter, are not infrequent (Weil<sup>4</sup>). *St. Louis encephalitis* differs from *encephalitis lethargica* in that the lesions are more widely distributed through the cerebrum, the meningitis is more severe, nerve-cell damage in the pallidum and the substantia nigra is less marked, and focal necrosis and microglial proliferation are more extensive. The picture in Japanese B encephalitis is indistinguishable from that of *St. Louis encephalitis* (Zimmerman<sup>5</sup>). Foci of necrosis with demyelination and in more chronic cases, gliosis and even calcification with giant-cell formation have been reported. In neither disease are inclusion bodies seen.

In *equine encephalitis* the lesions are also scattered widely throughout the nervous system: the brain stem, basal ganglions and cerebral cortex are involved. In the acute cases there are focal and

diffuse lesions with destruction of nerve cells and interstitial tissue and extensive infiltration of neutrophilic leukocytes, lymphocytes and mononuclear leukocytes. The endothelium of the arterioles and capillaries is proliferated, necrosis of endothelial cells, fibrin impregnation and thrombi are occasionally seen in some such vessels. Myelin is destroyed in some of the foci (Farber et al.<sup>6</sup>). The meningeal reaction is more intense, the extent of brain damage including nerve-cell degeneration is greater, and migration of neutrophilic leukocytes is more prominent in the Eastern variety, than in other forms of encephalitis. Actually however, there are only minor differences between equine, *St. Louis* and Japanese B encephalitis. In neither Eastern nor Western forms have inclusion bodies been found.

In acute cases of *poliomyelitis* extreme congestion of blood vessels and swelling of the spinal cord may be observed grossly. The greatest damage is in the spinal cord, where, regardless of the distribution of paralytic symptoms, lesions can be found in every segment. The motor cortex, globus pallidus, substantia nigra, subthalamus, tegmentum of the midbrain, pons and medulla and the cerebellum are also involved frequently (Bodian<sup>7</sup>). The lesions are confined to gray matter for the most part and vary in intensity. Nerve cells become shrunken and darkly stained and disintegrate in an incredibly short time. Migration of neutrophilic leukocytes into the affected tissue occurs in the first day or two of the infection and is accompanied and followed by the appearance of transitional forms of microglia and activated histiocytes. Infiltration of the perivascular spaces and meninges by neutrophilic leukocytes, lymphocytes and other mononuclear cells occurs. Neuronophagia is pronounced. Secondary degeneration of motor-nerve fibers and of tracts in the anterior and lateral columns of the spinal cord become evident later. Gliosis is prominent in the older lesions. Pathologists are not in complete agreement about the occurrence of intranuclear inclusion bodies. *Poliomyelitis* is distinguished from other forms of encephalitis by the more severe affection of the spinal cord and the relative paucity of focal-tissue necrosis.

In *herpes zoster* the lesions are usually confined to one or several contiguous dorsal-root ganglions and their corresponding peripheral nerves and spinal roots (Denny-Brown, Adams and Fitzgerald<sup>8</sup>). In severe cases, part or all of the sensory ganglion may undergo complete necrosis with or without hemorrhage, whereas in milder cases some of the nerve cells survive and necrosis of the interstitial tissue is less severe or does not occur at all. There is degeneration of the fibers of the damaged nerve cells in both the peripheral nerve and dorsal root. The adjacent ventral or motor root may also be affected. The involved ganglions, nerves and roots are infiltrated by lymphocytes, mononuclear cells and a variable number of plasma cells. Often,

similar cells are seen in the pia arachnoid, in the perivascular spaces and in the homolateral posterior and ventral horns of gray matter of related spinal segments. The latter findings, combined with nerve-cell destruction and microglial proliferation, have the aspect of a unilateral poliomyelitis. In addition, cells of the epidermis swell, coalesce, vacuolate and exhibit large intranuclear inclusion bodies (Lipschutz<sup>9</sup>). The latter are not found in the nervous system. In exceptional cases involvement of the brain and spinal cord is widespread, giving a picture of encephalitis or myelitis. Perivascular lymphocytic infiltrations and scattered small perivascular hemorrhages have been found by Biggart and Fisher<sup>10</sup> in the medulla, cerebellar nuclei, thalamus and hypothalamus. Nerve cells at various levels of the brain stem and cortex had undergone chromatolysis. In such cases it is sometimes difficult to exclude the possibility that the zoster infection is a complication of another type of encephalitis.

In the few autopsies that have been performed in cases of epidemic parotitis the principal lesions have comprised scattered leptomeningeal and perivascular infiltrations of lymphocytes and other mononuclear cells without definite parenchymatous changes (Larkin<sup>11</sup>). In isolated cases the typical foci of perivenous demyelination and microglial proliferation that are characteristic of post-infectious encephalomyelitis, or an associated thrombosis of venous sinuses, have been reported.

In the few reports of post-mortem examinations in benign lymphocytic choriomeningitis the only significant neuropathologic abnormalities consisted of a leptomeningitis with lymphocytes and other mononuclear cells in the pia arachnoid, subarachnoid and perivascular spaces. Around some of the veins in the cerebral white matter there were small numbers of lymphocytes. Inclusion bodies were seen in the cytoplasm of some of the nerve cells (Viets and Warren<sup>12</sup>).

In the few cases of encephalitis with Type A intranuclear inclusion bodies, there has been degeneration of the nerve cells in the cerebral cortex, especially the precentral and hippocampal convolutions, the basal ganglions, midbrain, pons, medulla and the anterior and posterior horns of the spinal cord. Numerous small foci of necrosis also occur in the gray and white matter. Proliferation of microglial cells and perivascular and slight leptomeningeal infiltrations of lymphocytes were most pronounced in places where the neuronal degeneration was severe (Brain, Greenfield, and Russell<sup>13</sup>).

The central-nervous-system involvement in infectious mononucleosis takes the form of a leptomeningitis with the infiltrating cells consisting of lymphocytes, plasma cells and other mononuclear elements of lymphocytic or histiocytic origin (so-called abnormal lymphocytes). In a few cases wide-

spread degeneration of the peripheral nerves and dorsal-root-ganglion cells and extensive infiltrations of these structures by inflammatory cells have occurred. Aside from swelling and chromatolysis of the spinal anterior-horn cells, scattered nodules of glial cells and lymphocytes are the only other important changes in the nervous system<sup>14-16</sup>.

In one of the very few fatal cases of *lymphogranuloma venereum*, post-mortem examination revealed a diffuse meningeal reaction with predominant lymphocyte and plasma-cell infiltration and localized areas of subpial necrosis.

In rabies, there are well marked inflammatory lesions in the sensory ganglions, spinal cord, mid-brain, cerebellar cortex, hippocampal convolutions, olfactory bulbs and, sometimes, other parts of the cerebral cortex. Infiltrations of neutrophilic leukocytes and lymphocytes, both diffuse and perivascular, proliferation of microglial cells and astrocytes, nodules of glial and inflammatory cells (Babes) and lymphocytic invasion of the meninges make up the pathologic picture. Nerve-cell destruction is prominent. Characteristic cytoplasmic inclusion bodies (Negri bodies) are found in intact relatively normal nerve cells, particularly those in the hippocampal gyrus and cerebellar cortex. The distribution of the lesions is determined, to some extent, by the location of the wound. In bites of the leg the gray matter of the lumbar sensory ganglions is involved. In some cases of so-called "dumb rabies" the changes are largely confined to the spinal cord and resemble poliomyelitis (Hurst and Pawan<sup>17</sup>).

The pathology of the encephalitudes of unknown cause is essentially one of myelin destruction, microglial proliferation and meningeal and perivascular lymphocytic and mononuclear infiltrations. Unlike the known neurotropic virus infections the greatest damage is to white matter, and the nerve cells are affected slightly or not at all—hence the common designation myelinoclastic or leukoclastic encephalitis for this group. The microglial reaction, which develops early in the course of the disease, is probably secondary to damage of myelinated nerve fibers<sup>18, 19</sup>. Thrombosis of veins, although hypothesized as the cause of the demyelination, has not been found in our material.

There are no important pathological differences between the acute disseminated encephalomyelitis that follows measles, chicken pox, smallpox, injection with cowpox or rabies vaccine, and possibly allergic reactions to heterologous protein such as horse serum. All are alike so far as the myelin is destroyed in minute perivascular or subpial foci, the axis cylinders are damaged to a much less degree and necrosis of interstitial tissue does not occur. Although this condition follows certain acute exanthems believed to be caused by a virus, no causative agent has been isolated from the nervous system.

It has been suggested that acute disseminated encephalomyelitis and acute multiple sclerosis or even Schilder's disease are related. At present, however, the differences between these diseases are far more impressive than the similarities, and there is no substantial evidence that either multiple sclerosis or Schilder's disease is inflammatory.

*Acute hemorrhagic encephalitis*, acute necrotizing hemorrhagic encephalopathy and hemorrhagic leukoencephalitis are names that refer to a pathologic process consisting of hemorrhage and necrosis of the brain tissue. Although cases of this type are more frequent during epidemics of encephalitis, they occur sporadically at other times. From a review of our material and other published cases,<sup>20</sup> we have concluded that at least two different disease entities had been described under this heading. In one type there is one large area or several smaller confluent areas confined either to the cerebral white matter or to the brain stem, with extensive necrosis of all tissue elements including many of the small blood vessels, exudation of fibrin and migration of neutrophilic leukocytes in the damaged brain and adjacent leptomeninges. This usually takes a rapidly fatal course, although subacute and chronic cases with corresponding differences in pathology are known. They have all the aspects of an allergic inflammation. The other type is essentially a brain purpura with petechial hemorrhages and small nonhemorrhagic perivascular foci of tissue damage that are widely disseminated through the white matter. A proliferation of microglial cells and histiocytes in these foci can usually be demonstrated, but inflammatory reaction is entirely absent. The degree of damage to myelinated nerve fibers and the ease with which it can be demonstrated depend somewhat on the duration of the disease. This type of brain purpura is more suggestive of a toxic damage to blood vessels than an encephalitis in the strict sense of the word. Viruses or bacteria have not been identified in either of these two types of lesion.

The other forms of encephalitis of indeterminate etiology lack precise pathological definition. In fatal cases of scarlet fever a variety of different pathological changes, such as brain hemorrhage, embolism and hemorrhagic necrosis, have been described. However, very few such cases have been examined by present-day pathological techniques. From the most authoritative writings on rheumatic fever it seems reasonably well established that Aschoff bodies do not occur in the nervous system. Furthermore, most of the reported cases of so-called rheumatic arteritis do not stand careful scrutiny. Even for Sydenham's chorea, an accepted neurologic complication of rheumatic fever, there is no assignable morbid anatomy. Additional pathological studies of cases of rheumatic fever and scarlet fever with aseptic meningitis and neurologic symptoms are needed.

There is the same uncertainty concerning the pathologic changes in the exceptional cases in which an injection of tetanus toxoid or T A B vaccine has been followed by a meningoencephalitis or myelitis (Palmer<sup>21</sup>). Autopsy has disclosed findings identical with or very closely resembling those of poliomyelitis in some cases and postvaccinal encephalomyelitis in others.

Acute "toxic" encephalopathy is another condition about which there is much difference of opinion. The brain edema, the acute changes in the cortical neurones, the congestion of meningeal vessels and the slight hyperplasia of the adventitial and endothelial cells of small vessels sometimes called "productive encephalitis" are held by some writers to be responsible for the neurologic symptoms. Others maintain that they are artifacts or nonspecific reactions to fever, shock, anoxia and so forth. It is clear that there is no sign of inflammation and that in such transient and reversible neurologic syndromes as this one the expected pathophysiology will be subtle and difficult to demonstrate by present-day methods.

#### CLINICAL ASPECTS

Each of the types of encephalitis due to visible microbes can usually be recognized by the symptoms and laboratory findings of that particular disease. There should, for example, be no difficulty in distinguishing diseases as different as general paresis, trichinosis and subacute bacterial endocarditis. In these, as well as in neurotropic virus infections, involvement of the nervous system is indicated by the occurrence of general symptoms such as drowsiness, confusion, stupor or coma and of focal symptoms such as convulsions, hemiplegia, aphasia, ataxia, cranial-nerve palsies, tremor, chorea, athetosis and rigidity and by evidence of meningeal irritation—that is, headache and stiff neck. The cerebrospinal fluid usually contains an excess of cells, mostly lymphocytes, and increased amounts of protein with normal sugar and chloride levels.

The clinical syndromes produced by virus diseases of the brain, which have been reviewed recently by Rivers,<sup>22</sup> depend not on any peculiarity of the virus itself but on the location of the major pathologic changes. For instance poliomyelitis differs from St. Louis encephalitis because of the presence of predominant spinal motor symptoms and a paucity of cerebral symptoms. In the differential diagnosis of virus diseases of the brain, reliance must be placed not only on the clinical picture but also on such epidemiologic features as the geographic location and season of the year, as well as on the coexistence of systemic symptoms and the presence of cerebrospinal-fluid abnormalities. Sometimes even pathological examination will not suffice, and the diagnosis can be established only by special laboratory procedures such as isolation of the virus after embronated egg inoculation.

similar cells are seen in the pia arachnoid, in the perivascular spaces and in the homolateral posterior and ventral horns of gray matter of related spinal segments. The latter findings, combined with nerve-cell destruction and microglial proliferation, have the aspect of a unilateral poliomyelitis. In addition, cells of the epidermis swell, coalesce, vacuolate and exhibit large intranuclear inclusion bodies (Lipschutz<sup>9</sup>). The latter are not found in the nervous system. In exceptional cases involvement of the brain and spinal cord is widespread, giving a picture of encephalitis or myelitis. Perivascular lymphocytic infiltrations and scattered small perivascular hemorrhages have been found by Biggart and Fisher<sup>10</sup> in the medulla, cerebellar nuclei, thalamus and hypothalamus. Nerve cells at various levels of the brain stem and cortex had undergone chromatolysis. In such cases it is sometimes difficult to exclude the possibility that the zoster infection is a complication of another type of encephalitis.

In the few autopsies that have been performed in cases of *epidemic parotitis* the principal lesions have comprised scattered leptomeningeal and perivascular infiltrations of lymphocytes and other mononuclear cells without definite parenchymatous changes (Larkin<sup>11</sup>). In isolated cases the typical foci of perivenous demyelination and microglial proliferation that are characteristic of post-infectious encephalomyelitis, or an associated thrombosis of venous sinuses, have been reported.

In the few reports of post-mortem examinations in benign *lymphocytic choriomeningitis* the only significant neuropathologic abnormalities consisted of a leptomeningitis with lymphocytes and other mononuclear cells in the pia arachnoid, subarachnoid and perivascular spaces. Around some of the veins in the cerebral white matter there were small numbers of lymphocytes. Inclusion bodies were seen in the cytoplasm of some of the nerve cells (Viets and Warren<sup>12</sup>).

In the few cases of encephalitis with Type A intranuclear inclusion bodies, there has been degeneration of the nerve cells in the cerebral cortex, especially the precentral and hippocampal convolutions, the basal ganglions, midbrain, pons, medulla and the anterior and posterior horns of the spinal cord. Numerous small foci of necrosis also occur in the gray and white matter. Proliferation of microglial cells and perivascular and slight leptomeningeal infiltrations of lymphocytes were most pronounced in places where the neuronal degeneration was severe (Brain, Greenfield, and Russell<sup>13</sup>).

The central-nervous-system involvement in *infectious mononucleosis* takes the form of a leptomeningitis with the infiltrating cells consisting of lymphocytes, plasma cells and other mononuclear elements of lymphocytic or histiocytic origin (so-called abnormal lymphocytes). In a few cases wide-

spread degeneration of the peripheral nerves and dorsal-root-ganglion cells and extensive infiltrations of these structures by inflammatory cells have occurred. Aside from swelling and chromatolysis of the spinal anterior-horn cells, scattered nodules of glial cells and lymphocytes are the only other important changes in the nervous system<sup>14-16</sup>.

In one of the very few fatal cases of *lymphogranuloma venereum*, post-mortem examination revealed a diffuse meningeal reaction with predominant lymphocyte and plasma-cell infiltration and localized areas of subpial necrosis.

In rabies, there are well marked inflammatory lesions in the sensory ganglions, spinal cord, midbrain, cerebellar cortex, hippocampal convolutions, olfactory bulbs and, sometimes, other parts of the cerebral cortex. Infiltrations of neutrophilic leukocytes and lymphocytes, both diffuse and perivascular, proliferation of microglial cells and astrocytes, nodules of glial and inflammatory cells (Babes) and lymphocytic invasion of the meninges make up the pathologic picture. Nerve-cell destruction is prominent. Characteristic cytoplasmic inclusion bodies (Negri bodies) are found in intact relatively normal nerve cells, particularly those in the hippocampal gyrus and cerebellar cortex. The distribution of the lesions is determined, to some extent, by the location of the wound. In bites of the leg the gray matter of the lumbar sensory ganglions is involved. In some cases of so-called "dumb rabies" the changes are largely confined to the spinal cord and resemble poliomyelitis (Hurst and Pawan<sup>17</sup>).

The pathology of the encephalitides of unknown cause is essentially one of myelin destruction, microglial proliferation and meningeal and perivascular lymphocytic and mononuclear infiltrations. Unlike the known neurotropic virus infections the greatest damage is to white matter, and the nerve cells are affected slightly or not at all — hence the common designation myelinoclastic or leukoclastic encephalitis for this group. The microglial reaction, which develops early in the course of the disease, is probably secondary to damage of myelinated nerve fibers<sup>18, 19</sup>. Thrombosis of veins, although hypothesized as the cause of the demyelination, has not been found in our material.

There are no important pathological differences between the acute disseminated encephalomyelitis that follows measles, chicken pox, smallpox, injection with cowpox or rabies vaccine, and possibly allergic reactions to heterologous protein such as horse serum. All are alike so far as the myelin is destroyed in minute perivascular or subpial foci, the axis cylinders are damaged to a much less degree and necrosis of interstitial tissue does not occur. Although this condition follows certain acute exanthems believed to be caused by a virus, no causative agent has been isolated from the nervous system.

It has been suggested that acute disseminated encephalomyelitis and acute multiple sclerosis or even Schilder's disease are related. At present, however, the differences between these diseases are far more impressive than the similarities, and there is no substantial evidence that either multiple sclerosis or Schilder's disease is inflammatory.

*Acute hemorrhagic encephalitis* acute necrotizing hemorrhagic encephalopathy and hemorrhagic leukoencephalitis are names that refer to a pathologic process consisting of hemorrhage and necrosis of the brain tissue. Although cases of this type are more frequent during epidemics of encephalitis they occur sporadically at other times. From a review of our material and other published cases,<sup>20</sup> we have concluded that at least two different disease entities had been described under this heading. In one type there is one large area or several smaller confluent areas confined either to the cerebral white matter or to the brain stem, with extensive necrosis of all tissue elements including many of the small blood vessels, exudation of fibrin and migration of neutrophilic leukocytes in the damaged brain and adjacent leptomeninges. This usually takes a rapidly fatal course, although subacute and chronic cases with corresponding differences in pathology are known. They have all the aspects of an allergic inflammation. The other type is essentially a brain purpura with petechial hemorrhages and small nonhemorrhagic perivascular foci of tissue damage that are widely disseminated through the white matter. A proliferation of microglial cells and histiocytes in these foci can usually be demonstrated, but inflammatory reaction is entirely absent. The degree of damage to myelinated nerve fibers and the ease with which it can be demonstrated depend somewhat on the duration of the disease. This type of brain purpura is more suggestive of a toxic damage to blood vessels than an encephalitis in the strict sense of the word. Viruses or bacteria have not been identified in either of these two types of lesion.

The other forms of encephalitis of indeterminate etiology lack precise pathological definition. In fatal cases of scarlet fever a variety of different pathological changes, such as brain hemorrhage, embolism and hemorrhagic necrosis, have been described. However, very few such cases have been examined by present-day pathological techniques. From the most authoritative writings on rheumatic fever it seems reasonably well established that Aschoff bodies do not occur in the nervous system. Furthermore, most of the reported cases of so-called rheumatic arteritis do not stand careful scrutiny. Even for Sydenham's chorea, an accepted neurologic complication of rheumatic fever, there is no assignable morbid anatomy. Additional pathological studies of cases of rheumatic fever and scarlet fever with aseptic meningitis and neurologic symptoms are needed.

There is the same uncertainty concerning the pathologic changes in the exceptional cases in which an injection of tetanus toxoid or T A B vaccine has been followed by a meningoencephalitis or myelitis (Palmer<sup>21</sup>). Autopsy has disclosed findings identical with or very closely resembling those of poliomyelitis in some cases and postvaccinal encephalomyelitis in others.

Acute "toxic" encephalopathy is another condition about which there is much difference of opinion. The brain edema, the acute changes in the cortical neurones, the congestion of meningeal vessels and the slight hyperplasia of the adventitial and endothelial cells of small vessels sometimes called "productive encephalitis" are held by some writers to be responsible for the neurologic symptoms. Others maintain that they are artifacts or nonspecific reactions to fever, shock, anoxia and so forth. It is clear that there is no sign of inflammation and that in such transient and reversible neurologic syndromes as this one the expected pathophysiology will be subtle and difficult to demonstrate by present-day methods.

#### CLINICAL ASPECTS

Each of the types of encephalitis due to visible microbes can usually be recognized by the symptoms and laboratory findings of that particular disease. There should, for example, be no difficulty in distinguishing diseases as different as general paresis, trichinosis and subacute bacterial endocarditis. In these, as well as in neurotropic virus infections, involvement of the nervous system is indicated by the occurrence of general symptoms such as drowsiness, confusion, stupor or coma and of focal symptoms such as convulsions, hemiplegia, aphasia, ataxia, cranial-nerve palsies, tremor, chorea, athetosis and rigidity and by evidence of meningeal irritation—that is, headache and stiff neck. The cerebrospinal fluid usually contains an excess of cells, mostly lymphocytes, and increased amounts of protein with normal sugar and chloride levels.

The clinical syndromes produced by virus diseases of the brain, which have been reviewed recently by Rivers,<sup>22</sup> depend not on any peculiarity of the virus itself but on the location of the major pathologic changes. For instance, poliomyelitis differs from St. Louis encephalitis because of the presence of predominant spinal motor symptoms and a paucity of cerebral symptoms. In the differential diagnosis of virus diseases of the brain, reliance must be placed not only on the clinical picture but also on such epidemiologic features as the geographic location and season of the year, as well as on the coexistence of systemic symptoms and the presence of cerebrospinal-fluid abnormalities. Sometimes even pathological examination will not suffice and the diagnosis can be established only by special laboratory procedures such as isolation of the virus after embronated egg inoculation.

the determination of the presence of neutralizing antibody or the demonstration of increasingly positive serologic reactions such as complement fixation and inhibition of erythrocyte agglutination.

In the New England states, during the past decade, there have been no verified cases of acute encephalitis lethargica, St. Louis encephalitis has not been reported in this area, and Eastern equine encephalitis has not occurred except possibly in isolated cases since 1938-1939. Japanese B, Australian X, Russian tick-borne and Western or Venezuelan encephalitis are unknown here. Mumps meningo-encephalitis, infectious mononucleosis, poliomyelitis, herpes zoster, herpes simplex, rabies, lymphocytic choriomeningitis and lymphogranuloma venereum are the diseases that have been and will undoubtedly continue to be encountered in this section of the country.

Acute disseminated encephalomyelitis can usually be recognized without difficulty if there is knowledge of preceding measles, chicken pox, smallpox or other exanthem or of vaccination with either highly active viruses or attenuated ones. These diseases occur sporadically throughout the year, being more frequent whenever the exanthems are prevalent. It should be stressed that acute disseminated encephalomyelitis occasionally occurs before the rash becomes apparent, as in measles, and that in infants and children the encephalomyelitis may be so mild as to go undetected at the time of the acute exanthem only to become manifest years later when marked abnormalities in behavioral patterns appear.

Diseases suspected of being caused by filterable viruses, such as infectious mononucleosis, acute infectious hepatitis and acute infective polyneuritis, are apparently endemic in this region. We have seen a few cases with central-nervous-system involvement each year.

A brief summary of the clinical and laboratory findings of each of the types of encephalitis likely to be seen in the United States is presented below.

### *Encephalitis Lethargica*

Although acute cases are not being seen in the United States, a considerable number of patients who exhibit the sequelae of this disease continue to visit the outpatient clinics of medical and neurologic services. The most common manifestations are tremor, rigidity and slowness of voluntary movements, which combine to form a clinical picture resembling in some ways the hepatolenticular degeneration of Wilson and, in others, paralysis agitans. Important differences that should be stressed are the absence of corneal pigmentation (Kaiser-Fleischer rings), of the mixed static and intentional tremor, and of the evidence of liver disease, which are common in Wilson's disease and the presence of bizarre postures and gaits, and other muscular spasms such as oculogyric crises, and

torticollis, of coarse tremors and behavioral peculiarities, which are rarely encountered in paralysis agitans. The disease follows a variable course, usually slowly progressive, and death results years later from a severe muscular rigidity, which immobilizes the patient and finally from intercurrent infection. The majority of these patients are afebrile, and the cerebrospinal fluid is normal. In other words, there is no indication of an infectious process during the chronic phases of the illness, and often no trace of an inflammatory reaction at autopsy. A unique feature of the disease is this progressive damage of the basal ganglia over a long period, often without manifest inflammatory activity at autopsy. The diagnosis is made entirely from the clinical features of the disease. There are no confirmative laboratory tests.

### *St. Louis Encephalitis*

This disease differs from the von Economo type of encephalitis in its greater incidence in patients over the age of forty-five and in its prevalence during the summer months. The clinical picture shows tremendous variability because of the differences in severity of the infection and localization of the lesions in the brain and spinal cord. Three different syndromes have been described. The first consists of signs of meningeal irritation and increased intracranial pressure with difficulty in speech, ataxia, mental confusion and tremors of the tongue, lips or hands appearing abruptly without prodromal manifestations. Lethargy is not present in every patient. Paralysis is uncommon and is usually spastic in character. Eye-muscle involvement is extremely rare. The deep reflexes are usually exaggerated, and the abdominal ones are absent. Fever, usually disappearing within seven to ten days, may persist, in some cases, for from four to six weeks. The second is a syndrome characterized by prodromal manifestations of headache, generalized muscular pain, sore throat, mild conjunctivitis and photophobia that may last for from one to four days. After this period, the course of the disease is essentially the same as that in the first type. The third syndrome consists of so-called "abortive" cases of St. Louis encephalitis in which only fever and headache are present. These cases are usually detected because they occur in an area where this type of encephalitis is present, and lumbar puncture reveals spinal-fluid abnormalities.

The cerebrospinal fluid may be under normal or increased pressure, the protein is elevated, and the sugar normal, and there is an increase in the number of cells, which are chiefly lymphocytes, although other mononuclear elements may be present. No bacteria are demonstrable. Neutralization and the complement-fixation test aid in establishing the diagnosis.

The mortality in St. Louis encephalitis averages about 20 per cent, although it is much higher in the older and lower in the younger age group. When recovery occurs, there are usually no progressive sequelae as in lethargic encephalitis.

### *Equine Encephalitis*

A Massachusetts epidemic of *equine encephalitis* in the autumn of 1938 coincided with an epidemic of this disease in horses in the southwestern part of the state. The disease may have been transmitted by mosquitoes, which were prevalent at that time. Children were affected more often than adults. The onset was usually quite abrupt, and the course rapidly progressive, death occurring within a few hours to a few days. The dominant symptoms were fever, headache, nausea and vomiting, rapidly developing stupor or coma, convulsions, hemiplegia and ocular paralyses. The cell count in the cerebrospinal fluid averaged up to 1500 per cubic millimeter, often with a preponderance of neutrophilic leukocytes. The pressure was raised, the protein values were elevated, and the sugar was normal. The mortality was high, and a few of the surviving patients have had permanent neurologic residua, such as mental enfeeblement and hemiplegia. The virus can be isolated from brain tissue in fatal cases by the intracerebral inoculation of mice. There are also specific neutralization and complement-fixation tests that can be carried out with serum of patients drawn during the acute and convalescent phases.

### *Acute Anterior Poliomyelitis*

This disease is usually prominent in the summer and early autumn, although sporadic cases occur throughout the entire year. Prodromal symptoms such as headache, vomiting, diarrhea and upper respiratory manifestations, particularly sore throat, may be present for a few days. The invasion of the nervous system is marked by pain in the back and in the extremities, headache, stiff neck, rigidity of the spine and tenderness of nerves and muscles. A flaccid paralysis with loss of tendon reflexes but preservation of sensation develops a day or two later. Abortive types, nonparalytic meningeal forms and bulbar types have been described. Drowsiness and apathy are sometimes observed, but convulsions, coma and other cerebral symptoms of encephalitis are rare. Usually, the paralysis is asymmetrical, most often involving one leg or one arm, part of the trunk or both legs. Death is usually the result of involvement of the cardiac regulating or respiratory centers in the medulla, or both. In the first few days the cerebrospinal fluid usually contains 10 to 200 cells per cubic millimeter, both neutrophilic leukocytes and lymphocytes. The protein is often normal in the acute stages of the disease and gradually rises in succeeding weeks. As in all virus infections, the sugar and chloride are normal. Most workers believe that the virus is

disseminated by human contact. The pathway of entrance is debated, there is considerable evidence that the virus passes through the wall of the gastrointestinal tract and reaches the spinal cord along sympathetic nerves. Another possibility is that it extends from the pharynx to the medulla and cervical part of the spinal cord. There is no quick laboratory test for confirmation of the diagnosis. Demonstration of the virus in the feces or the nasopharyngeal secretions is difficult, protracted and, at the moment, clinically impractical. Neutralization tests are unreliable because of antigenic differences between strains of virus, there is no serologic test of value. The diagnosis can be established at autopsy by the character and distribution of the lesions or, sometimes, by careful study of the clinical course of the disease.

### *Herpes Zoster*

Herpes zoster is a specific infectious disease, probably caused by a virus, which has not yet been isolated. The disease begins with malaise, slight fever and pain along one or several nerve roots and is followed within three or four days by the characteristic vesicular eruption and local lymphadenopathy. Segmental sensory or motor paralysis, or both, may occur. When cranial ganglions are involved, several distinctive syndromes may occur: ophthalmoplegic zoster, affecting the Gasserian ganglion, geniculate zoster (Ramsay Hunt syndrome), affecting the geniculate or and probably more frequently the glossopharyngeal ganglions, and glossopharyngeal and vagus zoster, affecting the petrosal and jugular ganglions. In some cases the cerebrospinal fluid contains 5 to 200 cells per cubic millimeter, mostly lymphocytes, and an elevated total protein. Severe neuralgia and occasionally sensory loss or paralysis of a group of muscles are lasting complications. Cases of encephalitis as evidenced by increasing drowsiness, confusion and sphincter incontinence, myelitis with paraplegia and polyneuritis have been reported. The virus has never been isolated even from pathological material, and there are no reliable laboratory tests to prove its identity.

### *Mumps Meningoencephalitis*

Symptoms of meningitis may develop before, during or after mumps. Swelling of the salivary glands may be slight and escape notice or may be entirely absent during the entire course of the disease. The infection may involve organs other than the salivary glands such as the testes, lacrimal glands, breasts and pancreas. Usually, the patients are not very sick. The onset of symptoms is marked by headache, occasionally by drowsiness and confusion, and in rare cases by convulsions and coma and cranial-nerve palsies, particularly the seventh and eighth nerves. Signs of meningeal irritation are prominent.

the determination of the presence of neutralizing antibody or the demonstration of increasingly positive serologic reactions such as complement fixation and inhibition of erythrocyte agglutination.

In the New England states, during the past decade, there have been no verified cases of acute encephalitis lethargica, St. Louis encephalitis has not been reported in this area, and Eastern equine encephalitis has not occurred except possibly in isolated cases since 1938-1939. Japanese B, Australian X, Russian tick-borne and Western or Venezuelan encephalitis are unknown here. Mumps meningo-encephalitis, infectious mononucleosis, poliomyelitis, herpes zoster, herpes simplex, rabies, lymphocytic choriomeningitis and lymphogranuloma venereum are the diseases that have been and will undoubtedly continue to be encountered in this section of the country.

Acute disseminated encephalomyelitis can usually be recognized without difficulty if there is knowledge of preceding measles, chicken pox, smallpox or other exanthem or of vaccination with either highly active viruses or attenuated ones. These diseases occur sporadically throughout the year, being more frequent whenever the exanthems are prevalent. It should be stressed that acute disseminated encephalomyelitis occasionally occurs before the rash becomes apparent, as in measles, and that in infants and children the encephalomyelitis may be so mild as to go undetected at the time of the acute exanthem only to become manifest years later when marked abnormalities in behavioral patterns appear.

Diseases suspected of being caused by filterable viruses, such as infectious mononucleosis, acute infectious hepatitis and acute infective polyneuritis, are apparently endemic in this region. We have seen a few cases with central-nervous-system involvement each year.

A brief summary of the clinical and laboratory findings of each of the types of encephalitis likely to be seen in the United States is presented below.

### *Encephalitis Lethargica*

Although acute cases are not being seen in the United States, a considerable number of patients who exhibit the sequelae of this disease continue to visit the outpatient clinics of medical and neurologic services. The most common manifestations are tremor, rigidity and slowness of voluntary movements, which combine to form a clinical picture resembling in some ways the hepatolenticular degeneration of Wilson and, in others, paralysis agitans. Important differences that should be stressed are the absence of corneal pigmentation (Kaiser-Fleischer rings), of the mixed static and intentional tremor, and of the evidence of liver disease, which are common in Wilson's disease, and the presence of bizarre postures and gaits, and other muscular spasms such as oculogyric crises, and

torticollis, of coarse tremors and behavioral peculiarities, which are rarely encountered in paralysis agitans. The disease follows a variable course, usually slowly progressive, and death results years later from a severe muscular rigidity, which immobilizes the patient and finally from intercurrent infection. The majority of these patients are afebrile, and the cerebrospinal fluid is normal. In other words, there is no indication of an infectious process during the chronic phases of the illness, and often no trace of an inflammatory reaction at autopsy. A unique feature of the disease is this progressive damage of the basal ganglia over a long period, often without manifest inflammatory activity at autopsy. The diagnosis is made entirely from the clinical features of the disease. There are no confirmative laboratory tests.

### *St. Louis Encephalitis*

This disease differs from the von Economo type of encephalitis in its greater incidence in patients over the age of forty-five and in its prevalence during the summer months. The clinical picture shows tremendous variability because of the differences in severity of the infection and localization of the lesions in the brain and spinal cord. Three different syndromes have been described. The first consists of signs of meningeal irritation and increased intracranial pressure with difficulty in speech, ataxia, mental confusion and tremors of the tongue, lips or hands appearing abruptly without prodromal manifestations. Lethargy is not present in every patient. Paralysis are uncommon and are usually spastic in character. Eye-muscle involvement is extremely rare. The deep reflexes are usually exaggerated, and the abdominal ones are absent. Fever, usually disappearing within seven to ten days, may persist, in some cases, for from four to six weeks. The second is a syndrome characterized by prodromal manifestations of headache, generalized muscular pain, sore throat, mild conjunctivitis and photophobia that may last for from one to four days. After this period, the course of the disease is essentially the same as that in the first type. The third syndrome consists of so-called "abortive" cases of St. Louis encephalitis in which only fever and headache are present. These cases are usually detected because they occur in an area where this type of encephalitis is present, and lumbar puncture reveals spinal-fluid abnormalities.

The cerebrospinal fluid may be under normal or increased pressure, the protein is elevated, and the sugar normal, and there is an increase in the number of cells, which are chiefly lymphocytes, although other mononuclear elements may be present. No bacteria are demonstrable. Neutralization and the complement-fixation test aid in establishing the diagnosis.

tains several hundred to a thousand or more cells, of which the majority are lymphocytes. The sugar level is usually normal though a few values below 40 mg per 100 cc were found twice in 19 lumbar punctures in 1 case<sup>28</sup>. The protein is elevated and the colloidal-gold readings are abnormal. Characteristic genital or rectal lesions should suggest the possibility of lymphogranuloma venereum and a positive Frei test is confirmatory; this reaction may, however, be negative. The virus can be isolated from the cerebrospinal fluid by the intranasal or intracerebral inoculation of mice, and from the genital lesion or regional lymph nodes but not the blood stream. Complement fixation is an accepted diagnostic procedure. Although usually benign, this disease may occasionally run a rapidly fatal course<sup>29, 30</sup>.

### *Encephalitides of Unknown Origin*

Among the encephalitides of unknown origin, some, like those following rubeola and rubella, are related to known virus infections, but the causative agents have not been isolated from nervous tissue and the pathological picture does not resemble that of a virus disease. Although it has been postulated that the neurologic disturbance is due to the activation of a latent virus, concrete evidence to support this viewpoint has not been advanced. Recently, data suggesting an allergic reaction to nervous tissue during the course of the exanthem as the etiologic factor concerned in post-infectious encephalomyelitis have been presented<sup>31-34</sup>. The causative factors concerned in the other encephalitides — acute hemorrhagic, those complicating scarlet fever and rheumatic fever and the "toxic" type — are completely unknown.

### *Acute Disseminated Encephalomyelitis*

This accompanies measles more often than any other infection and occurs in from 1/400 to 1/1000 cases of this exanthematous disease. It has also been reported after rubella, varicella, variola and mumps. It occasionally appears without any recognizable exanthem. Usually, the neurologic symptoms occur four to six days after the onset of the skin eruption and are accompanied by a rise of temperature and pleocytosis of the cerebrospinal fluid. The neural manifestations may be those of diffuse cerebral involvement, — that is, confusion, convulsions and coma, — focal brain lesions (hemiplegia, hemianesthesia, aphasia, blindness or hemianopia), brain-stem involvement with cranial-nerve palsies or pseudobulbar palsy and cerebellar or spinal lesions such as ataxia and paraplegia. Although 10 to 20 per cent of patients die and there may be serious residua in as high as 65 per cent of the cases, a surprising degree of recovery often occurs. A similar clinical picture may develop a week to ten days after the beginning of antirabies vaccination, the administration of smallpox vaccine

or rarely the injection of horse serum in the prophylaxis of tetanus or treatment of diphtheria. The pathology has been described above. There are no laboratory tests of any value, but in fatal cases the diagnosis can be confirmed by the characteristic anatomic lesions, a history of contact with one of the infections listed above and the clinical course of the disease.

### *Acute Hemorrhagic Encephalitis*

We have studied the brain in 10 fatal cases, 3 of which were examined during life. The correct diagnosis was not made in any case, though it was mentioned in the differential diagnosis in 1. After an upper respiratory infection or during an influenza-like illness, fever, deep confusion, coma, convulsions and hemiplegia or quadriplegia appeared without assignable cause. The cerebrospinal fluid was normal in the cases of brain purpura and contained several hundred cells, mostly neutrophilic leukocytes, elevated protein, normal sugar and chloride in the cases of acute hemorrhagic necrotizing encephalopathy. The prominence of neurologic symptoms always raises the question of an encephalopathy due to a toxin, metastatic infection or a vascular lesion of the brain. No virus has been isolated from these cases. At present the diagnosis can only be confirmed by autopsy.

### *Encephalitis of Scarlet Fever and Rheumatic Fever*

In exceptional cases of recurrent rheumatic fever, scarlet fever and possibly other of the so-called rheumatic diseases, persistent fever and pleocytosis of the cerebrospinal fluid are accompanied by neurologic symptoms. A confusional psychosis sometimes with paranoid coloring, delirium, ataxia of limbs, reflex changes, stupor or coma has constituted the clinical picture in some cases, but other patients have had relatively few complaints or signs referable to the nervous system. In the cases of scarlet fever the signs of meningeal irritation and the pleocytosis of the cerebrospinal fluid, which usually consists of 100 to 200 lymphocytes per cubic millimeter, occur when the rash is desquamating<sup>35, 36</sup>. The symptoms do not respond to sulfonamide drugs or antistreptococcus serum, and penicillin has not been given sufficient trial. It is not yet certain whether the neurologic sequelae are due to a streptococcal septicemia and an interstitial encephalitis similar to that found by Mallory and Keefer<sup>37</sup> in other viscera or whether the brain lesions are the result of embolism secondary to endocarditis — that is, focal embolic encephalomyelitis<sup>38</sup>. The unsettled state of rheumatic encephalitis was mentioned above.

### *Acute "Toxic" Encephalopathy*

In many acute and severe infectious diseases such as pneumonia, influenza, diphtheria, pertussis, septicemia, scarlet fever, dysentery and typhoid fever, stiffness of the neck and spine, convulsions

### *Lymphocytic Choriomeningitis*

This is a benign meningitis that is often preceded by one or two weeks by systemic symptoms not unlike influenza. The onset of meningeal involvement is announced by headache and stiff neck and sometimes drowsiness, irritability and confusion. In a few cases, focal cerebral symptoms have occurred. The cerebrospinal fluid is under normal or increased pressure and contains 50 to 1500 cells per cubic millimeter, mostly lymphocytes. Sugar and chloride values are normal. Usually, recovery occurs in two or three weeks, and only a few fatal cases have been reported. The virus can be obtained from both the blood and cerebrospinal fluid. It has also been found in wild mice and rodents around human dwellings. The feces or the bite of the rodents is the source of human infections. This disease must be distinguished from tuberculous meningitis and mumps meningoencephalitis. Neutralization and complement-fixation tests are helpful in establishing the diagnosis (Farmer and Janeway<sup>23</sup>).

### *Infectious Mononucleosis*

Infectious mononucleosis or glandular fever is a pleomorphic disease that is occasionally accompanied by headaches, stiff neck, giddiness, nausea and vomiting. Its more specific nervous manifestations include delirium, lethargy, stupor and diplopia. The cerebrospinal fluid, which contains an excess of cells, up to several hundred lymphocytes and other mononuclear elements and an elevated total protein, attests to a meningitis and more specific nervous symptoms such as delirium, coma and diplopia to parenchymatous damage. In a few exceptional cases an ascending polyneuritis indistinguishable from the usual acute infectious or acute febrile polyneuritis has developed, being preceded or followed by jaundice. The diagnosis rests on the demonstration of abnormal lymphocytes in the circulating blood, enlargement of lymph nodes generally and often of the spleen and liver, and the presence in the serum of heterophil-antibody agglutinins for sheep erythrocytes. Since the causative agent has not been isolated, the viral etiology can only be predicated from the nature of the pathologic findings.

### *Herpes Simplex Encephalitis and Myelitis*

Several cases of encephalitis with large Type A intranuclear inclusion bodies in nerve and glial cells have been reported in the past two decades<sup>24-25</sup>. In at least 2 of these the virus of fever blisters or acute stomatopharyngitis has been isolated and shown by rising titers of neutralizing antibodies to have been the causative agent. It is reasonable to suppose that all the reported cases in which these intranuclear inclusion bodies were demonstrated are due to this virus.

Most of the cases have occurred in children. The onset is insidious. Alteration of character, impaired vision, ataxia, hemiparesis, disturbances of movement and posture in the form of rigidity, athetosis or dystonia, facial spasm, trismus and finally coma are listed as the distinctive features of the disease. The course is subacute, with progression to a fatal termination in one to four months. Except for a few lymphocytes in some cases the cerebrospinal fluid has been normal.

Because of the common symbiosis between this virus and man, the etiology of these cases is difficult to prove. Some antibody to this virus is present in a great number of healthy persons, and hence only with rising and falling titers with reference to a particular illness can this agent be implicated.

The fatal case of ascending myelitis in a laboratory technician after the bite of a supposedly healthy monkey that was reported by Sabin and Wright<sup>27</sup> has excited much controversy. He believed that this virus differed from that of herpes simplex, but other workers have since stated that it belongs to the same group.

### *Rabies*

This is an old and, from the historical point of view, important neurotropic virus infection that still exists in this country. The virus is present in many lower animals besides dogs, such as foxes, coyotes, wolves, skunks and vampire bats, and is transmitted to human beings through the bites of rabid animals. The incubation period is twenty to sixty days. The first symptoms are pain and numbness in or near the bite. Within a few days, restlessness, irritability and excitement alternating with drowsiness appear. Headache, stiff neck and rigidity of the spine are usually present. Violent convulsions, involuntary movements and characteristic spasm of the pharynx and larynx occur and have been interpreted by laymen as hydrophobia. Coma develops later. Death is inevitable once symptoms of rabies appear, but the use of anti-rabies vaccine early in the incubation period is of prophylactic value. A clinical picture of ascending myelitis, so-called "dumb" rabies or "Trinidad rabies" has been described<sup>17</sup>. There is no laboratory test to aid in the diagnosis during life. The finding of cytoplasmic inclusion bodies (Negri bodies) in the nerve cells of the Gasserian ganglions, the hippocampal gyrus or Purkinje cells of the rabid animal or infected man will establish the diagnosis. The virus is not found in the blood or spinal fluid of man.

### *Lymphogranuloma Venereum*

The viral origin of this disease is now accepted, and a few cases of so-called meningoencephalitis have been reported. The symptoms are fever, headache, stiff neck, mental confusion and an occasional cranial-nerve palsy. The cerebrospinal fluid con-

general methods used in the laboratory diagnosis of viral diseases. These tests are complex and expensive and are being done in only a few large medical centers. The laboratories that have been most generous in their help are those of the Rockefeller Institute, the National Institute of Health, the Children's Hospital in Philadelphia and the Diagnostic Laboratories of the Massachusetts Department of Public Health, which limits its efforts to the diagnosis of mumps and influenza virus infections. If material is submitted to these laboratories in suitable form, appropriate tests will be done, and the results reported promptly.

In all the established virus diseases the causative agent can be obtained from the spinal cord and brain. However, only in lymphocytic choriomeningitis is the virus found consistently in the blood and cerebrospinal fluid in sufficient concentration to make such tests worth while. In all the virus diseases of known etiology with the exception of rabies, poliomyelitis and herpes simplex, complement-fixation or neutralization tests are now available and are of diagnostic value. If positive these tests show only that the patient has at some previous date had this infection. To prove that a specific illness was caused by the virus in question two samples of blood serum, one taken as early in the disease as possible and the other late in convalescence (usually six weeks) should be submitted. If the first specimen contains no antibody or only a low titer and the second one shows a rise in antibody content the evidence is strong that the suspected disease was due to the virus in question.

Aseptic precautions should be taken in the collection of blood. The serum should be removed from clot as soon as possible, frozen and kept at very low temperatures if immediate examination cannot be done. Brain, preferably pieces from the hippocampal convolution, sensorimotor cortex and pons or spinal-cord tissue should be frozen in a mixture of alcohol and dry ice under sterile conditions or put in a 50 per cent solution of neutral glycerin. The diagnostic tests useful in establishing the viral origin in a case of encephalitis are presented in Table I.

### SUMMARY

Aside from the forms of encephalitis due to visible microbes such as bacteria, parasites, rickettsias and spirochetes the class of inflammatory brain diseases caused by filterable viruses has been seen rarely in New England during the past few years. In fact the only neurotropic viruses that we have encountered are mumps, poliomyelitis, lymphocytic choriomeningitis, herpes zoster and rabies. Acute disseminated or postinfectious encephalomyelitis, which is probably not of direct viral etiology, occurs sporadically after exanthematous disease and certain immunization procedures. In the last six years there have been 15 cases diagnosed

during life as virus encephalitis that underwent pathological examination at the Mallory Institute of Pathology. The final anatomic diagnoses were acute confusional psychosis (2 cases), metabolic disease with disturbed brain function (1 case), lead encephalopathy (1 case), focal embolic encephalomyelitis due to subacute bacterial endocarditis (4 cases), acute disseminated lupus erythematosus (1 case), tuberculous meningitis (3 cases), torulosis of the meninges (1 case), basilar-artery thrombosis (1 case) and brain abscess (1 case). From these pathological data one must conclude that a diagnosis of virus encephalitis in New England has at the present time a large probability of error. It is recommended that the word encephalitis not be used without a qualifying adjective. Thus, the neurologic syndrome in question should be analyzed to determine whether or not it is consistent with encephalitis lethargica, mumps, postinfectious encephalomyelitis and so forth. Admittedly, the neurologic symptoms of the different types of encephalitis are not by themselves distinctive but by habitually thinking in terms of specific disease entities and taking into account epidemiologic and laboratory data one can avoid serious diagnostic errors.

### REFERENCES

1. Spielmeyer W. Über örtliche Vulnerabilität. *Ztschr f d ges Neurol u Psychiat* 118:116, 1928.
2. Greenfield, J. G. Pathology of measles encephalomyelitis. *Brain* 52:171-195, 1929.
3. von Economo C. *Encephalitis Lethargica, Its sequelae and treatment*. Translated by K. O. Nerman. 200 pp. London: Oxford University Press, 1931.
4. Weil A. Histopathology of central nervous system in epidemic encephalitis (St. Louis epidemic). *Arch Neurol & Psychiat* 31:1159-1162, 1934.
5. Zimmerman H. M. Pathology of Japanese B encephalitis. *Am J Path* 22:965-991, 1946.
6. Farber S, Hill A, Connerly M. L. and Dingle, J. H. Encephalitis in infants and children caused by virus of eastern variety of equine encephalomyelitis. *J A M A* 114:1725-1731, 1940.
7. Bodian D. Poliomyelitis: neuropathologic observation in relation to motor symptoms. *J A M A* 134:1148-1154, 1947.
8. Denny-Brown D, Adams R. D. and Fitzgerald P. J. Pathologic features of herpes zoster: note on geniculate herpes. *Arch Neurol & Psychiat* 51:216-231, 1944.
9. Lipschutz, B. Über Chlamydozoa-Strongyloplasmen. V. Zur Kenntnis der Ätiologie des Herpes febrilis. *Wien med Wochenschr* 71:252, 1921.
10. Biggart, J. H. and Fisher J. A. Meningo-encephalitis complicating herpes zoster. *Lancet* 2:944, 1958.
11. Larkin W. R. Mumps meningitis found at Camp Taylor Base Hospital with autopsy findings. *Illness M J* 38:133-135, 1920.
12. Viets H. R. and Warreo S. Acute lymphocytic meningitis. *J A M A* 108:357-361, 1937.
13. Brain R., Greenfield J. G. and Russell D. S. Discussion on recent experiences of acute encephalomyelitis and allied conditions. *Proc Roy Soc Med* 36:319-322, 1943.
14. Peters C. H., Wideman Blumberg A. and Ricker W. A. Jr. Neurologic manifestations of infectious mononucleosis with special reference to Guillain-Barré syndrome. *Arch. Int. Med* 80:366-373, 1947.
15. Ziegler E. E. Infectious mononucleosis: report of fatal case with autopsy. *Arch Path* 37:196-201, 1944.
16. Allen F. H., Jr., and Kellner A. Infectious mononucleosis: an autopsy report. *Am J Path* 23:463-477, 1947.
17. Hurst, E. W. and Pawan J. L. Outbreak of rabies in Trinidad without history of bites and with symptoms of acute ascending myelitis. *Lancet* 2:622-628, 1931.
18. Greenfield, J. G. Acute disseminated encephalomyelitis as sequel to influenza. *J Path & Bact* 33:453-462, 1930.
19. Perdian J. R. Histology of post-vaccinal encephalitis. *J Path & Bact* 31:17-22, 1928.
20. Adams R. D., Cammermeyer J. and Denny-Brown D. Acute necrotizing hemorrhagic encephalopathy. *J Neuropath & Exper Neurol* (in press).

and stupor or coma may occur. This is especially true in children, when the neurologic disorder at times even obscures the signs of the primary pathologic process. The cervical rigidity is often so pronounced as to suggest the presence of meningitis, particularly when there is pneumonia of the right

be controlled death frequently occurs, or if the child survives, serious and permanent brain damage may follow. The syndrome is nonspecific, it varies little regardless of the associated disease. The diagnosis is made on purely clinical grounds. The condition must be distinguished from intracranial

TABLE 1 *Laboratory Diagnosis of Virus Diseases of the Nervous System*

DISEASE	PRESENCE OF VIRUS			METHOD OF DEMONSTRATING PRESENCE OF VIRUS	NEUTRALIZATION TEST	COMPLEMENT-FIXATION TEST	OTHER TESTS	PATHOLOGICAL FEATURES
	BLOOD	CEREBROSPINAL FLUID	BRAIN AND SPINAL CORD					
Rabies	0	0	+	Intracerebral inoculation in mice	0	?	—	Typical virus encephalomyelitis—that is, nerve-cell destruction, microglial proliferation, lymphocytic infiltration of meninges and perivascular spaces and Negri bodies
Poliomyelitis	0	0	+	Inoculation of spinal-cord suspensions, stool emulsions or throat washings after filtration intracerebrally, subcutaneously or intranasally into monkeys	+	0	—	Typical virus encephalomyelitis with predominance of lesions in spinal cord, brain stem and motor cortex
St. Louis encephalitis	0	0	+	Inoculation into mice intracerebrally or in embryonated egg	+	+	—	Typical virus encephalomyelitis; lesions in cerebral cortex, basal ganglia and brain stem; focal areas of necrosis
Western equine encephalitis	0	0	+	Intracerebral inoculation in mice	+	+	—	Same as those of St. Louis encephalitis
Eastern equine encephalitis	+	+	+	Intracerebral inoculation in mice	+	+	—	Same as those of St. Louis and Western encephalitis
Mumps meningo-encephalitis	+	+	+	Inoculation of embryonated egg	+	+	Fowl red-cell agglutinin inhibition	Meningitis—perivascular and meningeal infiltrations of lymphocytes and other mononuclear cells
Lymphogranuloma venereum	+	0	+	Inoculation of embryonated egg	+	+	Frei test	Same as those of mumps
Herpes simplex	?	?	+	Scarification of rabbit cornea; growth on embryonated egg; intracerebral inoculation in mice	+	Not reliable	—	Intranuclear inclusion bodies otherwise similar to St. Louis and equine encephalitis
Herpes zoster	0	0	0	None	0	0	—	Destruction of 2 or 3 sensory ganglia; lymphocytic infiltration of ganglia; nerve roots, meninges and unilateral segmental polymyelitis; vesicles in skin with intranuclear inclusions
Encephalitis lethargica	0	0	0	None	0	0	—	Typical virus encephalomyelitis; lesions chiefly in globus pallidus, midbrain and pons; less tissue necrosis than in St. Louis and equine encephalitis
Infectious mononucleosis	0	0	0	None	0	0	Heterophil antibody; sheep red-cell agglutinin	Infiltration of peripheral nerves, sensory ganglia, sensory roots and sometimes meninges with lymphocytes, plasma cells and histiocytes
Benign lymphocytic choromeningitis	+	+	+	Culture on embryonated egg; inoculation in mice, guinea pigs and monkeys	+	+	0	Meningitis—perivascular and meningeal infiltration with lymphocytes, macrophages and a few neutrophilic leukocytes

upper lobe. However, the cerebrospinal fluid is within normal limits. The course is variable. If the convulsions are suppressed and the infection promptly controlled, consciousness may be regained within a few hours and the rigidity may disappear, leaving no sequelae or only transient and reversible focal neurologic symptoms. If the infection cannot

suppurative processes and other types of encephalitis.

#### LABORATORY DIAGNOSIS OF ENCEPHALITIS

Correct diagnosis of neurotropic virus infections requires the aid of special laboratory tests. Cheever<sup>39</sup> has written an excellent review of the

committee of the Committee on Postgraduate Medical Education. The Secretary moved that the Council approve this recommendation. The motion was seconded, and it was so ordered by vote of the Council. (3) The Executive Committee unanimously approved the proposal to have the Society sponsor the art exhibit of the Massachusetts Physicians Art Association at the annual meetings. The Secretary moved that the Council approve this recommendation. The motion was seconded, and it was so ordered by vote of the Council. (4) The Executive Committee unanimously voted to approve of the establishment of a Section on Physiology and Pathology. The Secretary moved that the Council approve the establishment of such a section. The motion was seconded, and it was so ordered by vote of the Council. (5) The Executive Committee voted unanimously to approve the request of Dr. Augustus Thorndike to have the President appoint a committee to confer with the directors of the Bay State Medical Rehabilitation Clinic, a charitable, nonprofit clinic not connected with the state or federal governments.

The Secretary moved that the request be approved by the Council. The motion was seconded, and it was so ordered by vote of the Council.

The President then made the following appointments to that committee and asked for the approval of the Council. On a motion duly made and seconded it was so voted:

*To the Committee to meet with the Officers of the Bay State Medical Rehabilitation Center*

Dr. Charles H. Bradford, *Chairman*  
 Dr. W. Irving Clark  
 Dr. Walter Bauer  
 Dr. Joseph S. Barr  
 Dr. Hermann L. Blumgart  
 Dr. Otto J. Hermann  
 Dr. Arthur L. Watkins

(6) The Executive Committee voted unanimously not to approve the recommendations of the now extinct Committee on Medico-Legal Testimony to amend the By-laws in order to establish a standing committee on Medico-Legal Testimony. The Secretary moved that the Council approve this action of the Executive Committee. The motion was seconded, and it was so ordered by unanimous vote of the Council.

The Secretary then moved that the report of the Committee on Membership as distributed to the Executive Committee concerning transfers, retirements, deprivations and resignations be approved by the Council. The motion was seconded, and it was so ordered by vote of the Council.

The Secretary then stated that new business before the Executive Committee included the following:

(1) The resolution presented to it by the Hampden District Society was discussed and the committee

voted that the matter of the resolution be laid on the table until the next meeting of the Committee.

(2) The committee voted unanimously to approve the request to change the name of the Section on Physiotherapy to Section on Physical Medicine. The Secretary moved that the Council approve of this change in name. The motion was seconded, and it was so ordered by vote of the Council.

(3) The Secretary stated that the Executive Committee had given him permission to confer with the secretaries of the district societies in order to select candidates for the General Practitioners Award, the Executive Committee would select one candidate for presentation to the Council. The Secretary moved that the Council approve this action by the Executive Committee. The motion was seconded. Dr. Carl Bearse, Norfolk, moved that the motion be amended to the effect that unless a candidate receive a majority vote of the Executive Committee the decision be referred to the Council for action. (There was no second to this motion.) The President called for a vote on the original motion, and it was so ordered by a vote of the Council.

(4) The Secretary stated that the Executive Committee had approved the action of the President in acceding to the request of our counsel, Mr. Twomey, to submit a brief as a friend of the court. The President then explained that the matter concerned one of our fellows who had been sued by a patient because she claimed morphine addiction as a result of his treatment. The Court had found for the plaintiff, and the judge had upset the verdict. The case was to be tried in the Supreme Court.

On motion made by the Secretary and duly seconded, the Council voted to approve the action of the Executive Committee in this respect.

The President said that he would interrupt the usual procedure at this point to permit Dr. James C. McCann, Worcester, to report to the Council on the affairs of Blue Shield. Dr. McCann thanked the President and addressed the Council (Appendix No. 3).

Dr. Reardon thanked Dr. McCann for his report and called for the Committee Reports.

*Committee on Cancer* — Dr. Shields Warren, Suffolk, *Chairman*

Since no member of the Committee on Cancer was present, the Secretary moved acceptance of the report (Appendix No. 4). The motion was seconded, and it was so ordered by vote of the Council.

Dr. George Papen, Norfolk, stated that at a pre-Council meeting of the Norfolk District Medical Society it had been voted that the recommendations of the Committee on Cancer — "That the Massachusetts Medical Society endorse the principle of voluntary registration of cancer cases" — be tabled.

- 21 Palmer, H A Encephalitis of unknown origin *Lancet* 2 562 1941
- 22 Rivers T M Virus diseases of nervous system. *J A M A* 132 427-430 1946
- 23 Farmer T W and Janeway C A Infections with virus of lymphocytic choriomeningitis *Medicine* 21 1 63 1942
- 24 Dawson J R Cellular inclusions in cerebral lesions of epidemic encephalitis *Arch Neurol & Psychiat* 31 685-700 1934
- 25 Smith M G, Lennette E H and Reames H R Isolation of virus of herpes simplex and demonstration of intranuclear inclusions in case of epidemic encephalitis *Am J Path* 17 55 68 1941
- 26 Akelaitis A J and Zeldis L J Encephalitis with intranuclear inclusion bodies clinicopathologic study *Arch Neurol & Psychiat* 47 353 366 1942
- 27 Sahin A B and Wright, A M Acute ascending myelitis following monkey bite with isolation of virus capable of reproducing disease *J Exper Med* 59 115 136 1934
- 28 Sahin A B, and Aring C D Meningoencephalitis in man caused by virus of lymphogranuloma venereum *J A M A* 120 1376-1381 1942
- 29 D Aunoy, R. and von Hamm E. Venereal lymphogranuloma *Arch Path.* 27 1032-1082 1939
- 30 Rajam R. V Report of fatal case of lymphogranuloma inguinale with meningo-encephalitis. *Brit J Ven Dis* 12 237-241, 1936
- 31 Morgan I M. Allergic encephalomyelitis in monkeys in response to injection of normal monkey nervous tissue. *J Exper Med* 85 131 140 1947
- 32 Kabat, E. A. Wolf A. and Bezer, A. E. Rapid production of acute disseminated encephalomyelitis in rhesus monkeys by injection of heterologous and monologous brain tissue with adjuvants. *J Exper Med* 85 117-130 1947
- 33 Freund J Stern E. R. and Pisani T M. Is allergic encephalomyelitis and radiculitis in guinea pigs after one injection of brain and mycobacteria in water in-oil emulsion *J Immunol* 57 179 194 1947
- 34 Kopeloff L. M. and Kopeloff N. Neurologic manifestations in laboratory animals produced by organ (adjuvant) emulsions. *J Immunol* 57 229 237 1947
- 35 Neal J B and Harrington H. Meningoencephalitis following scarlet fever. In *Encephalitis A clinical study* 563 pp. New York Grune & Stratton 1942
- 36 Sweet, L. K. and Lepper M H. Acute serous meningitis in scarlet fever *J Pediat* 24 295 303 1944
- 37 Mallory G K. and Keefer C S. Tissue reactions in fatal cases of *Streptococcus haemolyticus* infection *Arch. Path.* 32 334-335 1941.
- 38 Bruettsch W L. Late cerebral sequelae of rheumatic fever *Arch. Int Med* 73 472-476 1944
- 39 Cheever F S. General principles of laboratory diagnosis of viral infections. *New Eng J Med* 237 584-590 1947

## MASSACHUSETTS MEDICAL SOCIETY

### PROCEEDINGS OF THE COUNCIL

Stated Meeting, October 6, 1948

A STATED meeting of the Council was called to order by the president, Dr Daniel B Reardon, Norfolk South, on Wednesday, October 6, 1948, at 10 30 a m in John Ware Hall, 8 Fenway, Boston

Two hundred and fifteen councilors (Appendix No 1) were present

The Secretary presented the record of the May 24, 1948, annual meeting of the Council as published in the *New England Journal of Medicine*, issue of July 22, 1948, and moved its acceptance The motion was seconded and it was so ordered by vote of the Council

#### APPOINTMENTS

The President then announced the following appointments all of which had been presented to the Executive Committee, with the exception of the Subcommittee on Medical Education

##### *To the Subcommittee of the Executive Committee on Blue Cross-Blue Shield Problems*

Dr Charles J E Kickham, *Chairman*  
 Dr Joseph C Merriam  
 Dr Harvey A. Kelly  
 Dr John Fallon  
 Dr Paul M Butterfield

##### *To the Temporary Committee on Council Rules and By-laws*

Dr Edward P Bagg, *Chairman*  
 Dr Elmer S Bagnall  
 Dr Frank R Ober  
 Dr Albert A Hornor

##### *To the Committee on Medical Economics*

Dr Henry A Robinson

##### *To the Committee on Society Headquarters*

Dr Dwight O'Hara

##### *To the Committee on Tax-Supported Medical Care*

Dr Francis P McCarthy

##### *To the Advisory Subcommittee on Medical Education*

Dr Arthur Jankelson, *Chairman*  
 Dr George E Gardner  
 Dr Raymond H Goodale  
 Dr Donald A Nickerson  
 Dr William A Hinton  
 Dr C Guy Lane  
 Dr Augustus Thorndike

The President asked for approval of these appointments, and it was so ordered by vote of the Council

The Secretary, on behalf of the Society presented the President with a gavel with his name and the years 1948-1949 engraved upon it The President accepted the gavel with thanks and said that he heartily approved of establishing the custom of presenting a gavel to each newly elected President

#### REPORTS OF COMMITTEES

*Executive Committee* — Dr H Quimby Gallupe, Middlesex South, *Secretary*

The Secretary presented the minutes of the meeting of the Executive Committee held on September 8, 1948, as mimeographed (Appendix No 2) and mailed to the Councilors and moved their acceptance The motion was seconded, and it was so ordered by vote of the Council

The Secretary then stated that under the matters referred to the Committee by the Council, (1) the question of whether or not the Society should receive certain gifts, the committee had voted to defer action until the Treasurer received further information from the American Medical Association and the Treasury Department (2) The Executive Committee unanimously approved of making the Committee on Postgraduate Assembly a sub-

The Secretary moved that the recommendation to conduct a state-wide health meeting and that the Council appropriate the sum of \$500 toward this important activity be approved. The motion was seconded, and it was so ordered by vote of the Council.

The President then stated that the Executive Committee did not approve of the recommendation to endorse an ascending scale of membership dues and the study of the question by a proper committee.

The Secretary moved that the Council, also not approve of this recommendation. The motion was seconded.

Dr Eliot Hubbard, Jr., Middlesex South, said that he had objected because the issues had not been clearly defined, but that he would not object to having a committee study the whole question.

Dr Richard M. Smith, Suffolk, then made a motion that the recommendation of the Committee on Public Relations be amended to read "The Committee recorded itself as endorsing in principle such an ascending scale of membership dues and urges that this matter be referred to a proper committee for study." The motion to amend was seconded, put to a vote and carried.

Dr Lewis S. Pilcher, Middlesex South, said that the question was already before the Committee on Membership for study and moved to table the original motion. The President called for a vote on the motion to table and, on a show of hands, declared the motion carried.

The Secretary then moved that the recommendation of the Committee concerning awards to students in the approved medical schools of the Commonwealth be approved by the Council and stated that the committee proposed to study the question and to determine the proper means to select the recipients by the Committee on Medical Education. The motion was seconded, and it was so ordered by vote of the Council.

*Committee on Arrangements*—Dr Harold G. Giddings, Middlesex South, *Chairman*

Dr Giddings presented the report of the committee, as follows:

At the stated meeting of the Council on October 1, 1947, it was voted to accept the cordial invitation of the Worcester District Society to hold the 1949 Annual Meeting of the Massachusetts Medical Society in Worcester.

This will be the first time since 1939 that the Society has met elsewhere than in Boston.

A committee of the Worcester District Medical Society, of which Dr George R. Dunlop is chairman, is working in close co-operation with the Committee on Arrangements, and plans are already well under way for the meeting, which we recommend be held at Worcester on May 23, 24, 25 and 26, 1949.

Dr Giddings moved that the report be accepted. The motion was seconded and carried.

Dr Giddings moved that the recommendation concerning time and place of the next annual meet-

ing be approved. The motion was seconded and so voted.

*Committee on Public Health*—Dr Roy J. Ward, Worcester, *Chairman*

Dr Ward pointed out as a correction that the date of the committee meeting should read "June 5" and not "July 21."

The Secretary then moved that the report and the supplementary report (Appendix No. 10) be accepted. The motion was seconded, and it was so ordered by vote of the Council. The President asked that the request of the committee to have Dr Howard B. Sprague explain the heart demonstration program be approved. On a voice vote, the Council granted this request.

The President introduced Dr Sprague, who in turn introduced Dr David D. Rutstein. Dr Rutstein, in reply to a question by Dr John F. Conlin regarding whether speakers in the program should be selected on the basis of a ratio of 1 prominent speaker to 1 or 2 less well known speakers, agreed that this method of selection was desirable. In reply to a question from a councilor regarding the charge of \$10,000 for medical education listed in the budget of the heart demonstration program, he stated that the amount referred to was for work in co-operation with the New England Heart Association and the Massachusetts Medical Society, as well as for the education of nurses, teachers and other groups concerned with the problem.

The President then asked for action on the recommendation of the committee appearing in the report as follows:

The Committee approved Dr Phippen's resolution and a motion was made and adopted that we recommend to the President of the Massachusetts Medical Society that a committee be appointed to expedite the Massachusetts "Diabetes Week" program from December 6 to 12, 1948, that this committee be empowered to act, and that its efforts be co-ordinated with Dr Ohler's Committee on Postgraduate Education. It was also moved and adopted that the Council take necessary action relative to the final paragraph of Dr Phippen's resolution.

The Secretary made a motion that the Council approve this recommendation. The motion was seconded, and it was so ordered by vote of the Council.

*Committee on Benevolence*—Dr Dwight O'Hara, Middlesex South, *Chairman*

Dr O'Hara presented the report of the Committee (Appendix No. 11) and moved the adoption of the proposal of the committee. The motion was seconded, put to a vote and carried.

Dr O'Hara then moved that the recommendation that a temporary committee on benevolence be appointed to operate until such time as the by-laws may be amended to authorize such an arrangement be approved.

until the Committee on Cancer develops and presents a system for consideration to the Council

Dr Papen moved that the recommendation of the committee be tabled. The motion was seconded. On a voice vote, the President declared the motion carried.

The Secretary then stated that he was sorry that none of the committee were present, and that it was his duty to move that the second recommendation of the Committee on Cancer—"that the Committee on Publications be encouraged to prepare a revised edition of the Cancer Manual"—be approved by the Council. The motion was seconded, put to vote and unanimously carried.

(At this time there was much discussion concerning the motion to table made by Dr Papen but the President finally ruled that any discussion was out of order.)

*Committee on Tax-Supported Medical Care—Dr Albert A Hornor, Suffolk, Chairman*

Dr Hornor presented the report (Appendix No 5) and made the following remarks:

Mr President, before speaking about the recommendations of the Committee on Tax-Supported Medical Care, I would like to remind you that the Executive Committee voted not to accept the report of the Committee. I do, however, want to have the report of the Committee approved and its recommendations adopted.

As a result of the meeting of the Committee on Tax-Supported Medical Care on July 28, 1948, the following recommendation was made to the Council that the Council of the Massachusetts Medical Society approve "Medical Care Program—Policies and Procedures, from the Office of Veterans' Services Room 123, State House, Boston, Massachusetts, effective July 15, 1948," with the inclusion of the amendment to which Commissioner O'Day has agreed as follows: "You may rest assured that after your Massachusetts Medical Society meets and approves the program, I will be pleased to notify all of my agents throughout the Commonwealth of the action, and that this approval is effective subject to renegotiation."

I think that no member of your committee would have recommended acceptance of Mr O'Day's program without that agreement to renegotiation. Several have worked on this question of tax-supported medical care for a long time, and we all know that the people down at the State House have a fixed fee for all cases throughout the State.

That very definitely has to be there. I don't see how they can operate otherwise. I think, and in fact I am aware, that the Council has voted that we do not want to cut our fees for tax-supported medical care.

Now, after all, the commissioner and his associates are willing to renegotiate any time we wish. And I think that as a part of acceptance of the Committee on Tax-Supported Medical Care it would be worth while for the Council to tell us how they would like us to renegotiate it, and how long they would like to have us try this program before we ask for renegotiation.

Mr President, I move the adoption of the recommendation of the Committee on Tax-Supported Medical Care.

The motion was seconded. At the request of Dr Elmer S Bagnall, Essex North, Dr Hornor said that the salient features were contained in an inter-departmental letter from the Office of the Commissioner of Veterans' Services of the Commonwealth, as follows:

To all Veterans Agents

Enclosed herewith is a copy of our new program of Medical-Dental care. The program is effective as of July 15, 1948.

The co-operation of all agents is urgently requested to see that this policy is carried out to the fullest degree. This program has been submitted to the Massachusetts Medical Society for approval.

Dr Bagnall then stated that it was his feeling that the whole matter should be referred back to the committee for further study of the legislation concerning veterans' medical care and old-age services. After some further discussion, Dr Alexander J A Campbell, Suffolk, moved that the whole question be laid on the table, and that a full report of the committee including the veterans' services program (Appendix No 6) be published in the *New England Journal of Medicine*. The motion was seconded, and it was so ordered by vote of the Council.

*Advisory Committee to the Red Cross Blood Bank—Dr John F Conlin, Suffolk, Chairman*

At the request of Dr Conlin, the Secretary moved that the Council approve the report (Appendix No 7). The motion was seconded, and it was so ordered by unanimous vote of the Council.

*Committee on Veterans' Affairs—Dr Harvey A Kelly, Suffolk, Chairman*

Dr Kelly moved that the report (Appendix No 8) be accepted. The motion was seconded, and it was so ordered by vote of the Council.

Dr Kelly then moved the adoption of the resolution with a change in the wording of the second paragraph as follows: "Whereas many European schools are not approved by most accredited approving bodies in the United States."

The motion was seconded and passed by a unanimous vote of the Council.

*Committee on Public Relations—Dr Harold R Kurth, Essex North, Secretary*

Dr Kurth presented the report (Appendix No 9).

The Secretary then made the motion that the committee recommendation that the Massachusetts Medical Society initiate a public-health exhibit and that the President be empowered to appoint a committee consisting of a representative from each district to initiate such a program immediately be approved.

The motion was seconded, and it was so ordered by a unanimous vote.

The Secretary then moved that the recommendation to establish a student loan fund (which had been disapproved by the Executive Committee) be disapproved by the Council. The motion was seconded, and it was so ordered by a unanimous vote.

## MIDDLESEX NORTH

W. M. Collins  
S. A. Dibbins  
L. J. Hall  
J. Y. Rodger  
J. D. Sweeney

## MIDDLESEX SOUTH

J. M. Baty  
H. K. Bloom  
G. F. H. Bowers  
Madeline R. Brown  
R. N. Brown  
R. W. Buck  
E. J. Butler  
J. F. Casey  
C. W. Clark  
E. A. Cooney  
Oliver Cope  
W. H. Crosby  
J. A. Daley  
J. G. Downing  
A. G. Engelbach  
C. W. Finnelly  
H. Q. Gallupe  
V. A. Getting  
H. G. Giddings  
H. W. Godfrey  
Eliot Hubbard, Jr.  
H. A. Kontoff  
J. J. Lepore  
A. A. Levi  
A. N. Malechnie  
J. H. McSweeney  
J. C. Merriam  
Dudley Merrill  
C. E. Mongan  
Dwight O'Hara  
Fabryan Packard  
L. S. Pilcher  
Max Ritvo  
H. P. Stevens  
K. J. Tillotson  
A. B. Toppin  
J. H. Townsend  
J. E. Vance  
C. F. Walcott  
R. H. Wells  
B. M. Wein  
Hovhannes Zovickian

## NORFOLK

C. E. Allard  
B. E. Barton  
Carl Bearse  
Elizabeth Broyles  
G. L. Doberty  
Albert Ebnfried  
J. M. Faulkner  
H. H. Faxon  
P. S. Foiese  
Susannah Friedman  
T. R. Goethals  
D. L. Halhersleben  
J. A. Halsted  
H. B. Harris  
C. G. Hayden  
R. J. Heffernan  
P. J. Jakmauh  
I. R. Jankelson  
C. J. Kickham  
C. J. E. Kickham  
D. L. Lionberger  
D. S. Luce  
D. L. Lynch  
F. P. McCarthy  
F. J. Moran  
H. R. Morrison  
Hyman Morrison  
D. J. Mullane  
H. A. Novack  
R. S. Palmer

G. W. Papan  
S. H. Proger  
H. A. Rice  
S. A. Robins  
D. D. Scannell  
L. A. Sieracki  
S. L. Skvirski  
E. C. Smith  
Kathlene S. Snow  
J. W. Spellman  
A. R. Stagg  
N. A. Welch  
P. R. Withington  
E. T. Wiman

## NORFOLK SOUTH

D. L. Belding  
R. L. Cook  
Frederick Hinchliffe  
E. K. Jenkins  
D. B. Reardon  
H. A. Robinson  
R. G. Vinal

## PLYMOUTH

J. C. Angley  
A. L. Duncombe  
H. H. Hamilton  
C. D. McCann  
G. A. Moore

## SUFFOLK

T. J. Anglem  
C. H. Bradford  
W. J. Brickley  
W. E. Browne  
A. J. A. Campbell  
E. M. Chapman  
M. Henry Clifford  
A. P. Derhagopian  
N. W. Faxon  
Maurice Fremont-Smith  
Joseph Garland  
G. L. Gateh  
A. A. Hornor  
H. A. Kelly  
H. E. Kennard  
T. H. Lanman  
R. I. Lee  
C. C. Lund  
C. F. Maraldi  
L. S. McKittrick  
Donald Munro  
F. W. O'Brien  
J. P. O'Hare  
L. E. Parkins  
L. E. Phaneuf  
Helen S. Pittman  
J. H. Pratt  
J. J. Regan  
W. H. Rohev  
Horatio Rogers  
H. F. Root  
C. G. Shedd  
R. M. Smith  
Augustus Thorndike  
Conrad Wesselhoeft

## WORCESTER

A. W. Atwood  
George Ballantyne  
J. B. Butts  
F. B. Carr  
I. J. Dumphy  
G. R. Dunlop  
John Fallon  
Donald Hight  
Thomas Hunter  
H. L. Kirkendall  
D. G. Ljungherg  
J. A. Lundv

J. C. McCann  
D. K. McClusky  
J. M. Olson  
F. A. O'Toole  
E. L. Richmond  
N. S. Scarcello  
J. J. Tegelherg

R. J. Ward  
B. C. Wheeler

## WORCESTER NORTH

D. B. Cheetbam  
J. J. Curley  
C. B. Gay  
J. V. McHugh

## APPENDIX NO. 2

## REPORT OF THE EXECUTIVE COMMITTEE

A meeting of the Executive Committee was called to order at 4:00 p.m. on September 8, 1948 by the president, Dr. Daniel B. Reardon with half the members present. The officers present were, besides the President, the president-elect Dr. Arthur W. Allen, the treasurer, Dr. Eliot Hubbard and the Secretary.

## MATTERS REFERRED TO THE EXECUTIVE COMMITTEE BY THE COUNCIL IN MAY, 1948

## 1. Should the Society receive certain gifts?

Dr. Eliot Hubbard stated that the Council was not in favor of accepting monetary gifts, even though they were to be used only for charitable, scientific and educational purposes and that he was interested in the question because of the effect on the Society's income-tax status. He questioned the possible danger of accepting gifts from drug firms. Dr. Hubbard suggested that he might question the Treasury Department in a frank letter asking for information. Dr. Robert W. Buck, chairman of the Committee on Finance, stated that he could add no further information. The Secretary moved that the committee defer action until the Treasurer received replies from the American Medical Association and the Treasury Department concerning the whole matter. The motion was carried unanimously.

2. A proposal to make the Committee on Postgraduate Assembly a subcommittee of the Committee on Postgraduate Medical Education (approved by Dr. Leroy Parkins and Dr. Richard Ohler).

On a motion by the Secretary, seconded by Dr. John Curley, Worcester North, this proposal was unanimously approved by the committee.

3. A proposal to have the Society sponsor the art exhibit of the Massachusetts Physicians Art Association at the annual meeting.

Dr. Robert W. Buck pointed out that members of the Association are all fellows of the Society and that the expense to the Society would not be increased by sponsorship. Dr. Reardon stated that it would give the Woman's Auxiliary good work to do and that it would encourage art in the profession. The committee voted unanimously to approve the proposal.

4. The request by Dr. M. J. Schlesinger, Middlesex South, to establish a section on pathology among the membership of the Society.

Dr. Schlesinger stated that this was urged by the New England Pathological Society. He also said that 100 to 125 attended monthly meetings.

Dr. John Fallon, Worcester suggested that the name be "Section on Pathology and Physiology." Dr. Arthur W. Allen moved that the committee approve of the establishment of a section on pathology and physiology. This motion was seconded, and it was so voted.

5. Action on the request of Dr. Augustus Thorndike, Suffolk, that the President appoint a committee of the Society to confer with the officers and directors of the newly formed Bay State Medical Rehabilitation Clinic to consider in what manner the Society may best assist in the establishment of the clinic or clinics and to report its findings to the February meeting of the Council.

Dr. Henry Marble said he hoped the committee would favor this work of Dr. Thorndike's, and that it was an excellent private charity and had no connection with any federal agency. On a motion by Dr. John J. Curley the committee unanimously approved the appointment of such a temporary committee.

The motion was seconded, and it was so ordered by vote of the Council

Dr O'Hara moved acceptance of the report as a whole. The motion was seconded and carried.

Dr O'Hara, in answer to several questions, outlined the organization and functions of the Massachusetts Medical Benevolent Society and assured the Council that the fund would be an active one.

*Report of the Delegates to the House of Delegates of the American Medical Association*—Dr Walter G Phippen, Essex South

Dr Phippen moved for acceptance of the report as printed (Appendix No 12). The motion was seconded, put to vote and carried.

*Subcommittee on Mental Health*—Dr Walter E Barton, Norfolk, *Chairman*

Dr Barton moved for acceptance of the report (Appendix No 13). The motion was seconded, and it was so ordered by vote of the Council.

The Secretary then moved that the reports of the Executive Committee and the Committee on Public Relations as amended at this meeting be approved. The motion was seconded and so voted.

#### NEW BUSINESS

The President introduced Dr Henry A Robinson, Norfolk South, who had attended the meeting of the National Physicians Committee as a representative of the Massachusetts Medical Society. Dr Robinson said that he and Dr Howard F Root, Suffolk, the other representative, had been very favorably impressed with the work of the National Physicians Committee and that they would be glad to hear from any fellow interested in forming a state committee of the National Physicians Committee.

Dr William A R Chapin, Hampden, was recognized by the President and presented the following resolution, which had been passed by the New York State Medical Society and had been published in the *Journal of the American Medical Association*, issue of July 3, 1948: "RESOLVED, That, failing to obtain co-operation from the various Specialty Boards and hospitals, the American Medical Association is requested to withhold recognition from those hospitals which make certification by a Specialty Board a necessary qualification for appointment or promotion on a hospital staff."

Dr David L Halbersleben, Norfolk, moved that the rules be suspended for consideration and discussion of the matter. The motion was seconded, and it was so ordered by unanimous vote.

At the request of Dr Chapin, the President ruled that Dr Chapin would get both discussion and action on the question.

At this point, the President called for a recess until 2 00 p m.

The President called the Council to order at 2 00 p m and recognized Dr William Chapin.

Dr Chapin presented his arguments in favor of the resolution he had presented and moved that the Council endorse in principle the resolution as presented. The motion was seconded.

Dr Leroy E Parkins, Suffolk, moved that the Council go into Executive Session. The motion was seconded, and it was so ordered by a unanimous vote.

The motion was then discussed by Dr Bernard Appel, Essex South, Dr Parkins, Dr Howard Root, Suffolk, and Dr Lewis S Pilcher, Middlesex South, in opposition, and Dr David L Halbersleben, Norfolk, and Dr Carl Bearse, Norfolk, in favor.

The President stated the question and called for a vote by a show of hands, and announced the vote as 37 affirmative, 30 negative.

The President recognized Dr John F Conlin, Suffolk, who described the program of the New England Postgraduate Assembly and urged that there be a large attendance.

Dr Conlin also announced that the American Public Health Association would meet in Boston on November 8, 1948, and stated that all physicians are eligible for membership. He hoped that many would attend the meetings and the exhibits.

On motion duly made, seconded and voted, the meeting adjourned at 3 00 p m.

H QUIMBY GALLUPE, *Secretary*

#### APPENDIX NO 1

##### ATTENDANCE OF COUNCILORS

BERKSHIRE	Long Grimes
P J Sullivan	P P Johnson
	R T Moulton
BRISTOL NORTH	E L Peirson
M E Johnson	W G Phippen
J L Murphy	E D Reynolds
W M Stobbs	H D Stebbins
	P E Tivnan
BRISTOL SOUTH	C F Twomey
R B Butler	R J Williams
D F Gallery	
E D Gardner	FRANKLIN
R H Goodwin	L R Dame
William Mason	
H E Perry	HAMPDEN
A J Pothier	E P Bagg
C C Tripp	W A R Chapin
ESSEX NORTH	G B Corcoran
E S Bagnall	Adolph Franz, Jr
R E Blais	P E Gear
J A Bradley	A H Riordan
N F DeCesare	G L Schadt
A P George	
H R Kurth	HAMPSHIRE
P J Look	R S Clapp
R C Norris	
L C Peirce	MIDDLESEX EAST
F W Snow	J L Anderson
L T Stokes	Robert Dutton
F N Sweetser	R W Layton
C F Warren	K L MacLachlan
C A Weiss	H L Mueller
ESSEX SOUTH	M J Quinn
Bernard Appel	R R Stratton
S N Gardner	

directors of the corporation, by virtue of the positions that they hold, members of the Council

I think it was a very necessary and very wise step to take to keep a constant touch and contact between the medical group, its governing body and this corporation, created in 1940

Another important problem that should be considered is the mechanism for replacement of physicians who are members of the Board of Directors. That will be started through proper channels

We must think ahead to the time when men who have worked actively for nearly ten years on this corporation will ask for release, and it is very important that men come on who are informed about the problems and the past history of the Corporation so that proper action at all times may be taken by the representatives of the position of the Board of Directors. That is more important than possibly it might appear with the statement to the members of the Council this morning

I shall also bring up the question through proper channels of whether the by-laws should not be changed so as to have a provision established that the president of the corporation shall be a physician. We felt at times with the undefined future ahead of us that we might want that definitely stated in the by-laws. We might feel it desirable to have a layman as president of the Board of Directors. With the experience of nearly ten years, and the problems that arise it may be desirable to make certain that the president of the corporation at all times shall be a physician who of course will be a member of the Board of Directors

In the last few years a major reorganization has been made in the relation of Blue Shield and Blue Cross, which is based on the experience of many years. I think they are wise measures

The first, as outlined in this booklet that you all have received is that we have changed from our initial basic relation whereby the layman who was executive director of the Blue Cross was at the same time the Executive Committee director of the Blue Shield. At that time, we were a young and promising, we hoped, corporation, and we were not in a position to have a medical director. In the intervening years we have had the services of one of the outstanding young men in the country in this field. It seemed on the basis of this relation that, as the problems that have developed were worked out and since we now have a medical director, we should be established as two distinct corporations, with our own director, who is a physician. I think that was a very fine move and it was accepted by our Board of Directors, the Blue Shield Board of Directors and the Joint Board of Blue Shield and Blue Cross meeting together. That is now our established relation

It is still necessary, of course, to keep liaison between the two groups. That is accomplished, as you may or may not know, by the fact that there are three members who constitute interlocking members between the two groups. That number of three has been established informally by the Commissioner of Insurance as a number that shall not be exceeded

We have also established plans for joint meetings of the executive committees of the two boards of directors for problems that may arise between the two corporations, and such problems have arisen, we do need a method of resolving them, and we consider this to be the effective method of approach. We had a joint committee, but it seemed wiser that the new president eliminate that joint committee and have our joint problems discussed by meetings of the two executive committees of the boards

Now with reference to other matters, the contract, as you know, has been broadened since my last report to include medical care. That is the second step placed in this group in 1939 in the over-all planning of the evolution of the program

The next step, the problem of including services in the home and office, will certainly have to wait on time and experience. How far that should be gone into with the prospect of keeping the organization solvent is still debatable despite the ardent propaganda of some agents in Washington and some lay propagandists who believe as the Washington agents do. It is still debatable, however how far these minor services should be included in the insurance program. That certainly is a matter for time and study

We have tried to effectuate our contact with the local groups. It really takes a great deal of plugging, and in this, of course, our medical director is chiefly responsible—he has to do a good deal of plugging to keep the local committees, which were provided for in our initial setup, active and busy

The reason is chiefly that there has not been enough pertinent material that we can give to them regularly, so as to keep their teeth chewing on this problem. I do feel that, as progress is made, these local groups will be brought into ever-increasing active functioning with the central groups. And if for the present there does not seem to be too much to place in your hands when Dr. Hayden and the representatives of the corporation come into the county, please accept it as evidence that we feel that for the future the local groups will be active and are an important part of our over-all functioning organization

Furthermore to keep our contacts locally active and to help the physicians, as you know, we have had periodic meetings with the physicians' secretaries, who were informed of our functions and our program

Another change since the previous report has been the shifting of the method of claim by the physicians. We moved from the activating of claims from the hospital, where a good many problems were raised and a good many inconveniences created for the physicians, to the initiation of claims directly by the physician. That was done in our local area first in one county, and it did seem to be an improvement and then it was placed on a state-wide basis. If there are difficulties, it is still in its early stage of development and I hope you will bear with us, and certainly constructive criticism will be appreciated

I think the physician should keep in mind that the complicated problems of administration have been greatly simplified which in turn has reduced costs of administration, and that will also be a major responsibility of our group—to keep administrative costs at the lowest point possible

The local problems that arise from this new method of initiating claims I think, may be placed in the hands of the hospitals. I believe we must have all hands thoroughly imbued with the need to create smooth functioning. Before we put this on a state-wide basis, we approached all the hospitals, and the administrators were only too happy to co-operate right straight across the State. The problem is the changing personnel in hospitals. Two out of three office administrators may carry this through, whereas the third either may not understand or may fail to grasp its importance, and I think that most of the trouble has probably arisen from such lack of understanding, which I think time will resolve

The financial situation continues satisfactory. We are still operating in the black with a substantial surplus, which is required by good actuarial planning. This group, in its wisdom on the recommendation of a committee of the Council, raised the income level for eligibility for service to \$3000

This demonstrates that the physician can put the problem of cost of medical care on a proper base. It was a very sound strategic move as well as, I think, a perfectly proper move with reference to the needs of the people

The question of fee schedule has again been studied by a committee of the Society, Dr. McAttrick's fee-schedule committee, which has a very large representation from across the State. It was felt that at present it was not strategic to make any change in the fee schedule, and this was talked over very thoroughly and the decision was arrived at with reference to three pertinent problems: the major objective of proving that the physician on a voluntary basis can handle this problem of prepaid medical care from the solvency of the corporation, it can be seen that we are running it satisfactorily as far as the finances are concerned, but it was very apparent that an increase in the fee schedule at the present time could not be accomplished without an increase in premiums, and, with the squeeze that the people are subjected to and the inflationary prices at the present time and the declining enrollment rate, it seemed definitely poor judgment in the opinion of this committee to advise the change of fee-schedule rates

As you know, with reference to income limitations for service and with reference to items such as fee schedules the Blue Shield group adopted a policy of referring the matter to the Society, and a committee of the Society advises how to proceed. It is felt that this group, small as it is, is wholly

6 The question of a standing committee on medicolegal testimony (The former Committee to Consider Expert Testimony had recommended that the by-laws be amended to produce such a standing committee.)

The Secretary pointed out that the chief purpose of the committee would be to discover improper testimony by fellows of the Society at various trials for malpractice cases and that such questions of ethics might well be referred by anyone to the Committee on Ethics and Discipline. The President pointed out that the suggestion of appointing listeners at trials might include all cases in which medical testimony is given.

On a motion by Dr Lawrence R Dame, Franklin, seconded by Dr Curley, Worcester North, the committee voted unanimously not to approve the request to amend the by-laws to produce a standing committee on medicolegal testimony.

## COMMITTEE REPORT

### Committee on Membership

The Committee met on August 24, 1948, and the Secretary submitted the report, which concerned requests for retirement and resignations and those fellows deprived of membership for nonpayment of dues. With a few minor corrections submitted by the Treasurer, the Executive Committee accepted the report.

## NEW BUSINESS

The Secretary read the following resolution submitted by the Hampden District Medical Society:

WHEREAS, Hospital trustees in order to maintain and insure the best possible care of patients in their institutions are increasingly demanding certification in specialties and/or membership in certain national colleges or specialties and,

WHEREAS, It has come to our attention that an irregular situation exists in selection of candidates for membership in the aforesaid organizations, such as the exclusion of candidates from membership by prejudiced local fellow workers followed by the acceptance of some of these men through the intercession of more celebrated practitioners in other areas and,

WHEREAS, We have examples here of failures in board examination followed by marking up of these examinations to an acceptable figure when the mortality of the examination has hit influential and responsible leaders of that particular field of medicine,

The Hampden District Medical Society, at its annual meeting on April 27, 1948, petitions the Executive Committee of the Massachusetts Medical Society for the appointment of a committee to investigate such irregularities and evidences of partialities so that personalities may be further minimized and candidates for the organizations mentioned above be treated in an equal and fair manner, such committees to hold hearings and report back to the Society at an early date and the Hampden District Medical Society be later informed of any action which is taken on this resolution.

The Secretary stated that he believed the Committee on Ethics and Discipline could handle any situation that might arise in this regard.

Dr John J. Curley moved that the matter be laid on the table until the next meeting of the committee. There was a second, and the motion was carried unanimously.

The Secretary read a communication from the Section on Physiotherapy requesting a change of name to "Section on Physical Medicine." On motion duly made and seconded the committee voted unanimously to recommend the change requested.

The Secretary reported the program of the House of Delegates of the American Medical Association to select a candidate for the General Practitioners Award at the interim session, suggested that the Massachusetts Medical Society ought to take steps to select the outstanding general practitioner in Massachusetts in 1949 and asked for permission to notify the district secretaries to present names of candidates to the Executive Committee in time for the interim

session in 1949. On motion made and seconded the committee gave unanimous permission.

Dr Reardon then related a request from Mr Twomey of the firm of Palmer-Dodge, our attorneys, to have the Society adopt the attitude of *amicus-curiae* and approve of a brief submitted to the court by our attorneys in the case of a physician in the western part of the State who had been sued by a patient for allegedly instituting the narcotic habit. Dr Reardon stated that the Berkshire District Medical Society was much upset by the case and that the doctor concerned was held in high esteem. On motion of the Secretary the Committee voted to support Mr Twomey's request to send such a brief to the Supreme Court.

## REPORTS OF COMMITTEES IN CIRCULAR OF ADVANCE INFORMATION

### Committee on Cancer

The Executive Committee voted to approve the recommendations of the committee beginning on page 1, line 27.

The Executive Committee voted to approve the recommendation of the committee beginning on page 2, line 4.

### Committee on Tax-Supported Medical Care

After considerable discussion the Executive Committee by a small majority voted not to approve the recommendation that the "Medical Care Program" of the Office of Veterans' Services of Massachusetts be approved by the Society.

### Advisory Committee to the Red Cross Blood Bank

The Executive Committee voted unanimously to approve the request of the committee beginning on page 4, line 19.

### Committee on Veterans' Affairs

The Executive Committee voted unanimous approval of the resolution beginning on page 5, line 16.

### Committee on Public Relations

The Executive Committee voted unanimously to approve of the recommendation found in the motion beginning on page 6, line 33.

The Executive Committee voted to disapprove of the resolution of the committee beginning on page 7, line 4 (Dr Hubbard had stated that he believed students would be poor risks.)

After hearing from Dr John Conlin concerning the statewide health meeting to be held early in 1949, the Executive Committee voted unanimously to approve the action of the committee beginning on page 7, line 33.

After hearing from the Treasurer and the Secretary the Executive Committee voted unanimously to disapprove of the action of the committee beginning on page 8, line 33.

The Executive Committee approved the recommendation of the committee beginning on page 8, line 46, and recommended that the Committee on Medical Education be the committee to handle the matter.

### Committee on Public Health

The Executive Committee approved the recommendation of the committee beginning on page 10, line 49.

The Executive Committee voted approval of the recommendation beginning on page 11, line 43.

The Executive Committee also voted approval of the last paragraph of Dr Phippen's resolution beginning on page 12, line 39.

### Committee on Benevolence

The Executive Committee unanimously voted approval of the recommendation beginning on page 13 line 9, the proposal of the committee and the recommendation beginning on page 14 line 4.

The meeting was adjourned at 6 10 p.m.

H. QUIMBY GALLUPE, Secretary

## APPENDIX NO 3

### AFFAIRS OF BLUE SHIELD

In the past few years basic changes have been taking place in our organization. This group has seen fit in its wisdom to make the president of the corporation and the medical

sufficient data for a report on this point. In the meantime it is suggested that in all cases of vague or ill defined gynecologic signs or symptoms with no obvious abnormality to account for them found on pelvic examination, the vaginal smear be used as an additional means of diagnosis.

During this past year, with the aid of the Massachusetts Division of the American Cancer Society, lectures on cancer were provided for each of the district societies. Its interest in the lectures varied, and it is hoped that the most effective method for presentation of points of diagnostic and therapeutic value can be evolved.

SHIELDS WARREN, *Chairman*  
THOMAS J. ANGLEM  
ALLEN G. RICE  
CHANNING C. SIMMONS

## APPENDIX NO 5

### REPORT OF THE COMMITTEE ON TAX-SUPPORTED MEDICAL CARE

As a result of the meeting of the Committee on Tax-Supported Medical Care on July 28, 1948, the following recommendation was made to the Council that the Council of the Massachusetts Medical Society approve — "Medical Care Program — Policies and Procedures, from the Office of Veterans' Services, Room 123, State House, Boston, Massachusetts Effective July 15, 1948," with the inclusion of the amendment to which Commissioner O'Day has agreed as follows:

You may rest assured that after our Massachusetts Medical Society meets and approves the program, I will be pleased to notify all of my agents throughout the Commonwealth of the action, and that this approval is effective subject to renegotiation.

ALBERT A. HONOR, *Chairman*  
FREDERICK S. HOPKINS  
FRANCIS P. MCCARTHY  
FRANK W. SNOW

## APPENDIX NO 6

### MEDICAL CARE PROGRAM OFFICE OF VETERANS' SERVICES

#### PURPOSE

A recent survey discloses a large amount of apparently unnecessary medical expense having been incurred with a corresponding increase in medical cost. Because of this, it is imperative that policies for procedures and cost control be adopted. It is not our intention to curtail necessary medical care, but only to provide a needed uniform plan of payment for those items of medical care furnished to all persons accepted by the Office of Veterans' Services. It is your responsibility to see that this plan is carried out. The following are the instructions:

#### 1 Physicians' Services

##### 1 Eligibility

When physicians' services are needed, payment will be provided as an addition to the regular budget. On temporary cases such payment is not to be encouraged unless an emergency arises.

##### 2 Authorization

Permanent recipients will be allowed two visits in any one month by a physician. Additional visits thereafter must be authorized by the Local Agent and substantiated by a written statement from the physician giving the diagnosis, prognosis, and an estimate of the number of calls necessary to complete the treatment.

##### 3 Fee Schedule

The following uniform fee schedule is to be hereafter adopted by this Office:

Office Visit — \$2.00  
Home Visit — \$3.00

#### Multiple Visits

When more than one patient is seen during one call at the office, home, or nursing home, full fee will be allowed for the first visit. Thereafter, full fee for one patient and \$1.00 for each additional patient.

*Travel Allowance* — \$2.00 extra in rural communities where the physician is compelled to travel a considerable distance.

*Night Calls* — \$1.00 additional, between 11 p.m. and 7 a.m.

**NOTE** — Extra fees for medication, either home or office visit, will not be allowed unless fully explained and approved by this Office.

## II Hospitalization

### 1 Eligibility and Notice

Eligibility for hospital remains as heretofore and will be provided only when financial need exists.

All Agents must notify this Office within three (3) days following the entrance of an applicant into a hospital, either by letter or application, and this must be followed by a thorough investigation by the Local Agent to determine if financial need exists. This investigation should disclose all available resources of the applicant and whether part or all of the expense can be paid either by the applicant or by members of the family.

If the applicant has Blue Cross, or Blue Shield or any other hospital insurance, this must be used before hospital expense will be assumed by this Office.

#### A General Policy Re "Service" Care

All recipients or applicants for Veterans Benefits who apply for hospitalization must be immediately notified by you that only "service" care in a ward will be provided.

##### (1) Definition

"Service" care is defined as care in hospitals where the staff of physicians provides free medical treatment and/or surgery to ward patients. Therefore, no fees for doctors are allowed.

##### (2) Rate of Payment

Payment through this Office to a hospital will be provided at a maximum daily all-inclusive rate not to exceed \$8.00 per day.

##### (3) Hospital Extras

Certain hospital cases may require unusually expensive drugs such as streptomycin or large quantities of penicillin. Individual consideration will be given to such extras as charged by the hospital, but to no other extra charges submitted, such as use of operating room, laboratory fees, etc.

Charges for blood transfusions will not be allowed. Any necessary blood will be provided through this Office in exchange for any used by the hospital and given to the recipient. In hospitals west of the City of Worcester, this Office will not be able to provide this blood at the present time. Blood banks will be used in that area soon after July 1st, 1948.

##### (4) Notice to Hospitals and Physicians

All Agents on receiving these instructions must immediately contact the hospitals in their district and notify them of the above policy. The attending physician must be notified, either by the applicant or by the Agent, that Veterans' Benefits patients are to enter hospitals under the above-specified "service" care plan, and that no allowance will be provided for the care furnished by a doctor in the hospital.

capable of arriving at a decision regarding such pertinent matters

How about public relations? We have in conjunction with the Blue Cross engaged the services of a very effective public-relations man, and I think that you have been aware through the newspapers of more activity and a more active effort to enlighten the public about our methods and our objectives. There is one matter that is very vital with reference to public relations. It is subtle and more apparent to those involved in the work in your behalf than to the individual practitioner. There is the question of enough instances to disturb management, to disturb the public, of an excessive differential charge by the physician, in the instance of the patient who is just a little above the level of the income set by this Council. That problem is under study by the Fee Schedule Committee, and of course is a matter in which Blue Shield would not take any action unless instructed by the Committee or the Council, which means, of course, that it will be referred to the Council until we are advised on how to proceed. It is a matter that should be considered very seriously because public relations in the end are going to determine the failure or success of these voluntary prepaid ventures. Our current problems are definite, and of course we hope they will be resolved.

Everybody will make an effort to see that the problems are resolved fairly in the interest of everyone involved. As you know, from the circularized statement, we have had a year and a half of no growth in Blue Shield, and this has also been somewhat characteristic of Blue Cross. Some of the difficulties that confronted Blue Cross a year and a half ago arose primarily from the forces of inflation, and resulted in temporary financial difficulties for that organization. That, of course, held up growth of both corporations. That was inevitable, and the problem is to get the good ship of voluntary prepayment back into the water and under sail. That is the difficulty at this time. It will take judicious consideration of all problems involved, and it will require a very definite stand in protection of the basic principles on which we have dealt.

Now, we are moving definitely toward a solution of those problems, and I am sure of that because I think we must assume that there is goodwill on all sides. Basically, the problems are different, and they have got to be talked out very frankly and resolved across the board, and to that end the two executive committees of the respective corporations are meeting tomorrow night, from that meeting we may achieve the very close and confidential co-operation that, up until a year and a half ago, existed between the two corporations. And from that confidential co-operation all current problems may be effectively resolved, and then we may see more active sales for both corporations. We must realize that this movement is under very close scrutiny, as shown in the hearings last spring in Washington, and basic error or failure to grow or failure to meet the needs of the people, or any demonstration of anything but full capacity in meeting the problems and administering them, will put us in a very vulnerable position, so I am sure all parties involved will devote themselves to resolving all current problems, and our hope and belief is that this will be accomplished.

Regarding the question of competition from commercial insurance companies, it might be that Dr Hayden could give that better in figures. I will say that it is very definite and serious. Our only strength was in the service contract, in addition to the fact that operating on a nonprofit basis we should have been able to offer a better contract than the commercial companies. At present I think it is fair to say that with reference to the present hospitalization contract, it can be met by commercial insurance companies, but there is also this fact, which must always be kept in mind: the commercial insurance groups will only move into large groups. They will not take the small groups, which Blue Cross does give service to. They also have pretty excessive enrollment requirements, almost always 75 per cent, and when there is a revamping of the Blue Cross program, the Blue Cross may be able to write a commercial contract that competes favorably. Our program can still compete because the commercial insurance companies can never offer the physician services on a service basis, and I am sure we can work down the financial basis, if we maintain a fee schedule within the present limit that the companies cannot compete with, as far as treatment is concerned.

## APPENDIX NO 4

### REPORT OF THE COMMITTEE ON CANCER

The Committee met on August 9, 1948, with Drs John Conlin, Arthur W. Allen, Thomas J. Anglem, Channing C. Simmons and Shields Warren present.

The problem of the registration of cancer cases was considered. Both compulsory and voluntary registration of cancer cases has been tried. The compulsory registration is far from effective. At present 12 states have some type of cancer registration. The objectives of a registration system are to obtain adequate information regarding the size of the cancer problem and its nature and to obtain information that will be of advantage from the standpoint of better understanding of the factors of importance in etiology. Registration should also greatly improve follow-up systems. Registration in itself is of little value. The use that is made of the registered cases is of importance.

The chief advantage for the patient is that it will aid in encouragement of periodic follow-up examinations. The three potential sources of registration are private practitioners, clinics and hospitals and laboratories of pathology.

The best and most effective source is the private practitioner. The compulsory-registration system has proved to be somewhat ineffective. Unless there is full co-operation of all interested, no real value would be obtained from the mere fact of registration.

It is therefore recommended that the Massachusetts Medical Society endorse the principle of voluntary registration of cancer cases and that the Committee on Cancer be instructed to develop a system for consideration by the Council.

In 1940 the Committee on Publications, an offshoot of the American Cancer Society and the group in Massachusetts interested in cancer control, prepared a manual on cancer for the general practitioner. This was distributed by the Massachusetts Department of Public Health to all practitioners in the State, and a number of copies were sold outside the State.

The total edition was approximately 14,000 copies. There still continues a demand for this volume, but in the eight years that have elapsed, considerable advances in the knowledge of cancer have taken place. The Committee on Publications, of which Dr Channing C. Simmons is chairman, has expressed its willingness to prepare an up-to-date edition of this manual.

It is recommended that the Committee on Publications be encouraged to prepare a revised edition of the *Cancer Manual*.

Of considerable interest is the amount of money being raised for cancer and spent for cancer in Massachusetts.

In the period from September 1, 1947, to August 10, 1948, the Massachusetts Division of the American Cancer Society received \$519,336.69. During that period the national society made grants totaling \$457,204 in Massachusetts, and the Massachusetts Division made additional grants totaling \$273,325.90, a grand total of \$730,529.90, or \$211,193.21 more money made available for service and research in Massachusetts than was raised here.

In addition, construction grants of over \$1,000,000 were made by the United States Public Health Service for the construction of cancer facilities, and several hundred thousand dollars were made available for research in Massachusetts. The federal Government made \$75,286 available for cancer to the Massachusetts Department of Public Health in the fiscal year 1948.

Great interest has been aroused during the year in the vaginal-smear method of diagnosis of cervical and uterine cancer, particularly by ill advised advertising in newspapers and lay periodicals. The Committee on Cancer has studied the problem regarding whether vaginal-smear diagnosis should be encouraged as a routine procedure in pathological laboratories. At the present time, it is our belief that further work needs to be done on the evaluation of the test before a definite statement can be made.

There is no question that the vaginal-smear examination offers an added means of diagnosis of cancer of the female genital tract—perhaps the best means in certain types of cases. We are not yet sure that the time and money consumed in making a routine vaginal smear in every woman of cancer age are warranted. We hope in another year to have

sufficient data for a report on this point. In the meantime it is suggested that in all cases of vague or ill defined gynecologic signs or symptoms with no obvious abnormality to account for them found on pelvic examination, the vaginal smear be used as an additional means of diagnosis.

During this past year, with the aid of the Massachusetts Division of the American Cancer Society, lectures on cancer were provided for each of the district societies. Its interest in the lectures varied and it is hoped that the most effective method for presentation of points of diagnostic and therapeutic value can be evolved.

SHIELDS WARREN, *Chairman*

THOMAS J. ANGLE

ALLEN G. RICE

CHANNING C. SIMMONS

## APPENDIX NO. 5

### REPORT OF THE COMMITTEE ON TAX-SUPPORTED MEDICAL CARE

As a result of the meeting of the Committee on Tax-Supported Medical Care on July 28, 1948, the following recommendation was made to the Council that the Council of the Massachusetts Medical Society approve — "Medical Care Program — Policies and Procedures, from the Office of Veterans' Services, Room 125, State House, Boston, Massachusetts Effective July 15, 1948," with the inclusion of the amendment to which Commissioner O'Day has agreed as follows:

You may rest assured that after your Massachusetts Medical Society meets and approves the program I will be pleased to notify all of my agents throughout the Commonwealth of the action and that this approval is effective subject to renegotiation.

ALBERT A. HONOR, *Chairman*

FREDERICK S. HOPKIN

FRANCIS P. MCCARTHY

FRANK W. SNOW

## APPENDIX NO. 6

### MEDICAL CARE PROGRAM OFFICE OF VETERANS SERVICES

#### PURPOSE

A recent survey discloses a large amount of apparently unnecessary medical expense having been incurred with a corresponding increase in medical cost. Because of this, it is imperative that policies for procedures and cost control be adopted. It is not our intention to curtail necessary medical care, but only to provide a needed uniform plan of payment for those items of medical care furnished to all persons accepted by the Office of Veterans' Services. It is your responsibility to see that this plan is carried out. The following are the instructions:

#### I Physicians' Services

##### 1 Eligibility

When physicians' services are needed, payment will be provided as an addition to the regular budget. On temporary cases such payment is not to be encouraged unless an emergency arises.

##### 2 Authorization

Permanent recipients will be allowed two visits in any one month by a physician. Additional visits thereafter must be authorized by the Local Agent and substantiated by a written statement from the physician giving the diagnosis, prognosis, and an estimate of the number of calls necessary to complete the treatment.

##### 3 Fee Schedule

The following uniform fee schedule is to be hereafter adopted by this Office:

Office Visit — \$2.00

Home Visit — \$5.00

#### Multiple Visits

When more than one patient is seen during one call at the office, home, or nursing home, full fee will be allowed for the first visit. Thereafter, full fee for one patient and \$1.00 for each additional patient.

*Travel Allowance* — \$2.00 extra in rural communities where the physician is compelled to travel a considerable distance.

*Night Calls* — \$1.00 additional, between 11 p.m. and 7 a.m.

*NOTE* — Extra fees for medication, either home or office visit, will not be allowed unless fully explained and approved by this Office.

## II Hospitalization

### 1 Eligibility and Notice

Eligibility for hospital remains as heretofore and will be provided only when financial need exists.

All Agents must notify this Office within three (3) days following the entrance of an applicant into a hospital either by letter or application and this must be followed by a thorough investigation by the Local Agent to determine if financial need exists. This investigation should disclose all available resources of the applicant and whether part or all of the expense can be paid either by the applicant or by members of the family.

If the applicant has Blue Cross, or Blue Shield or any other hospital insurance, this must be used before hospital expense will be assumed by this Office.

#### A General Policy Re "Service" Care

All recipients or applicants for Veterans' Benefits who apply for hospitalization must be immediately notified by you that only "service" care in a ward will be provided.

##### (1) Definition

"Service" care is defined as care in hospitals where the staff of physicians provides free medical treatment and/or surgery to ward patients. Therefore, no fees for doctors are allowed.

##### (2) Rate of Payment

Payment through this Office to a hospital will be provided at a maximum daily all-inclusive rate not to exceed \$8.00 per day.

##### (3) Hospital Extras

Certain hospital cases may require unusually expensive drugs such as streptomycin or large quantities of penicillin. Individual consideration will be given to such extras as charged by the hospital but to no other extra charges submitted, such as use of operating room, laboratory fees, etc.

Charges for blood transfusions will not be allowed. Any necessary blood will be provided through this Office in exchange for any used by the hospital and given to the recipient. In hospitals west of the City of Worcester, this Office will not be able to provide this blood at the present time. Blood banks will be used in that area soon after July 1st, 1948.

##### (4) Notice to Hospitals and Physicians

All Agents on receiving these instructions must immediately contact the hospitals in their district and notify them of the above policy. The attending physician must be notified, either by the applicant or by the Agent, that Veterans' Benefits patients are to enter hospitals under the above-specified "service" care plan, and that no allowance will be provided for the care furnished by a doctor in the hospital.

### B Policy Re Hospitals Where Free "Service" Care Is Not Available

The basic policy of this Office is to use those hospitals providing free "service" care to ward patients to the fullest extent wherever possible throughout the State. However, this Office recognizes that there are certain areas in the State, chiefly rural, where there are no hospitals in the vicinity in which the staff of physicians gives free care to ward patients.

Therefore, when there is no hospital within a fifteen-mile radius of the recipient's town where such free medical or surgical service for ward patients is available, recipients of Veterans' Benefits may be admitted to the local hospital and this Office will provide payment to the attending physician or surgeon at Blue Shield rates. It is important to note that the Blue Shield rate for an operation includes the fee for the assistant surgeon. No extra payment to an assistant will be allowed by this Office. A fee for the anesthetist within Blue Shield rates will be allowed.

The above-outlined policy (regarding the all-inclusive rate not to exceed \$8.00) as paid to the hospital for hospital care will remain in effect and have no bearing on this plan to pay for physicians' services.

### NOTICE TO BE GIVEN HOSPITALS, DOCTORS AND RECIPIENTS

All Agents, on receiving these instructions, must immediately contact the hospitals in their district and notify them of the above policy. The attending physician must be notified either by the Agent or by the recipient that only ward care will be provided through this Office.

Payment for physicians' fees will be made in the following list of hospitals only:

Plunkett Memorial Hospital	Adams
Farren Memorial Hospital	Montague
Franklin County Public Hospital	Greenfield
Fairview Hospital	Great Barrington
North Adams Hospital	North Adams
Wing Memorial Hospital	Palmer
Mary Lane Hospital	Ware
Community Memorial Hospital	Ayer
Webster District Hospital	Webster
Emerson Hospital	Concord
St. Luke's Hospital	Middleboro
Claffin Hill Hospital	Milford
Norwood Hospital	Norwood
Jordan Hospital	Plymouth
Cape Cod Hospital	Hyannis
Tobey Hospital	Wareham
Nantucket Cottage Hospital	Nantucket
Martha's Vineyard Hospital	Oak Bluffs
Winchendon Hospital, Inc.	Winchendon

### FEES ALLOWED

1 For medical care cases where no surgery is involved (as in pneumonia, etc.) the allowed fee for the attending physician in the above-listed hospitals will be \$4.00 for the first visit in the hospital and \$2.00 for each visit thereafter. During any one hospital stay, for the first two months the total fee to be paid the physician shall not exceed \$150.00.

2 For surgical care in these above-listed hospitals this Office will provide payment at Blue Shield rates.

NOTE — Veterans seeking hospitalization must avail themselves of facilities offered by the Veterans' Administration and the Soldiers' Home in Chelsea. On temporary cases, hospitalization will not be considered unless they are emergencies. Applicants must assume the responsibility of temporary hospitalization bills when they return to work.

### III Drugs

The purchase of medicines and other supplies through local drugstores has been much abused in many localities. From the effective date of this order only those medicines, or drugs, or supplies that have been prescribed by a physician will be accepted as legitimate charges. Whenever possible, the physician should be asked to prescribe U.S.P. (United States Pharmacopeia) or N.F. (National Formulary) drugs because of the economy that would result without loss of efficiency. If the patient is still under care for the same illness as when a medicine is prescribed, refills may be authorized. Refills on prescriptions written over a six months' period previously will not be allowed. Local Agents are required to instruct recipients that all drugs or orders for supplies are hereafter to be authorized by the Agent before their purchase.

Ordinary medicine chest supplies, such as aspirin, band-aids, disinfectants, etc., must be purchased from the allowance under personal needs as contained in our budget.

Itemized bills must be submitted in duplicate by the drugstore to the Local Agent and one copy sent to this Office. These must show the name of the purchaser, the date purchased, and the names and quantities of drugs. Current cases, where the purchase of drugs has already been authorized, will continue under the same policy as heretofore without any impairment of service. Bills for such medication already authorized will be submitted as outlined above.

### A Clinics and Out-Patient Services

Agents must advise applicants of Veterans' Benefits to take advantage of available out-patient clinics or other type of clinics. Admission fees as charged by the clinics to persons who may be classed as being in these circumstances will be allowed, except in the case of tax-supported hospitals and clinics where this Office is not legally committed to pay.

Veterans who are eligible for out-patient treatment at a Veterans' Administration hospital or through a Veterans' Administration contract doctor must use this type of service in preference to any service available through this Office to non-service connected disability cases.

### B Visiting Nurse Service

The fullest use of the Visiting Nurses must be employed wherever they are available. Agents should consult the physician regarding the advisability of delegating appropriate tasks whenever possible. The prevailing community rate charged by the Visiting Nursing Association per visit will be allowed by this office for eligible cases.

### Family Responsibility

It is noted on many of our cases that members of the family have been contributing to the medical expenses of the applicants. This policy should be continued and encouraged.

### Agents' Authorization Notice

Medical bills not in excess of \$10.00 a month shall be submitted only at the termination of a two months' period with a copy of the bills. Before they are charged on the monthly returns, authorization must be made by this office. All medical bills must be submitted within sixty days.

### Physical Examination

In cases where there is a question of an applicant's ability to work, this office will authorize a medical bill for a physical examination. The Agent should authorize two or more doctors from which the applicant may select one for such an examination.

*Special Nurses*

Special nurses will be provided for only in cases when the applicant is in such an extremely dangerous condition that the attending physician orders this additional service. Agents must notify the Commissioner by telephone for this special service.

*Enforcement*

The foregoing rules must be adhered to by all Veterans' Agents if you anticipate reimbursement by this office. They will be amended or changed only by official order or authority by the Commissioner.

By order of

HENRY V O'DAY, Commissioner  
Office of Veterans' Services

State House  
Boston, Massachusetts

is permissible only as a life-saving measure when other adequate measures are not possible.

The Committee advocates that the use of pooled plasma, unless processed by current methods of inactivating the virus of hepatitis be abandoned except under the rare instance noted above. The assistance of the Committee on Postgraduate Medical Education is requested in bringing this to the attention of all physicians.

At the next meeting of the Committee it is planned to request the attendance for information and consultation representatives of the Massachusetts Hospital Association, officials of the American Red Cross Blood Program and representatives of the American Association of Blood Banks and of the Greater Boston advisory group of blood-bank directors.

JOHN F CONLIN, Chairman  
F HAROLD ALLEN  
STEPHEN BROWN  
WILLIAM B CASTLE  
WILLIAM P MURPHY  
JOSEPH E ROSS  
C STUART WELCH

## APPENDIX NO 7

REPORT OF THE ADVISORY COMMITTEE TO THE RED CROSS  
BLOOD BANK

On July 28 a meeting of the Advisory Committee to the Red Cross Blood Bank was held at 8 Fenway.

Present were Dr John F Conlin, chairman, Dr F Harold Allen, Dr Stephen Brown, Dr Joseph E. Ross, Dr C Stuart Welch, Dr Arthur W Allen and Dr H Quimby Gallupe.

Some difficulty was experienced in determining the background of the appointing of this committee and the scope of its work. Many of the key persons having information on these matters were not available for consultation prior to the committee meeting.

The question was raised concerning Rh typing of blood collected by the American Red Cross and processed at the laboratory operated by the Massachusetts Department of Public Health. Funds have been made available for the Rh typing of this blood and Rh typing of prenatal blood specimens continues.

Recently publicized shortages of blood for transfusion purposes were discussed. It was agreed that increased publicity concerning the aims of the American Red Cross blood program in Massachusetts is needed. The co-operation of physicians in this matter is urged.

The House of Delegates of the American Medical Association has twice approved the Red Cross National Blood Bank Program "in principle." In June, 1948 more specific action was taken by the House of Delegates. Among items there approved were the following: local control of blood banks must rest with the county medical society; no publicity is to be released except by mutual consent of the local medical society and of the local Red Cross chapter; differences of opinion should be arbitrated by joint committees from the state medical society and from the American Red Cross; and finally "any provision of free medical service or supply without regard to ability to pay violates the principle that it is each individual's responsibility to assume the obligations of medical expenses just as he does for other living expenses. We deplore the use of the term 'free blood' in Red Cross publicity."

Discussion was had concerning privately operated blood banks notably in hospitals. Some institutions have shifted to the statewide program. It is understood that there is no attempt to interfere with continuing operation of private blood banks.

There is considerable confusion in the mind of the public as the result of recent appeals for blood through the press and radio. Numerous organizations, hospitals, veterans groups and others, in addition to the American Red Cross have made public appeals for donations of blood.

The problem of the use of pooled plasma was discussed. In certain instances the use of surplus wartime-collected plasma continues. Recent studies show that the incidence of virus hepatitis following the use of such plasma is approximately 4 per cent. It is or should be common knowledge among physicians that virus hepatitis is by no means a benign disease and that fatal cases do occur. The American Red Cross has sent out letters advising the return of surplus plasma which has been distributed. The use of such pooled plasma

## APPENDIX NO 8

## REPORT OF THE COMMITTEE ON VETERANS' AFFAIRS

The committee met at 8 Fenway August 4 1948 with Drs. Harvey A Kelly, chairman, Kenneth A Brown, Samuel Bachrach, John M Barry, John F Conlin, Arthur W Allen and H Quimby Gallupe present.

A brief report was rendered by officers of the Society concerning matters affecting veterans returning from military service during the past two years. A report was rendered on services that have been available and have been utilized by returning veterans through the Society headquarters.

The Selective Service Act of 1948 as set forth in Public Law 759 Eightieth Congress was briefly discussed. Current demands of the military services for medical officers were also discussed as informational matters.

Certain matters pertaining to the Veterans Administration and its relations to veterans and to physician veterans were discussed as orientation for the new committee.

The need for certain courses and assistance to physician veterans working for qualification for membership in various specialty boards was discussed. As data on this matter are accumulated they will be referred to the Committee on Medical Education.

The matter of Veterans Administration approval of foreign medical schools for veterans under the G I Bill was discussed. It was unanimously agreed that such a situation should be given the widest possible publicity as leading toward a situation that would jeopardize current standards of medical education.

The following resolution was adopted:

The Committee on Veterans Affairs of the Massachusetts Medical Society meeting at 8 Fenway Boston on August 4, 1948 unanimously presents the following resolution for adoption by the Council of the Society at its meeting on October 6, 1948:

WHEREAS It has been brought to the attention of the committee through an article appearing in the May 1, 1948 issue of the *Journal of the American Medical Association* and again by a letter to the Editor of the *New England Journal of Medicine* in the issue of July 22, 1948 written by Dr A J A Campbell a fellow of the Society, that the Veterans Administration in Washington is advising veterans that they may attend any medical school in Europe at the expense of the Government and

WHEREAS Such European schools are not approved by any accredited approving body in the United States and

WHEREAS Such European schools have not been approved by the approving authority for medical schools in this Commonwealth and

WHEREAS It follows that graduates of such European schools would not be eligible for examination for registration in Massachusetts and

WHEREAS, To permit such graduates to become eligible for examination in Massachusetts would lower the high standards of medical licensure already established in Massachusetts by the present medical practice act, therefore be it

RESOLVEN, That the Council of the Massachusetts Medical Society protest against the present policy of the Veterans Administration in this respect, and be it further

RESOLVEN, That a copy of this resolution be sent to the Veterans Administration and all other interested parties and organizations

HARVEY A KELLY, *Chairman*  
SAMUEL BACHRACH  
JOHN M BARRY  
KENNETH A BROWN  
JOHN F CONLIN  
JAMES M FAULKNER  
GEORGE S REYNOLDS

## APPENDIX NO 9

### REPORT OF THE COMMITTEE ON PUBLIC RELATIONS

The meeting of the Committee on Public Relations was held at the Harvard Club at 6:00 p.m. on August 4, 1948. In addition to the representatives of thirteen district societies there were present President Daniel B. Reardon, chairman, Dr. Arthur W. Allen, president-elect, Dr. H. Quimby Gallupe, secretary of the Society, Dr. John F. Conlin, director of medical information and education, and Mr. Robert St. B. Boyd, executive secretary.

The report of the Secretary as printed in the advance notice of the meeting of the Council on May 24, 1948, was accepted.

President Reardon read a letter from Dr. Howard F. Root, Suffolk District, in which Dr. Root suggested to the Committee on Public Relations that the Massachusetts Medical Society initiate a "Health Week Program" in November of 1949. This "Health Week Program" would consist essentially of a public exhibit of the most recent advances in medicine, emphasizing preventive medicine as well as treatment. Allied organizations such as the Massachusetts Department of Public Health, the State Nurses' Association, the State Hospital Association and particularly the Woman's Auxiliary of the Massachusetts Medical Society would be invited to take an active part in such a program.

Dr. Bernard Appel, Essex South, stated that the City of Lynn has had such a health exhibit annually for the past fifteen to eighteen years. It was his opinion that there was much public interest in this type of medical educational program. Many of the civic organizations such as the service clubs and parent-teachers' associations lent active support in the conduct of the Lynn program.

Because of the amount of preparation that would be necessary in the initiation and creation of such a health exhibit, it was felt that a program of this type would require at least a year of preparation, hence the date, November, 1949.

A motion was made by Dr. Henry A. Robinson, Norfolk South "that the Committee on Public Relations recommend to the Council that it initiate such a public-health exhibit" and "that the president of the Massachusetts Medical Society be empowered to appoint a committee consisting of a representative from each district to initiate such a program immediately."

The motion was unanimously carried.

Dr. Howard F. Root, Suffolk, called the attention of the Committee to the problem of how to meet the needs of medical students in the future when the G. I. Bill of Rights ceases to function. It is evident that within a measurable period many students in medical schools who are at present receiving support from the United States Government will be in need of some financial assistance in order to complete their medical education. The Committee on Public Relations is well aware of the fact that the establishment of a loan fund for medical students by the Massachusetts Medical Society represents a change in fundamental policies but nevertheless considers it to be good public relations. This committee therefore endorsed the following resolution "That the ques-

tion of the establishment of a student loan fund be referred to the Council for its serious consideration."

As a matter of information, President Reardon reported to the Committee that Dr. Howard F. Root has been appointed by the American Diabetes Association as chairman of a committee for the establishment of a national "Diabetes Week," December 6 to 12, 1948. The function of this committee is to consider ways and means of securing the earlier diagnosis and treatment of approximately a million patients in the United States and Canada who at present are unknown and therefore untreated.

Dr. John F. Conlin, director of medical information and education, discussed with the Committee on Public Relations the desirability of a state-wide health meeting to be held early in 1949. It is the intention of this meeting to bring together approximately one thousand delegates from the various consumers and suppliers of medical service to discuss matters pertaining to a future program for health and medical care within this Commonwealth.

Numerous agencies and groups, such as the parent-teachers' associations, the dental profession, service clubs and the Massachusetts Hospital Association, have already been informally approached and have expressed an interest and a willingness to co-operate in such a venture. Dr. Conlin stressed the fact that such a meeting would consist in a panel and section discussion of matters pertaining to medicine and health. It is planned to hold brief meetings in major population centers of the state, following the Boston meeting, in order to disseminate material from this initial Boston meeting in the widest possible manner. It was therefore unanimously approved by the Committee on Public Relations that such a state-wide health meeting be conducted and that the Council be requested to appropriate the sum of \$500 as the Society's contribution toward this important activity.

Dr. Conlin then gave a very informative talk with reference to the work of his office. He stated that much progress had been made in the formation of the Woman's Auxiliary to the Massachusetts Medical Society. Many projects were under consideration for the continuation and extension of the work of this organization, such as legislation leading to the obtaining of animals from public pounds for the purpose of teaching and medical research, informational programs leading to better understanding of matters of medical economics and so-called, "socialized medicine", the gathering of medical journals and certain medical supplies for needy overseas areas, the matter of a long-range plan for a health museum, and the planning of activities leading to better relations with medical students, interns, and residents, and in particular with their wives.

Report was made of the general value of the "fact sheet" published by the Massachusetts State Nurses' Association, for which the Society contributed \$50.

The matter of exclusive rights of the Massachusetts Medical Society to the radio program, "Doctor's Orders," was discussed. Up to the present there has been no charge by the broadcasting stations with reference to this program. From now on, however, there would be an estimated charge of \$140 for an initial twenty-six-week period, with renewal at \$170 for the next thirteen weeks, and \$210 for an additional thirteen weeks. Some dissatisfaction was expressed by the members of the Committee with reference to the recorded dramatizations, and particularly with the musical backgrounds. The particular value of this program was held to be derived from the interviews with local physicians, "preferably on a live basis." No action was taken with reference to the matter of "Doctor's Orders" as a public-relations instrument.

Increased use of the work of various committees of the Society for bringing its activities before the public was also discussed. It was emphasized that certain committees, such as those on cancer, industrial health, school health and mental health, in addition to serving as reference committees, could well report from time to time on matters of general and current interest in their various fields. Such reports to the Council could well furnish the basis of periodic news releases and so keep the Society and its interest in medical progress and public health before the public eye through an interested and co-operative press.

Dr. Conlin pointed out the importance of making every effort to interest medical students, interns and residents in the desirability and importance of membership in the Medical Society. It was felt that the present flat fee for member-

ship in the Massachusetts Medical Society was a barrier to many eligible physicians during their early years of formal postgraduate training. The policy of an ascending scale of membership dues to ease the financial burden of these physicians might be a desirable policy to be initiated by the Society.

The Committee on Public Relations recorded itself as endorsing such an ascending scale of membership dues and urges that this matter be referred to a proper committee for study.

As further evidence of the interest of the Massachusetts Medical Society in this select group of students now in our approved medical schools in the Commonwealth, the matter of granting some sort of annual award to a fourth-year student in each of our three medical schools, presumably in the course of the annual meeting of the Society, was discussed. It was brought out that such an award would not necessarily be based entirely on scholastic attainment or on "likelihood to succeed," but would represent an attempt to single out certain persons as exemplifying intangible qualities that serve to designate him as "the good physician."

It was moved and unanimously approved that the Committee on Public Relations recommend to the Council the appointment of a committee to determine the nature of such an award and the proper means of selection of the recipients of this award after due consultation with the deans and faculties of the medical schools.

Dr Conlin furthermore urged that the members of the Public Relations Committee use the Society headquarters as a clearing house and central source of information. He urged that newsbreaks on matters detrimental to good medicine be reported promptly to Society headquarters. He furthermore suggested that reports of radio programs, forums and other special events within the districts are matters of public relations, and such information should be sent to him as Director of Medical Information and Education.

A major defect that continues is the absence of a qualified and co-ordinated speaker's bureau. Fellows of the Society, capable and willing to address various groups are requested to communicate with their district public-relations councilors. Demand for such speakers is increasing, and at times it is impossible to comply with all requests. Future months will see a marked increase in the demands for qualified speakers. Recently, there were received requests from the Massachusetts Department of Public Health and from a considerable number of organizations to furnish speakers for various programs. Such activities are nearly always without monetary compensation and represent a major contribution to public service and to better mutual understanding within the community.

DANIEL B REARDON, *Chairman*  
HAROLD R KURTH, *Secretary*

## APPENDIX NO 10

### REPORT OF THE COMMITTEE ON PUBLIC HEALTH

At the first meeting of the Committee on Public Health held June 5, 1948, the following members were present: Drs Roy Ward (chairman), Conrad Wesselhoeft, Warren R Sisson and John J Poutas. Dr L Jackson Smith of Springfield was unable to be present. Also present were Dr Arthur W Allen, president-elect, and Dr H Quimby Gallupe, secretary of the Massachusetts Medical Society.

The first item of business was the election of a secretary. Dr John J Poutas was elected secretary for the third consecutive year.

At the request of Dr Ward, the secretary then read to the Committee a letter from Dr Walter E Barton, dated October 29, 1947. Dr Barton submitted this letter as chairman of the subcommittee on mental health, pointing out that in August, 1948, a congress will be held in England dealing with mental-health problems. This International Medical Congress has asked that medical societies sponsor regional meetings in the interest of the prevention of sexual psychopathy. It was pointed out that on July 16, 1947, the Massachusetts Medical Society offered to co-operate in any way possible with the Massachusetts Recess Commission, which studied this problem. It was Dr Barton's request that the regional meetings desired be sponsored by the Society rather than through the specialists' channels of the Massachusetts Psychiatric Association. It is the opinion of the subcom-

mittee on mental health that this project is too cumbersome to be included in the annual meeting of the Society. A discussion of Dr Barton's letter elicited the approval of the Committee, and Dr Wesselhoeft made a motion that the chairman of the subcommittee, Dr Walter E Barton, communicate with Dr W Richard Ohler, chairman of the Committee on Postgraduate Medical Education, and develop with him the inclusion of this subject in the postgraduate program, being mindful of the fact that this was in effect a pediatric problem more effectively covered by a panel of speakers covering all age groups rather than by one single speaker.

The next item on the agenda was a report by Dr Sisson of his analysis of the data submitted by the various medical schools in New England, outlining the educational program with respect to preventive medicine, including accident prevention. Dr Sisson reported that in his opinion this problem is being very effectively attacked by the various life-insurance companies. He was of the opinion that medical schools should enlarge the scope of their program to include more adult lay education. He recommended to the committee that no particular action be taken at this time other than to communicate our interest in this matter to the Director of Medical Information and Education. His recommendation was approved by the Committee.

The secretary then read to the Committee two communications from Dr Lewis C Robbins of the Heart Demonstration Program being conducted in the City of Newton by the United States Public Health Service. This program, together with an epidemiologic study of heart disease being conducted by the Public Health Service in the Town of Framingham, was endorsed in principle by this committee in March, 1948. As a result of this endorsement, the Council approved these studies. Monthly reports of April and May, 1948, of the program as conducted in Newton were read. It was agreed by the Committee that the Public Health Service physicians conducting the program in the City of Newton and in the Town of Framingham should be invited before the next meeting of the Committee on Public Health to give a report of progress. It was also recommended by the Committee that Dr Howard B Sprague be invited to the meeting of the Council to answer any questions about these programs.

The next matter on the agenda was a reading of a letter from Mr Parker Wheatley, of the Lowell Institute Co-operative Broadcast Council. In this letter Mr Wheatley outlined a radio program with health topics, particularly infant care. This program is endorsed by all of the Boston universities and colleges and is indirectly supervised by the deans of the three Boston medical schools. In his letter, Mr Wheatley asked for the committee's consideration of his educational program and, if possible, its endorsement.

It was decided by the Committee that we communicate our interest and endorsement to the Director of Medical Information and Education with the recommendation that he further study the matter of Society co-operation in this regard. It was recommended that Dr Conlin get in touch with Mr John E Farrell, executive secretary of the Rhode Island State Medical Society, relative to this program in the interest of avoiding conflict with a similar program sponsored by the Council of New England Medical Societies.

The next matter for discussion was a recent editorial in the *New England Journal of Medicine* relative to the advisability of active immunization against tetanus. After considerable discussion as to the advisability of general community active immunization against tetanus the following resolution was adopted: that the Committee is interested in the proper and judicious use of tetanus toxoid in active immunization and was pleased to note that it was the subject of editorial comment in the *New England Journal of Medicine*.

Next on the agenda was a reading of a letter from Mr Gates, of the New England Heart Association. This letter outlined the proposed program of that association whereby a certain amount of money would be available for the provision of penicillin in cases of subacute bacterial endocarditis. This program has the approval of Drs Edward F Bland, Samuel A Levine and Maxwell Finland.

No test for indigency will be carried out. A statement from the patient's physician to the effect that treatment would be a financial hardship and that funds for penicillin are not available from other sources is expected to suffice.

WHEREAS, To permit such graduates to become eligible for examination in Massachusetts would lower the high standards of medical licensure already established in Massachusetts by the present medical practice act, therefore be it

RESOLVED, That the Council of the Massachusetts Medical Society protest against the present policy of the Veterans Administration in this respect, and be it further

RESOLVED, That a copy of this resolution be sent to the Veterans Administration and all other interested parties and organizations

HARVEY A. KELLY, *Chairman*  
SAMUEL BACHRACH  
JOHN M. BARRY  
KENNETH A. BROWN  
JOHN F. CONLIN  
JAMES M. FAULKNER  
GEORGE S. REYNOLDS

## APPENDIX NO 9

### REPORT OF THE COMMITTEE ON PUBLIC RELATIONS

The meeting of the Committee on Public Relations was held at the Harvard Club at 6:00 p.m. on August 4, 1948. In addition to the representatives of thirteen district societies there were present President Daniel B. Reardon, chairman, Dr. Arthur W. Allen, president-elect, Dr. H. Quimby Gallupe, secretary of the Society, Dr. John F. Conlin, director of medical information and education, and Mr. Robert St. B. Boyd, executive secretary.

The report of the Secretary as printed in the advance notice of the meeting of the Council on May 24, 1948, was accepted.

President Reardon read a letter from Dr. Howard F. Root, Suffolk District, in which Dr. Root suggested to the Committee on Public Relations that the Massachusetts Medical Society initiate a "Health Week Program" in November of 1949. This "Health Week Program" would consist essentially of a public exhibit of the most recent advances in medicine, emphasizing preventive medicine as well as treatment. Allied organizations such as the Massachusetts Department of Public Health, the State Nurses' Association, the State Hospital Association and particularly the Woman's Auxiliary of the Massachusetts Medical Society would be invited to take an active part in such a program.

Dr. Bernard Appel, Essex South, stated that the City of Lynn has had such a health exhibit annually for the past fifteen to eighteen years. It was his opinion that there was much public interest in this type of medical educational program. Many of the civic organizations such as the service clubs and parent-teachers' associations lent active support in the conduct of the Lynn program.

Because of the amount of preparation that would be necessary in the initiation and creation of such a health exhibit, it was felt that a program of this type would require at least a year of preparation, hence the date, November, 1949.

A motion was made by Dr. Henry A. Robinson, Norfolk South, "that the Committee on Public Relations recommend to the Council that it initiate such a public-health exhibit" and "that the president of the Massachusetts Medical Society be empowered to appoint a committee consisting of a representative from each district to initiate such a program immediately."

The motion was unanimously carried.

Dr. Howard F. Root, Suffolk, called the attention of the Committee to the problem of how to meet the needs of medical students in the future when the G. I. Bill of Rights ceases to function. It is evident that within a measurable period many students in medical schools who are at present receiving support from the United States Government will be in need of some financial assistance in order to complete their medical education. The Committee on Public Relations is well aware of the fact that the establishment of a loan fund for medical students by the Massachusetts Medical Society represents a change in fundamental policies, but nevertheless considers it to be good public relations. This committee therefore endorsed the following resolution: "That the ques-

tion of the establishment of a student loan fund be referred to the Council for its serious consideration."

As a matter of information, President Reardon reported to the Committee that Dr. Howard F. Root has been appointed by the American Diabetes Association as chairman of a committee for the establishment of a national "Diabetes Week," December 6 to 12, 1948. The function of this committee is to consider ways and means of securing the earlier diagnosis and treatment of approximately a million patients in the United States and Canada who at present are unknown and therefore untreated.

Dr. John F. Conlin, director of medical information and education, discussed with the Committee on Public Relations the desirability of a state-wide health meeting to be held early in 1949. It is the intention of this meeting to bring together approximately one thousand delegates from the various consumers and suppliers of medical service to discuss matters pertaining to a future program for health and medical care within this Commonwealth.

Numerous agencies and groups, such as the parent-teachers' associations, the dental profession, service clubs and the Massachusetts Hospital Association, have already been in formally approached and have expressed an interest and a willingness to co-operate in such a venture. Dr. Conlin stressed the fact that such a meeting would consist in a panel and section discussion of matters pertaining to medicine and health. It is planned to hold brief meetings in major population centers of the state, following the Boston meeting, in order to disseminate material from this initial Boston meeting in the widest possible manner. It was therefore unanimously approved by the Committee on Public Relations that such a state-wide health meeting be conducted and that the Council be requested to appropriate the sum of \$500 as the Society's contribution toward this important activity.

Dr. Conlin then gave a very informative talk with reference to the work of his office. He stated that much progress had been made in the formation of the Woman's Auxiliary to the Massachusetts Medical Society. Many projects were under consideration for the continuation and extension of the work of this organization, such as legislation leading to the obtaining of animals from public pounds for the purpose of teaching and medical research, informational programs leading to better understanding of matters of medical economics and so-called, "socialized medicine", the gathering of medical journals and certain medical supplies for needy overseas areas, the matter of a long-range plan for a health museum, and the planning of activities leading to better relations with medical students, interns, and residents, and in particular with their wives.

Report was made of the general value of the "fact sheet" published by the Massachusetts State Nurses' Association, for which the Society contributed \$50.

The matter of exclusive rights of the Massachusetts Medical Society to the radio program, "Doctor's Orders," was discussed. Up to the present there has been no charge by the broadcasting stations with reference to this program. From now on, however, there would be an estimated charge of \$140 for an initial twenty-six-week period, with renewal at \$170 for the next thirteen weeks, and \$210 for an additional thirteen weeks. Some dissatisfaction was expressed by the members of the Committee with reference to the recorded dramatizations, and particularly with the musical backgrounds. The particular value of this program was held to be derived from the interviews with local physicians, "preferably on a live basis." No action was taken with reference to the matter of "Doctor's Orders" as a public-relations instrument.

Increased use of the work of various committees of the Society for bringing its activities before the public was also discussed. It was emphasized that certain committees, such as those on cancer, industrial health, school health and mental health, in addition to serving as reference committees, could well report from time to time on matters of general and current interest in their various fields. Such reports to the Council could well furnish the basis of periodic news releases and so keep the Society and its interest in medical progress and public health before the public eye through an interested and co-operative press.

Dr. Conlin pointed out the importance of making every effort to interest medical students, interns and residents in the desirability and importance of membership in the Medical Society. It was felt that the present flat fee for member-

not been able to adhere completely to the suggestions of the American Heart Association, owing to lack of funds. These clinics can be helped either by the purchase of equipment, by furnishing of service for indigent patients or by assistance in providing personnel. Approval by the American Heart Association shall be the goal of the cardiac-clinic subsidization. Funds will not be available to clinics unless such funds will permit the clinic to meet the standards of the Association. Available funds will be furnished cardiac clinics approved by the technical committee.

**Selection of a demonstration area.** The northeastern district, consisting of 10 cities and 35 towns will be chosen for a demonstration area. There are 18 hospitals in the 10 cities and 1 in each of 7 towns. The total bed capacity is 2008. This area had a total population of about 600,000 in 1940 with 240,000 persons over the age of forty. The distribution of the population in this district ranges from a town of about 800 to a city of approximately 100,000. The establishment of relations with the local and state heart-association officials will be made at the earliest opportunity. The Massachusetts Department of Public Health will approve the association of program plans and discuss the most effective methods of co-operation. Goals will be established as a part of the program for co-operative projects.

**Survey of the facilities in the demonstration area.** The facilities for diagnosis, treatment and care of cardiac disease should be ascertained and made use of. Information regarding the presence of heart disease and various environmental factors regarding living conditions that may be detrimental to the well-being of the patient will be ascertained by spot surveys similar to those conducted in cancer.

**Establishment of a demonstration heart registry.** In the demonstration area a heart registry will be started. This registry will be of great assistance to the profession. It will elicit facts on incidence and permit evaluation studies of the most worthwhile parts of the program, the degree to which patients follow the recommendations of the professions and many epidemiologic facts. It will enable physicians, who so desire, to make use of the part of the program discussed below under public health services for cardiac patients.

**Inauguration of a state-wide educational program in heart diseases for the laity.** After the indoctrination of the medical profession in the basic principles of control is well underway a state-wide educational program for the laity should be inaugurated. Preparation for this activity could begin at an earlier date. The scope of education in heart diseases shall be determined by the Advisory Committee and then put into concrete form by the Department. Use will be made of all the educational mediums, such as lectures, radio pamphlets, charts, exhibits, newspaper articles and movies.

**Development and extension of public-health services for cardiac patients in local health departments.** The local health organization in the demonstration area should furnish such follow-up and other services for cardiac patients as are consistent with the disease and requested by the attending physician. Such a program will be designed to increase the effectiveness of the practicing physician through health education and making available such services as rehabilitation, nutrition, nursing and epidemiology. Co-operation with the local heart association will increase the effectiveness of the program.

**Personnel training.** The contemplated expansion of the heart program will necessitate more personnel trained in public health and heart disease. A personnel-training program will be started on a small scale. This program will be designed to give public-health training to physicians, health educators, nurses and other public-health workers commensurate with the needs of the program.

**Statistical studies.** Statistical studies to measure the effectiveness of the program will be frequently done as well as other statistical studies on heart diseases similar to those found useful in cancer and diabetes control.

Throughout the program every effort will be made to avoid duplication of effort and to furnish the utmost co-operation among the various groups involved. The Heart Disease Epidemiology Study, the Heart Demonstration Program, Rheumatic Disease Program and Division of Hospitals will co-ordinate their efforts to accomplish the greatest results. Early liaison will be established with the New England Heart Association and local affiliates.

## FEDERAL BUDGET FOR HEART PROGRAM

*Breakdown of Costs*

01	Assistant director	\$5,400 00	
	Public-health social work supervisor	2,880 00	
	Public-health nursing (2) supervisors	5,760 00	
	Assistant biometrician	2,460 00	
	Supervisor of public-health education	2,800 00	
	Senior statistical clerks (2)	4 520 00	
	Senior clerk and stenographer	1 980 00	\$25,600 00
02			
03	Consultant	\$1,500 00	1 500 00
07	Aid to existing heart clinics	15 000 00	15 000 00
10	Travel and automobile expense	1,500 00	1,500 00
11	Advertising and printing	1 000 00	1 000 00
13	Personnel training	6,000 00	
	Medical education	10,000 00	
	Nonprofessional education	1,000 00	17 000 00
14	Office expenses	1,000 00	1 000 00
15	Automobiles (2)	3,300 00	
	Office equipment	1 200 00	4,500 00
16	Garage rental	360 00	
	Other rent	3,000 00	3,360 00
	Total budgeted		\$70 460 00

## HEART CLINICS IN MASSACHUSETTS

Name of Hospital	Cardiac Clinic
Springfield Hospital	Every Saturday by appointment
Lawrence General Hospital	Once a week
Bessie M. Burke Hospital, Lawrence	Once a week
Worcester City Hospital	Fridays 8 30 to 10 00 a.m.
Memorial Hospital, Worcester	Wednesdays 9 a.m.
St. Luke's Hospital, New Bedford	Tuesdays 9 a.m.
Union Hospital, Fall River	Dr. Leach by appointment
Boston	
Massachusetts General	Cardiac Clinic
Massachusetts Memorial	Cardiac Clinic
Massachusetts Osteopathic	Cardiac Clinic
Peter Bent Brigham	Cardiac Clinic
Carver	Weekly by appointments
Beth Israel	Cardiac Clinic
Boston City	Cardiac Clinic
Boston Living-In	Cardiac Clinic
St. Elizabeth's	Cardiac Clinic
Cambridge	
Mt. Auburn	Weekly by appointments
Cambridge City	Weekly by appointments
Chelsea	
Soldier's Home	Cardiac Clinic
Newton-Wellesley Hospital	Cardiac Clinic
Waltham Hospital	Weekly by appointments
The best available information on private clinics are	
Baker Clinic	Cardiac Clinic
Labet Clinic	Cardiac Clinic
Pratt Diagnostic Clinic	Cardiac Clinic
Boston Dispensary, Bennet Street	Cardiac Clinic

## GENERAL AND ALLIED SPECIAL HOSPITALS IN NORTHEASTERN HEALTH DISTRICT

City or Town	Name of Hospital	No. of Beds
Amesbury	Amesbury	35
Beverly	Beverly	166
Danvers	Hunt Memorial	20
Gloucester	Addison Gilbert	71
Haverhill	Benson	34
	Hale Municipal	161
Ipswich	Benjamin Cable	19
Lawrence	Bessie Burke	125
	Clover Hill	55
	Lawrence General	183

The Committee approved of this program of the New England Heart Association and recommended that when agreeable to the New England Heart Association it might be the subject of editorial comment in the *New England Journal of Medicine*.

Dr Howard F Root appeared before the Committee and outlined the responsibility of the medical profession in the earlier discovery and treatment of diabetes mellitus. He read to the Committee a proposed resolution of Dr Phippen, as follows:

WHEREAS, The medical profession has always recognized its obligation for the discovery, treatment, and prevention of diabetes mellitus, and

WHEREAS, The number of latent and undiscovered diabetic patients in the United States, according to surveys, is much larger than had been supposed, and is estimated to be about one million persons, and

WHEREAS, There exists also a large number of patients whose diabetes is neglected and who are therefore under ineffective or no treatment, and

WHEREAS, The American Diabetes Association, Incorporated, whose membership consists of more than a thousand doctors interested in diabetes, has appointed a committee to formulate plans for a national "Diabetes Week," December 6 to 12, 1948, and

WHEREAS, The purpose of this effort is to assist doctors and local committees in effectively carrying out continuing plans for discovering the unknown diabetics and guiding them to their physicians, and for spreading widely to the public, information about diabetes, and

WHEREAS, This is to be a doctors' project, of the profession, by the profession, and for the public, and

WHEREAS, To achieve the aims of "Diabetes Week," the American Diabetes Association seeks to enlist the formal support and active co-operation of the medical profession through the American Medical Association and its constituent and component societies, therefore be it

RESOLVED, That the Council of the Massachusetts Medical Society heartily endorse the efforts of the American Diabetes Association in behalf of the undiscovered and untreated diabetic and approve of the plans for a "Diabetes Week" from December 6 to 12, 1948.

Furthermore, be it resolved that the delegates from the Massachusetts Medical Society to the House of Delegates of the American Medical Association be instructed to present this resolution to the House and recommend that the trustees of the American Medical Association and all state, county and other medical societies co-operate and participate in the effort to find as many as possible of the unknown diabetics in order to bring them under medical treatment.

The Committee approved Dr Phippen's resolution and a motion was made and adopted that we recommend to the president of the Massachusetts Medical Society that a committee be appointed to expedite the Massachusetts "Diabetes Week" program from December 6 to 12, 1948, that this committee be empowered to act, and that its efforts be co-ordinated with those of Dr Ohler's Committee on Post-graduate Education. It was also moved and adopted that the Council take necessary action relative to the final paragraph of Dr Phippen's resolution.

The final item of business was a discussion of the need for active interest of the medical profession in the problem of geriatrics. It was recommended that Dr Ward inform Dr Robert Monroe of the Committee's interest and desire to be of assistance.

ROY J. WARD, *Chairman*  
JOHN J. POUTAS, *Secretary*  
WARREN R. SISSON  
L. JACKSON SMITH  
CONRAD WESSELHOEFT

#### SUPPLEMENTARY REPORT OF COMMITTEE ON PUBLIC HEALTH

During the last session of Congress the sum of \$500,000 was appropriated to make effective the National Heart Act. This sum is to be distributed to a group of states yet to be selected. It is the desire of the Department of Public Health that Massachusetts be included in this group of states, and that a portion of this fund be allotted to them to further

their study of heart disease already initiated here. The Department has drawn up the following program for the development of this study. This program has the approval of the Committee on Public Health.

A National Heart Institute has been established by Congress this year. As a part of this over-all heart program, the Massachusetts Department of Public Health is hoping to inaugurate a heart demonstration program in this state. It is concerned with attempting to meet the growing problem of heart disease, which, according to Dr Paul D White, is the greatest public-health problem of the day. The proposed program recognizes that the physician in private practice is the key man in the control of heart disease. This program is an attempt to assist the physician, aid him where possible and increase his effectiveness in the community without establishing new services.

*Appointment of advisory committees.* Two committees shall be appointed: one shall be a technical advisory committee composed of specialists in heart disease. This committee shall discuss matters of policy and, by a fine screening, review the important policy matters. The second committee shall be called the operating committee. This committee shall be composed of representatives of the several agencies and interests in heart disease in the local area. It shall be concerned with making a continuous study of the operations of the demonstration program, as well as other heart activities of the area. It shall make recommendations to official and other agencies concerning the better operation of the program.

*Inauguration of an educational program for physicians.* Success in this program depends on participation by physicians. Pessimism on the part of many general practitioners, together with lack of knowledge on the part of some, is an obstacle to heart-disease control. The Department of Public Health will inaugurate, in co-operation with the professional medical groups, a state-wide program of physician education. As part of the Massachusetts Medical Society's graduate courses, sessions on heart diseases, better to train physicians for general practice, will be arranged by the Department with the assistance of the New England Heart Association. No attempt will be made to develop cardiologists. The purpose will be to develop an awareness on the part of physicians concerning the cardiac problem, the difficulties of diagnosis of certain types and the limitations within which the general practitioner can safely operate without harming the patient. No certificate will be given by the Department for completion of the course. The demonstration of heart sounds by the use of a multiple stethoscope amplifier will be provided physicians. Preliminary discussions have been held with Society officials, and tentative plans made. Physicians not only will receive information concerning the clinical aspects of heart disease and the sociologic and psychologic aspects, but also will be constantly informed of the progress of the heart program. Methods of providing the physicians with important recent literature on heart disease will be one of the prime functions of the technical advisory committee. Whether this be in the form of a lending library in co-operation with the Boston Medical Library, the preparation and distribution to all physicians of a heart manual similar in style to the cancer manual or some other medium will be decided by the Committee. Approximately a quarter of the physicians in Massachusetts are not members of the Society. They are graduates of substandard schools. This group constitutes the greatest need in physician education.

*Inauguration of an educational program for nonmedical health personnel.* The nurses, social workers, biometricians, educators and other health-department personnel, together with lay members and employees of local boards of health who may be assigned to a heart program, should have an adequate knowledge of the public-health aspects of heart disease. Courses should be planned to meet this need, and furnished to key members of the various public-health professions. The instruction should begin with the health workers in the demonstration area and expand as rapidly as possible. Eventually, all members of these professions who will engage in heart-control projects must be oriented.

*Development of facilities of existing clinics.* In Massachusetts there are 19 hospitals with heart clinics meeting regularly, and 6 additional ones by appointment, which follow to a greater or lesser extent the procedures outlined by the American Heart Association. Some of these clinics have

not been able to adhere completely to the suggestions of the American Heart Association, owing to lack of funds. These clinics can be helped either by the purchase of equipment, by furnishing of service for indigent patients, or by assistance in providing personnel. Approval by the American Heart Association shall be the goal of the cardiac-clinic subsidization. Funds will not be available to clinics unless such funds will permit the clinic to meet the standards of the Association. Available funds will be furnished cardiac clinics approved by the technical committee.

**Selection of a demonstration area.** The northeastern district, consisting of 10 cities and 55 towns, will be chosen for a demonstration area. There are 18 hospitals in the 10 cities, and 1 in each of 7 towns. The total bed capacity is 2008. This area had a total population of about 600,000 in 1940, with 240,000 persons over the age of forty. The distribution of the population in this district ranges from a town of about 800 to a city of approximately 100,000. The establishment of relations with the local and state heart-association officials will be made at the earliest opportunity. The Massachusetts Department of Public Health will appraise the association of program plans and discuss the most effective methods of co-operation. Goals will be established as a part of the program for co-operative projects.

**Survey of the facilities in the demonstration area.** The facilities for diagnosis, treatment and care of cardiac disease should be ascertained and made use of. Information regarding the presence of heart disease and various environmental factors regarding living conditions that may be detrimental to the well-being of the patient will be ascertained by spot surveys similar to those conducted in cancer.

**Establishment of a demonstration heart registry.** In the demonstration area a heart registry will be started. This registry will be of great assistance to the profession. It will elicit facts on incidence and permit evaluation studies of the most worthwhile parts of the program, the degree to which patients follow the recommendations of the professions and many epidemiologic facts. It will enable physicians, who so desire, to make use of the part of the program discussed below under public health services for cardiac patients.

**Inauguration of a state-wide educational program in heart diseases for the laity.** After the indoctrination of the medical profession in the basic principles of control is well underway, a state-wide educational program for the laity should be inaugurated. Preparation for this activity could begin at an earlier date. The scope of education in heart diseases shall be determined by the Advisory Committee and then put into concrete form by the Department. Use will be made of all the educational mediums, such as lectures, radio, pamphlets, charts, exhibits, newspaper articles and movies.

**Development and extension of public-health services for cardiac patients in local health departments.** The local health organization in the demonstration area should furnish such follow-up and other services for cardiac patients as are consistent with the disease and requested by the attending physician. Such a program will be designed to increase the effectiveness of the practicing physician, through health education, and making available such services as rehabilitation, nutrition, nursing and epidemiology. Co-operation with the local heart association will increase the effectiveness of the program.

**Personnel training.** The contemplated expansion of the heart program will necessitate more personnel trained in public health and heart disease. A personnel-training program will be started on a small scale. This program will be designed to give public-health training to physicians, health educators, nurses and other public-health workers commensurate with the needs of the program.

**Statistical studies.** Statistical studies to measure the effectiveness of the program will be frequently done, as well as other statistical studies on heart diseases similar to those found useful in cancer and diabetes control.

Throughout the program every effort will be made to avoid duplication of effort and to furnish the utmost co-operation among the various groups involved. The Heart Disease Epidemiology Study, the Heart Demonstration Program, Rheumatic Disease Program and Division of Hospitals will co-ordinate their efforts to accomplish the greatest results. Early liaison will be established with the New England Heart Association and local affiliates.

## FEDERAL BUDGET FOR HEART PROGRAM

## Breakdown of Codes

01	Assistant director	\$5,400 00	
	Public-health social work supervisor	2,880 00	
	Public-health nursing (2) supervisors	5,760 00	
	Assistant biometrician	2,460 00	
	Supervisor of public-health education	2,800 00	
	Senior statistical clerks (2)	4,520 00	
	Senior clerk and stenographer	1,980 00	\$25,600 00
02			
03	Consultant	\$1,500 00	1,500 00
07	Aid to existing heart clinics	15,000 00	15,000 00
10	Travel and automotive expense	1,500 00	1,500 00
11	Advertising and printing	1,000 00	1,000 00
13	Personnel training	6,000 00	
	Medical education	10,000 00	
	Nonprofessional education	1,000 00	17,000 00
14	Office expenses	1,000 00	1,000 00
15	Automobiles (2)	3,500 00	
	Office equipment	1,200 00	4,500 00
16	Garage rental	360 00	
	Other rent	3,000 00	3,360 00
	Total budgeted		\$70,460 00

## HEART CLINICS IN MASSACHUSETTS

Name of Hospital	Cardiac Clinic
Springfield Hospital	Every Saturday by appointment
Lawrence General Hospital	Once a week
Bessie M. Burke Hospital, Lawrence	Once a week
Worcester City Hospital	Fridays 8:30 to 10:00 a.m.
Memorial Hospital Worcester	Wednesdays 9 a.m.
St. Luke's Hospital New Bedford	Tuesdays 9 a.m.
Union Hospital, Fall River	Dr. Leach by appointment
Boston	
Massachusetts General	Cardiac Clinic
Massachusetts Memorial	Cardiac Clinic
Massachusetts Osteopathic	Cardiac Clinic
Peter Bent Brigham	Cardiac Clinic
Carney	Weekly by appointments
Beth Israel	Cardiac Clinic
Boston City	Cardiac Clinic
Boston Living-In	Cardiac Clinic
St. Elizabeth's	Cardiac Clinic
Cambridge	
Mt. Auburn	Weekly by appointments
Cambridge City	Weekly by appointments
Chelsea	
Soldier's Home	Cardiac Clinic
Newton-Wellesley Hospital	Cardiac Clinic
Waltham Hospital	Weekly by appointments

The best available information on private clinics are

Baker Clinic	Cardiac Clinic
Labey Clinic	Cardiac Clinic
Pratt Diagnostic Clinic	Cardiac Clinic
Boston Dispensary, Bennet Street	Cardiac Clinic

## GENERAL AND ALLIED SPECIAL HOSPITALS IN NORTHEASTERN HEALTH DISTRICT

City or Town	Name of Hospital	No of Beds
Amesbury	Amesbury	35
Beverly	Beverly	166
Danvers	Hunt Memorial	20
Gloucester	Addison Gilbert	71
Haverhill	Benson	34
	Hale Municipal	161
Ipswich	Benjamin Cable	19
Lawrence	Bessie Burke	125
	Clover Hill	55
	Lawrence General	183

Lynn	Lynn Health Department	50
	Lynn	202
	Union	52
Marblehead	Mary A Alley	18
Melrose	Melrose	101
Methuen	Mary E McGowan	26
Newburyport	Anna Jacques	53
	Worcester Memorial	24
Peabody	Josiah B Thomas	65
Salem	North Shore Babies	50
	Salem Health Department	52
	Salem	224
Saugus	Saugus General	20
Stoneham	N E Sanitarium & Benevolent Association	150
Woburn	Charles Choate Memorial	52
Total number of hospitals, 25, total number of beds, 2008		

## APPENDIX NO 11

## REPORT OF THE COMMITTEE ON BENEVOLENCE

This committee was appointed to implement the suggestion that the Society give thought and take action in regard to aid for physicians who are incapacitated through no fault of their own. It has also been suggested that in certain cases we might assist widows and orphans of physicians.

These functions are not new among doctors in Massachusetts. They have been performed for nearly a hundred years by the Massachusetts Medical Benevolent Society. Because this organization was especially designed for these purposes your committee decided at its first meeting that it would be undesirable to duplicate such activities. Instead, it is hoped that we may actively co-operate with the Massachusetts Medical Benevolent Society and together with it render a single amplified service.

Your committee believes that this could be accomplished if a new standing committee to be known as the Committee on Benevolence were first established. This committee would then represent the Council and could deal with the Benevolent Society in the following manner:

The Committee on Benevolence would ask the Committee on Finance and the Council for an annual budget of not more than \$10,000. The Benevolent Society would make an annual estimate of its needs as applied to Massachusetts Medical Society members. The Committee on Benevolence would then pay the Benevolent Society the amount estimated, within the annual budgetary limit of \$10,000. All applicants would apply to the Benevolent Society, and the dispensing of benevolence would be entirely in the hands of this group.

At the end of each year, any money paid to the Benevolent Society by the Benevolent Committee, but not used, would stand at the credit of the Committee on the Benevolent Society's books and would be applied to the following year. The amount of such credit would be shown in a statement made to the Committee by the Benevolent Society on or before December 31 of each year. If, on the other hand, the needs were to rise above the Benevolent Society's estimate during the year, the Committee on Benevolence might authorize further payments to the Benevolent Society up to the amount of the annual budget.

If the actual needs did not absorb the annual budget—that is, if they were less than \$10,000—the balance would be earmarked in a Committee on Benevolence account, to be invested by the Treasurer in liquid securities, which, with their interest, would provide a Benevolent Fund. This Benevolent Fund could be drawn upon at the discretion of the Committee on Benevolence if in any given year extraordinary demands for relief created a need above and beyond the budget allotment for that particular year.

For example, the Benevolent Society estimated a need of \$8000, this amount would be given to them. If they used but \$7000, a balance of \$1000 would remain on their books to the credit of the Benevolent Committee, and the next year's estimate would be correspondingly reduced. If the Benevolent Society found that it was going to need more than the \$8000 estimated, the needed amount could be advanced by the Benevolent Committee up to, but not

beyond, the \$10,000 originally budgeted. If the Benevolent Society used just the \$8000 estimated, the remaining \$2000 or whatever was left unpaid from the annual budget for any given year would be invested in the Benevolent Fund and thus held in reserve for future emergency.

Your committee feels that this proposal will provide a flexible working arrangement and will at the same time permit the development of a permanent fund for the future. For these reasons, it recommends that this proposal be adopted.

If this proposal is adopted your committee further recommends that a temporary committee on benevolence be appointed to operate until such time as the by-laws may be amended to authorize a permanent arrangement.

DWIGHT O'HARA, Chairman

THEODORE L BADGER

ROBERT W BUCK

CHARLES C LUND

ELIOT HUBBARD, JR.

## APPENDIX NO 12

## REPORT OF DELEGATES TO HOUSE OF DELEGATES OF AMERICAN MEDICAL ASSOCIATION

The House of Delegates met in Chicago June 21 to 24, inclusive. All members of the Massachusetts delegation or their alternates attended. The distinguished service award was given to Dr. Isaac A. Abt, of Chicago, at the first session. The Judicial Council presented a very careful revision of the Code of Ethics that was adopted unanimously. A special committee on the constitution and by-laws, which has been working for two years, presented a revision, which was also adopted after considerable discussion. These actions were time consuming but necessary. Several distinguished guests addressed the House—Admiral Swanson, surgeon general of the Navy, the president of the British Medical Association and General Hawley, co-ordinator of the Blue Cross and Blue Shield plans.

Component societies were urged to appoint their delegates to the House before January 1 so that the Speaker can appoint reference committees at least a month before the meeting of the House. Our society should take cognizance of this rule, since otherwise delegates will not be given reference-committee appointments.

The House voted to change the method of selecting candidates for the distinguished service award for general practitioners. Hereafter each county or district society will be asked to nominate one of its members, if it sees fit, to the state society. The state society will then select one of these nominations to be sent to the American Medical Association headquarters. Three of these will be selected by the Trustees to be voted upon by the House at its interim session.

The House went on record in favor of one year's rotating internship for every graduate of medicine and requested the Council on Medical Education and Hospitals to activate this procedure.

It was also announced that the Council on Medical Education and Hospitals was undertaking a survey and revision of medical education with special reference to the curriculum of medical schools.

Also contemplated is a foundation for the solicitation and distribution of funds to help finance medical schools and medical education.

The Council on National Emergency Medical Services suggested certain basic principles to guide the American Medical Association under the threat of national emergency, which were unanimously adopted. It affirmed that the services of physicians must be carefully conserved and judiciously allocated in time of war to ensure adequate medical, health and sanitary care for all Americans, whether in or out of uniform. It recommended, among other things, a single physical examination of recruits and inductees and deferment of properly selected and duly registered premedical and medical students and essential teachers. The call of medical officers to military duty should be in the following order: those educated at Government expense, those who did not serve in World War II, and those who served least in World War II. State and county societies should use every effort to induce such men to volunteer.

MASSACHUSETTS MEDICAL SOCIETY

Vol. 2:9 No 23

A resolution that received considerable publicity sought to amend the constitution of the American Medical Association so as to prohibit the exclusion of certain classes of physicians from membership in component county societies. It was pointed out that the American Medical Association has never excluded physicians on the basis of race but that the component medical society is the sole judge of whom it elects to membership provided the applicant shall meet the medical requirements for membership.

From testimony presented at several hearings concerning the American Red Cross blood bank it was evident that there has been some confusion and misunderstanding between local chapters of the Red Cross and the medical profession at local levels. The House of Delegates, recognizing the professional ability of the physicians constituting the Advisory Committee of the American Red Cross and the efforts they have made in behalf of this program, as well as the efforts of a similar committee, approved by the House of Delegates of the American Medical Association in January, 1948, felt that this intimate co-operation would be continued but that even greater effort and co-operation would be necessary in the future. It therefore recommended that the Advisory Committee be increased to nine members with definite instructions to meet at stated intervals, and to report from time to time to the House.

Resolutions pertaining to what is somewhat loosely known as the "practice of medicine by hospitals" have been introduced annually to the House of Delegates for several years. They have dealt largely with the specialties of anesthesiology, radiology and pathology. The House has repeatedly taken the position that these specialties are the practice of medicine and not hospital practice and that these departments should not be used to finance other departments of the hospital. The sore still festers. The House of Delegates has no police power to implement its decisions.

To clarify this troublesome problem the trustees of the American Medical Association appointed a committee of five under the chairmanship of Elmer Hess, of Erie, Pennsylvania. I was asked to serve on this committee. The full committee held many meetings at Chicago and heard representatives of the various specialties. The subject is so broad and has so many ramifications, and practice differs so much in different parts of the country that the committee could not reach any definite opinion to the time at its disposal. It was asked to be continued and that the Bureau of Legal Medicine and Legislation of the American Medical Association be instructed immediately to make a study of the various state laws defining the legal status of corporations attempting to practice medicine in the various states, defining in each instance the difference in the various state laws concerned with the problem. The committee will continue at work and will be glad of any suggestions or comments sent to Dr. Elmer Hess, Erie, Pennsylvania, or to me at 51 Chestnut Street, Salem, Massachusetts.

More resolutions than usual were presented, but all received meticulous hearings in the various reference committees and the reports they rendered to the House were so carefully considered and worded that they were usually adopted without lengthy debate. On the whole one must be impressed with the smoothly running machinery of the House of Delegates under the skillful guidance of the Speaker, Dr. Roy Foots, who is retiring this year after serving several years. He will be succeeded by Dr. Francis F. Borzell, of Philadelphia, who has been the vice-speaker for several terms.

WALTER G. PHIPPS

ity of existing agencies to deal with them. Trained personnel is scarce therefore, it became one of the primary purposes under the federal Mental Health Act to train more skilled workers for work in the field of psychiatry. An amount of \$1,450,000 was appropriated for use in this country to train doctors, nurses, social workers and other members of the psychiatric team. A fund of \$100,000 was established for the entire country, to be used for research fellowships and \$470,000 was set up for research. Money for training and research has been allotted by federal committees in Washington to centers of training and research throughout the country on the basis of need and the quality of supervising personnel available. It is to be regretted that Congress made a substantial cut in the amount of money originally set up to do the work.

The need for trained workers in psychiatry is tremendous. The money made available is far below the need and what could be spent to advantage. There are many excellent training centers and research institutions that could have been participating but the lack of funds which were not appropriated, made it impossible for them to co-operate. There are many excellent men applying for training in psychiatry who cannot follow the long course because of lack of funds.

A total of \$3,550,000 was appropriated in the United States for psychiatric community service. This money is allotted directly to states and federal funds are matched at the rate of \$2.00 for \$1.00. The share of Massachusetts was \$101,200 which is expended under the supervision of the Department of Mental Health.

The following projects have been carried out in the Commonwealth with the money granted:

Assistance to certain overcrowded clinics for the emotional problems of children so that more children were helped and the waiting time for such help was reduced. This resulted in better and earlier community adjustment.

Regular psychiatric advisory service to the three state training schools for delinquent children. Two of these schools are for boys, and one for girls. This service is pertinent to the study of aggression and the cause of community rehabilitation of children whose aggressive acts have exceeded the limitations of social acceptance.

Regular psychiatric advisory service to several of the more important and active courts, all of which try substantial numbers of children as well as adults. This is a humane and economical effort to reduce hospital examinations and to give advisory service to the presiding justices and their probation officers "on the spot" prior to disposition.

Supervisory service to organize and promote more fully the preparation or training program for nurses, licensed attendants and attendants. This is a fundamental need aimed to offer a fair degree of orientation to these groups from all fields of medicine and public health. It is one of the most important considerations. A central film library dealing with psychiatric subjects to assist in teaching has been established in the Department of Mental Health.

During the war, as a matter of necessity, it became important to bring into the mental hospitals certain general practitioners from the community. Their purpose was to do routine physical examinations, blood tests, conduct employee choices and give inoculations, thereby freeing the scarce resident psychiatric doctors to utilize more fully their own skills to the greater advantage of patients. These physicians became better oriented in psychiatric work, and the community reaped the benefit of this experience. This program has been greatly expanded.

Of particular importance in the long-range program has been the training, on a part-time basis, of general practitioners from the smaller communities. These doctors were assigned in four mental hospitals for training in psychiatry. There was no intention to make specialists of the family physicians but rather to help them meet demands for more information regarding incipient mental illnesses and emotional disturbances.

Assistance was given to teaching hospitals with outpatient work in psychiatry. Grants for personnel and supplies were made for the training of personnel who might later be able to operate such facilities.

Some aid was given also to local psychiatric clinics.

APPENDIX NO 13

REPORT OF THE SUBCOMMITTEE ON MENTAL HEALTH

The Committee on Mental Health met on August 12, 1948, with Drs. Barton, Taddell and Malamud and Dr. William C. Inman, invited as a consultant, present.

Your committee recommends that this report be made accessible to the members of the Society in order that they may know how federal funds are being spent in the Commonwealth to procure mental health. The demands for psychiatric help for children and for adults, both in and out of institutions, far exceeds the capacity

### State Hospitals

Our medical colleagues, in particular, and the public in general, should be aware of the plight of the state hospitals. Mental hospitals have suffered severely during recent years from a shortage of trained personnel. This shortage has been made worse by the provision of salaries that will not attract workers to the Commonwealth, since the surrounding states offer higher wages in competition. Hospitals are extremely overcrowded, making management of patients difficult. There is need for new construction. Adequate funds must be appropriated for operation.

Appropriation increases have not realistically adhered to patient-care standards and have not kept pace with the rising costs of things that must be bought.

Doctors and their patients must exert pressure on the Legislature to make adequate provision for the care of the mentally ill, the feeble-minded and the epileptic, in our state hospitals.

### Massachusetts Psychiatric Society

It was recommended that the Massachusetts Psychiatric Society (a district society of the American Psychiatric Asso-

ciation) be invited to meet jointly at the annual meeting of the Massachusetts Medical Society and to arrange a program of general interest on a psychiatric topic.

It seems highly desirable that there be less separation among specialty groups with a greater awareness of common medical problems. Instead of suggesting the creation of a new section on nervous and mental diseases that would hold special sessions at the annual meeting, it seems desirable to invite the existing state psychiatric society to convene in joint session and to provide a suitable program from which all would profit as a part of the Massachusetts Medical Society's annual scientific program.

### Education of the Public

This committee understands that the Massachusetts Medical Society has sponsored a radio series designed to educate the public on health needs. It would appear advantageous to have some of the programs devoted to the topic of mental health.

WALTER E. BARTON, *Chairman*  
WILLIAM MALAMUD  
HENRY A. TADGELL

## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

EDITH E. PARRIS, *Assistant Editor*

### CASE 34491

#### PRESENTATION OF CASE

A forty-one-year-old housewife was admitted to the hospital because of multiple fractures.

Six years before entry she began to have attacks of vomiting, which were attributed to gall-bladder disease. She became pregnant and suffered from toxemia but managed to deliver a full-term infant. The baby had convulsions for three weeks after birth. Three years before entry her menses ceased and she had had hot flashes. During the same year a laparotomy was performed, with removal of a chronically inflamed gall bladder containing stones. Soon after operation she began to notice definite malaise, generalized pains, easy fatigability, irritability and attacks of chest pain, dyspnea and palpitation. She was treated by a physician with Lugol's solution without improvement. She then developed swellings of the bones of the lower limbs and some deformity and later had a spontaneous fracture of the right tibia and fibula when getting up from a chair. She was hospitalized for one month. The bones were reported to be soft—"they could not tell the difference between tissues and bones." Finally an exploration of the neck

was carried out and a tumor nodule 2.5 cm in diameter was removed from below the right lobe of the thyroid gland. This was reported as "parathyroid adenoma." She apparently had postoperative tetany, which responded to hytakerol and calcium. She improved considerably, and by the next year she was able to get about, using only a high sole to correct for the shortening of the right leg. However, she never completely regained her strength, and x-ray studies showed cysts forming in the right femur. Six months before entry another neck exploration was done, and the right lobe of the thyroid gland was removed as well as two nodules on the right side. The pathological report was "chronic interstitial thyroiditis." She did not improve, and two months later the neck was again explored, but no parathyroid tumor was found. A biopsy removed from the left side was reported as showing "epithelial hyperplasia of the parathyroid gland." The next week while still in the hospital she fractured the right femur while getting on the bedpan. The following week the mediastinum was explored, with removal of a "parathyroid adenoma showing suspicious epithelial hyperplasia." She was transferred to this hospital by plane. On the way she fractured the left femur while getting on the bedpan.

Over the past three years she had had polyuria, polydipsia and moderate constipation. The fingernails became "much stronger."

Physical examination revealed nodular tender swellings of the ribs anteriorly and flattening of the ribs posteriorly, bony thickening and irregularity of the left iliac crest and a fracture deformity of the left thigh. The right lower limb was in a plaster cast, with Steinmann pins incorporated above and below the fracture of the femur. The tongue and mucous membranes were dry, and both corneas showed abortive but definite band keratopathy and a "fish-egg" appearance to the conjunctiva.

The temperature was 99.2°F, the pulse 110, and the respirations 25. The blood pressure was 110 systolic, 82 diastolic.

The hemoglobin was 11.6 gm, and the white-cell count 8800, with 68 per cent neutrophils. The serum calcium was 15.4 mg, and the phosphorus 3.6 mg per 100 cc, the potassium 2.6 milliequiv per liter, and the alkaline phosphatase 20.6 Bodansky units. The serum nonprotein nitrogen was 37 mg per 100 cc and the carbon dioxide content was 24.4 milliequiv per liter. The serum protein, chloride and prothrombin time were normal. A twenty-four-hour specimen of urine contained 359 mg of calcium. Albuminuria was noted in only one of several urine specimens.

X-ray films of the jaws showed that the lamina dura was missing. There was marked decalcification of all visualized bones of the lower limbs, especially in the shafts of the femurs, with fractures. A plain film of the abdomen showed a staghorn renal calculus on the left side.

An operation was performed on the eighteenth hospital day.

#### DIFFERENTIAL DIAGNOSIS

DR. WALTER BAUER: On the basis of the history and the laboratory findings it appears that this forty-one-year-old woman was suffering from hyperparathyroidism of at least three years' duration. The problem, as I see it, is to determine, if possible, the nature of the hyperparathyroidism. Was it due to hyperplasia of the parathyroid glands? If so, was it the result of chronic renal disease? Surely we have little evidence favoring such an interpretation. Was the hyperparathyroidism due to an excess of the parathyrotropic hormone from a parathyroid adenoma or some other condition? I think this case might be easier to interpret if we knew whether or not calcium, phosphorus and phosphatase determinations were done prior to admission to this hospital and whether or not these values were altered following removal of the "parathyroid tumors." Obviously they were not influenced for long following removal of the mediastinal parathyroid adenoma. One would like very much to know whether this first parathyroid adenoma was removed with ease or whether the surgeon, by any chance, had difficulty in resecting it. One would also like to know whether the two nodules removed from the right side of the neck at the time of the hemithyroidectomy were examined and if, by chance, they showed any evidence of parathyroid tissue. I take it that we do not have any knowledge of the nature of these nodules, nor do we know what was biopsied on the left side of the neck, later reported as showing "hyperplasia of the parathyroid gland."

DR. JOSEPH C. AUB: When was the last operation before she came in?

DR. BAUER: About four months before admission to this hospital. I would like to know whether she had a hypercalcemia, a hypophosphatemia and an increase in the alkaline phosphatase prior to the first operation. If so, did these values return to normal? They would not necessarily have to.

DR. BENJAMIN CASTLEMAN: At the time of the first operation the serum calcium was 16 mg per 100 cc. The final levels before she came here ranged from 14 to 16 mg, essentially unchanged by the operative procedures.

DR. BAUER: The patient continued to have a hypercalcemia from the time she first came under observation?

DR. CASTLEMAN: Yes.

DR. BAUER: May we see the x-ray films?

DR. STANLEY M. WYMAN: The films of the teeth show absence of the lamina dura. All the visualized bones are markedly osteoporotic, and there is some tendency to cyst formation, particularly in the shaft of the right femur. Old fractures of the right lower leg are seen in this view. There are stones in the pelvis and calyces of the right kidney. The lungs appear clear, and there is no evidence that I can see of a definite mass in the mediastinum or hilar region. It is the picture of marked bone atrophy with cyst formation and fractures.

DR. BAUER: We can say that the x-ray evidence is consistent with the diagnosis of hyperparathyroidism. From what Dr. Castleman tells us this patient apparently continued to have hypercalcemia despite the removal of the two tumors, both of which were interpreted as "parathyroid adenomas."

On reading this record I was intrigued by these quotations, "epithelial hyperplasia of the parathyroid gland" and "parathyroid adenoma, showing suspicious epithelial hyperplasia." Largely on the basis of these two statements I wondered whether, in this case, we might be dealing with a person who had cancer of the parathyroid gland. I have never seen such a case, and I have only looked up one article, namely, the one presented by Dr. Norris\* from this hospital. He reviews the literature and calls attention to 16 cases that he thinks might readily be termed cancer of the parathyroid gland. He then points out some of the difficulties in cases of this type as opposed to a lone adenoma and the cases of hyperparathyroidism due to generalized hyperplasia. In 12 cases the tumor was readily felt in the neck, and in 9 the patient was aware of its presence. It is of further interest that these nodules had been present for some time—in 1 patient as long as thirty-five years, and in others, two, three, five, eight and ten years. In 5 cases the tumor was actually observed to enlarge under observation. I inquired about the ease with which the first "adenoma of the para-

\*NORRIS, E. H. Carcinoma of parathyroid glands. *Internat. Abstr. Surg.* 86:1-21, 1948.

thyroid gland" was removed, thinking that this would be of help to me concerning the presence of cancer of a parathyroid gland. It is apparent that resection of this type of parathyroid tumor is much more difficult because of invasion of the surrounding tissue. All cases had hypercalcemia. One patient was operated on twice, and on each occasion following removal of a "tumor," the serum calcium returned to normal only to become elevated at a later date. In another case the hypercalcemia returned to normal following each of the three operations. Finally, this type of lesion can metastasize or spread locally. The metastases most commonly seen have been in the lungs, although in 1 case the liver and, in another, the bone were involved. This brings up the question whether or not a parathyroid adenoma can become malignant. From the evidence that Dr. Norris has collected it appears that such degeneration can and does take place. Certain precautions should always be taken when one is dealing with a patient of this type. The surgeon should first locate all four glands—occasionally there are more than four—before attempting removal of any tissue. It is important to have present a pathologist who is capable of diagnosing parathyroid lesions. He must tell the surgeon whether he is dealing with a lone adenoma, a hyperplastic gland or cancer of the parathyroid gland. I do not know how difficult it would be to make a diagnosis of carcinoma of the parathyroid gland on a frozen section. It is conceivable that it might be an extremely difficult job, but if any of the gross characteristics are observed, certainly it would behoove the surgeon to do as radical a resection as possible if he hoped to obtain a complete cure, that being of course the only way of curing such a lesion because it does not respond to x-ray therapy. Therefore, largely on the basis of the pathologist's referring to the presence of "epithelial hyperplasia" in two of three specimens revealing parathyroid tissue, I shall make a diagnosis of carcinoma of the parathyroid gland rather than hyperplasia of the parathyroid glands.

DR. OLIVER COPE: We were very much helped in this case by the fact that the blocks of tissue previously resected were sent along with the patient, and Dr. Castleman and Dr. Mallory obtained adequate sections and gave us a diagnosis beforehand.

#### CLINICAL DIAGNOSIS

Carcinoma of parathyroid gland

#### DR. BAUER'S DIAGNOSIS

Carcinoma of parathyroid gland

#### ANATOMICAL DIAGNOSIS

*Carcinoma of parathyroid gland*

#### PATHOLOGICAL DISCUSSION

DR. TRACY B. MALLORY: We thought that this was a definite carcinoma of the parathyroid gland. It was growing with sufficient rapidity to have mitotic figures, which are unusual in adenoma, and in the second specimen, although not in the first, there was definite invasion.

DR. COPE: The initial problem presented by this patient was whether she had hyperparathyroidism or a carcinoma elsewhere with metastases invading the entire skeleton. Rapidly spreading bone metastases may mimic hyperparathyroidism from the chemical point of view, in such patients the serum calcium is elevated, and there is an excessive excretion of calcium in the urine. These findings were present in this patient, and the serum phosphorus level was normal. This last can exist in hyperparathyroidism if there is impairment of renal function. Because of the presence of carcinoma in the parathyroid adenoma already removed, hyperparathyroidism was the diagnosis, and it seemed right to attempt a radical excision of the parathyroid tissue. The operation was divided into three stages. The left side of the neck was exposed at the first stage because that was the side opposite where the large tumor had been found, and it was important if possible, to save the normal parathyroid tissue before doing a radical excision and attempting to excise all the hyperfunctioning carcinomatous tissue. A cluster of carcinomatous lymph nodes was found just above the upper end of the thoracic duct on the left—a common finding from carcinoma on the right side of the neck spreading in the lymphatics. The second operation was the exploration of the right side, it was disappointing. Only one large lymph node, swollen with carcinoma, was found. No other parathyroid tissue was encountered. We hoped that enough tissue—metastases in lymph nodes—could be found in the mediastinum to account for the continued hyperactivity. The third operation was, therefore, a mediastinal exploration, but only one small carcinomatous lymph node could I find. Removal of this small amount of carcinomatous tissue did not alter the function as judged by the absence of changes in the blood levels of calcium and phosphorus. The only assumption left to us, since there was no evidence of metastases in the lungs, was that somewhere in the bones or in the liver there must be carcinomatous tissue. That is a presumption. Dr. Lerman and Dr. Koch have been trying to inactivate the patient's parathyroid hormone by sensitizing her to the crude parathyroid extract. So far they have not been able to demonstrate inactivation. She has returned to the city from which she came, with incurable disease as far as our present abilities go.

## CASE 34492

## PRESENTATION OF CASE

A fifty-four-year-old man was admitted to the hospital because of crampy abdominal pain and diarrhea.

He had been well all his life until three years preceding admission, when he went to another hospital because of crampy pains in the lower abdomen and diarrhea without gross blood in the stool. A barium meal was said to demonstrate a duodenal ulcer, and on a dietary regime the symptoms disappeared entirely. Four weeks before entry to this hospital the same type of pain, again associated with three or four loose stools daily, returned. This time he was unable to obtain relief by changing his diet. The original episode had been accompanied by a 36-pound weight loss, which he subsequently regained, and the current attack with a 10-pound weight loss.

The family and past histories were irrelevant. The system review revealed nocturia of three or four times for the past six years without other genitourinary complaint.

Physical examination revealed a well developed, well nourished man who did not appear to be ill. The heart and lungs were normal. On deep inspiration the liver was felt two fingerbreadths below the costal margin. The prostate was enlarged to one and a half times the normal size and was smooth and symmetrical.

A urinalysis was negative. The white-cell count was 8000, and the hemoglobin was 15.5 gm (photoelectric-cell technic). Two x-ray examinations of the colon demonstrated a large, polypoid mass, measuring slightly more than 4 cm in diameter in the transverse colon (Fig 1). A colocolic intussusception, 10.1 to 12.7 cm in length, was observed, the tumor initially being in the transverse colon near the hepatic flexure, but partial reduction occurred during filling so that it took a final position near the splenic flexure. Two other rounded defects in the colon near the hepatic flexure were seen on one examination, measuring 1 and 2 cm in diameter, respectively. There was a questionable, small, polyp-like defect in the sigmoid region.

On the fourth hospital day an operation was performed.

## DIFFERENTIAL DIAGNOSIS

DR CLAUDE E. WELCH: Let us see the x-ray films before starting the discussion.

DR STANLEY M. WYMAN: I think you can all see the large, somewhat lobular, but relatively smooth mass lying in the lumen of the bowel with a sleeve of intussusception running around it. Also, there is an increase in the number of folds over the region of the tumor, which is evidence of intussusception. The fluoroscopist noted that in the beginning the mass lay in the general region of the

splenic flexure, and as the barium column progressed it forced the mass proximally and, I think, in effect reduced the intussusception rather than caused it. There is no definite pattern of mucosal destruction that one can see in any of the films. All one can say is that there is a round, somewhat lobular, rather smooth, intraluminal mass, which has caused intussusception of the colon and during the examination was partially reduced. The small, questionable areas described in the protocol lie in the sigmoid. In view of the obviously poor condition of



FIGURE 1

the bowel as far as preparation is concerned, these areas cannot be taken too seriously.

DR WELCH: Dr Wyman's report and description of the x-ray film here are going to force me to change my original diagnosis as I will point out later.

It is fair to state that the first attack of pain three years before entry was not due to duodenal ulcer but was caused by the same type of disease for which the patient was admitted. This long interval suggests a benign rather than a malignant lesion. The loss of weight with subsequent complete recovery is also very suggestive of that diagnosis. There is nothing else remarkable in the history or physical findings.

About ten years ago I looked up the intussuscepting lesions of the large bowel in this hospital, stimulated by a patient of Dr Arthur W. Allen who entered with carcinoma extruding from the anus. At operation the tumor was found to arise from

the midsigmoid Dr Allen did a resection and an easy anastomosis. During a ten-year period I was able to find records of 18 intussuscepting lesions of the colon. In this group the final diagnosis was carcinoma in 13 cases, lipoma in 3, benign polyp in 1 and hemangioendothelioma in 1. Two thirds of the cases, therefore, were cancer, and the remainder of the patients had intussusception because of benign tumors.

The description of the x-ray films in the protocol at first suggested to me that the patient had benign polyps at the outset and that the polyp in the transverse colon had, after three years, developed into low-grade carcinoma. I think that is less likely now because the bowel was poorly prepared, and the suggestive polyps mentioned in the protocol are much more typical of fecal matter on the x-ray films that Dr Wyman has shown us. The surface of the mass is also quite smooth in the x-ray film. In other words, I now do not believe we are dealing with carcinoma, and the absence of other findings in the bowel inclines me definitely toward the diagnosis of lipoma since it is the most common simple benign tumor that produces intussusception in the colon.

I might state also that there are no other diagnostic features that would give help unless proctoscopy was done and polyps demonstrated. So far as stool examinations are concerned, intussusception will lead to strongly positive guaiac reactions in both benign and malignant tumors.

I will rest on the diagnosis of lipoma as the intussuscepting tumor in the transverse colon.

DR ROY E. MABREY: This is a patient of mine who had received x-ray study at another hospital three years before admission, when the diagnosis of duodenal ulcer was made. A barium enema was not done at that time. When I saw him he complained of low abdominal pain, crampy diarrhea and weight loss. Sigmoidoscopy was done, and nothing found to suggest polyposis. I then asked

for a barium enema, which revealed the findings discussed above.

I explored him, and at the time of operation I found a mass in the transverse colon. The transverse colon was redundant so that there was wide mobility of the tumor mass. On the serosal surface there were three or four grayish plaques, which I believed were carcinoma invading the serosa, and I went ahead and did a wide resection of the transverse colon with end-to-end anastomosis.

#### CLINICAL DIAGNOSIS

Carcinoma of transverse colon

#### DR WELCH'S DIAGNOSIS

Lipoma of transverse colon, with intussusception

#### ANATOMICAL DIAGNOSIS

*Submucous lipoma of transverse colon, with previous intussusception*

#### PATHOLOGICAL DISCUSSION

DR BENJAMIN CASTLEMAN: The resected specimen was unusual in that the tumor, a benign lipoma, did not seem to be as big as the x-ray shadow suggests. I suppose a large part of the x-ray shadow is due to the intussusception, which was not present when we received the specimens. The tumor itself was less than 3 cm. in diameter and was only slightly elevated above the surrounding mucosa, most of the tumor being located in the submucosa. The central third of the mucosa over the tumor was ulcerated, disclosing grayish-yellow fat. This ulceration was almost certainly due to repeated attacks of intussusception that were occurring time and time again, causing gangrene of the mucosa.

Had he had any blood in the stools as far as you know?

DR MABREY: No.

# The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established 1828

Official Organ of

THE MASSACHUSETTS MEDICAL SOCIETY

and

THE NEW HAMPSHIRE MEDICAL SOCIETY

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND

PUBLISHED WEEKLY UNDER THE JURISDICTION OF THE

COMMITTEE ON PUBLICATIONS

James P. O'Hare M.D. Richard M. Smith M.D., *Chairman*  
Oliver Cope M.D. Conrad Wesselschoeff M.D.  
John Fallon M.D.

Joseph Garland M.D. *EDITOR*

*ASSOCIATE EDITORS*

Thomas H. Lanman M.D. Donald Munro M.D.

Henry Jackson Jr. M.D.

Clara D. Davies *EXECUTIVE EDITOR*

Robert O. Leary *ASSISTANT EDITOR*

*EDITORIAL BOARD*

C. Gay Lane M.D. Maxwell Finland M.D.  
Henry R. Viets M.D. James M. Faulkner M.D.  
Robert M. Green M.D. Carroll B. Larson M.D.  
Dwight O'Hara M.D. Francis D. Moore M.D.  
Fletcher H. Colby M.D. C. Stuart Welch M.D.  
Robert L. Goodale M.D. Vernon P. Williams M.D.  
Chester M. Jones M.D. Benjamin Castleman M.D.  
Harvey R. Morrison M.D. Hugh R. Leavell M.D.

**SUBSCRIPTION TERMS** \$7.00 per year in advance, postage paid for the United States (medical students \$4.00 per year) Canada \$8.00 per year (Boston funds) \$9.50 per year for all foreign countries belonging to the Postal Union.

**MATERIAL** should be received not later than noon on Thursday three weeks before date of publication.

**THE JOURNAL** does not hold itself responsible for statements made by any contributor.

**COMMUNICATIONS** including those concerning classified advertising but not those regarding other advertising should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts. Telephone AE 6-2094.

**NEW ENGLAND ADVERTISING REPRESENTATIVE** (except for classified advertising) Edwin B. Tyler, 89 State Street, Boston, Massachusetts. Telephone LA 3-5516.

## THE MASSACHUSETTS MEDICAL BENEVOLENT SOCIETY

THE Massachusetts Medical Benevolent Society, the oldest of its kind in continuous existence in the United States, was first organized at a meeting of physicians held in Boston on March 19, 1857. Its formal Article of Association reads "Whereas it sometimes happens that worthy members of the medical profession become reduced in circumstances, we, whose names are underwritten (all being residents of Massachusetts), do hereby associate ourselves as a body corporate for the relief of such, or of their families, should they need assistance." After fourteen years of activity as a voluntary association it was legally incorporated on

May 8, 1871, and has continued active to the present day. Funds are raised and invested, annual dues are levied upon the members and the sum thus accumulated, increased from time to time by gifts and legacies, has been held in trust. For ninety years the Society has annually devoted its entire income to the charitable relief of unfortunate physicians and their widows or minor children, whom circumstances have made dependent upon the pecuniary aid of others. Such has been the quiet but constant beneficence of this peculiarly characteristic medical organization.

With the growth in numbers of physicians in the Commonwealth, however, the legitimate needs of assistance have outrun the ability of the Benevolent Society to meet them. For some time, the individual members and groups within the Massachusetts Medical Society have endeavored to fill some of these needs by their own charitable activities. Obviously it is desirable that such assistance to physicians should be under a single administration, combining and correlating the work of both organizations. To this end, an arrangement has recently been formulated and adopted whereby financial relief to deserving destitute physicians in the Commonwealth shall be administered by a "Board composed of representatives of the Massachusetts Medical Society and of the Massachusetts Medical Benevolent Society." Each society retains its separate identity, but the funds of both, available for needed assistance to indigent physicians, are to be allocated and disbursed under a joint management. This seems to be an eminently just and desirable arrangement, which should meet with general approval.

It has always been an established point of honor in the profession of medicine that its members and their families should freely receive professional service in sickness. It should be felt as an equally honorable duty among physicians to see that none of their professional brethren, in old age or adversity, suffer from destitution or personal hardship.

## LOCAL HEALTH UNITS

ELSEWHERE in this issue of the *Journal* Archibald and his associates point out some critical deficiencies in the distribution of health services in Massachu-

setts To those long accustomed to regarding the Commonwealth as a leading state in point of health facilities, it is somewhat of a shock to be informed that there is no complete, statewide coverage by local health units properly governed, financed and staffed to render basic health services to all citizens. The authors present a precise enumeration of existing facilities and no less carefully define the shortcomings in quality and distribution. The most important step in the solution of the problem is stated to be enlightenment of the public concerning the need for new laws and increased facilities to keep Massachusetts abreast of progress in public health, the small communities, which cannot afford these facilities and are unwilling to relinquish autonomy to the extent of forming co-operative units to meet their joint requirements, present a particularly difficult problem. Adequately trained physicians, nurses, sanitarians and accessory personnel, in sufficient numbers to conduct a modern full-time, health organization, must be provided. And, finally, the legislature must be persuaded to appropriate sufficient funds to enable local health departments to do a creditable job.

That Massachusetts is not the only state that has failed to furnish basic health services to all citizens was revealed as long ago as September, 1947, when the National Conference on Local Health units presented a study of public-health conditions throughout the country. The six vital functions, defined at the conference and applied by Archibald et al. to Massachusetts in particular, are as follows: vital statistics, control of communicable disease, environmental sanitation, public-health laboratory services, maternity, infant and child health services, and health education so far as it is not covered in schools and colleges.<sup>1</sup> The National Health Council has also offered suggestions for improving and extending health services at the community level: joint co-operation of official and voluntary health agencies, professional societies, consumer groups and members at large to publicize existing inadequacies and promote efforts at correction.<sup>2</sup>

What may be considered the raw materials necessary for effective action are thus at hand. It remains for those most interested to exert every

effort to attain adequate distribution of health services. In view of the ever-present threat of governmental interference in the free practice of medicine, there is an ominous overtone to the statement of Archibald and his co-workers: "Until such local health units become a reality, a sound public-health program cannot be administered in an efficient, economic and competent manner." The medical and public-health professions should exert every effort to achieve the goal envisaged. Massachusetts, the cradle of many liberties, can do much to continue the free status of public-health practice: every effort to overcome the present shortcomings in health services helps to hold off the heavy, blighting hand of political pressure and dictation.

#### REFERENCES

1. *Proceedings of the National Conference on Local Health Units*, 95 pp. New York: American Public Health Association, 1947. P. 5.
2. Lyon Y. *Stepping Stones to a Health Council*. 28 pp. New York: National Health Council, 1947.

#### CURE GUARANTEED OR MONEY BACK

A DRUG manufacturing firm, nationally known, has this fall suddenly released a barrage of newspaper advertising that leaves no possible doubt as to its ethical standards in this instance. Among reputable pharmaceutical manufacturers direct advertising to the public simply is not done. So far as the acceptance of full-page weight-reduction advertisements with notarized testimonial letters is concerned, it can only be said that each newspaper will adhere to its own standards.

In this day and generation and in what might be considered good journalistic society, the flamboyant advertising direct to the public of drugs of any sort is bad taste. When the advertising matter contains testimonial letters, before-and-after-treatment photographs, money-back guarantees and certification as to safety by noted physicians (names not given), the total result is another disheartening blow to those who have worked diligently in the interests of health, the protection of the public, and the better distribution of good medical care.

The advertisement in question makes certain concessions to modern ethical considerations, showing, at least, that the advertiser is aware of

their existence. The statements are made, for instance, that the advertised product is not for glandular obesity, and that endorsement by the purchaser's physician is recommended. If the advertisers had not shown this awareness of current medical ethics, their lapse might be more readily understood.

The medical profession, as is to be expected, incurs the suspicion of self-interest when it criticizes the practice of medicine by others than its own members. Let it be admitted that an element of honest professional self-protection exists. Let it also be recognized that the physician in treating a patient assumes a responsibility that no manufacturing druggist is capable of assuming.

He assumes, in particular, the responsibility of determining to the best of his ability that the advice he offers is suited to the needs of the individual patient. He attempts, when permitted to practice his profession according to its accepted precepts, to make as accurate a diagnosis as possible before prescribing treatment. This cannot be done under the system of self-medication recommended in the advertisement under discussion and sanctioned by the newspapers that accept it.

## NEW ENGLAND HEART ASSOCIATION PENICILLIN FUND

SUBACUTE bacterial endocarditis, a complication of cardiovascular disease that has been hitherto almost universally fatal, represents another conquest of the penicillin era. In this disease particularly of the young, the mortality rate has been changed by adequate treatment with penicillin from practically 100 per cent to the vicinity of only 25 per cent.

Adequate treatment, however, consists of an enormous amount of penicillin — approximately a million units a day for a period of thirty days — a most expensive therapeutic procedure and quite beyond the resources of many patients. In this contingency and in order that no patient in New England may be deprived of suitable treatment, the New England Heart Association has set aside a special portion of the fund donated by the public last year, to provide free penicillin for those patients with subacute bacterial endocarditis who cannot otherwise procure it.

This fund is under the supervision of a special committee that has issued recommendations and established criteria as follows:

The diagnosis of subacute bacterial endocarditis is to be established by at least two positive blood cultures, although the committee may approve a request, under exceptional circumstances, when the clinical data seem adequate even with sterile blood cultures.

The treatment shall consist of a million units per twenty-four hours, in divided intramuscular doses every three hours, by continuous intramuscular drip or by slow continuous intravenous infusion unless modifications seem advisable under exceptional circumstances.

Application forms for free penicillin under the terms of this offer have been sent to all New England hospitals and are in the hands of each member of the Heart Association.

The funds for the program are limited, but, in the words of the announcement, "within its resources this association is determined that no victim of bacterial endocarditis in New England shall succumb because of a lack of adequate treatment with penicillin."

## BOOK REVIEW

*Hodgkin's Disease and Allied Disorders*. By Henry Jackson, Jr., and Fredenc Parker, Jr. Oxford Medical Publications, 4°, cloth, 177 pp., with 15 plates. New York: Oxford University Press, 1947. \$6.50.

This monograph admirably summarizes existing knowledge of a group of conditions of increasing clinical importance. The authors discuss Hodgkin's disease, reticulum-cell sarcoma, lymphocytoma and lymphoblastoma, lymphosarcoma, giant-follicle lymphoma and plasmocytoma; they advise discarding the term "endothelioma" as used by some for a member of this group.

All phases of each group, including excellent clinical descriptions, are presented. There are numerous well reproduced illustrations, particularly valuable as giving a clear idea of a varying pathological histology. Since, as the authors point out, prognosis in each patient depends very largely upon histologic appearances, biopsy study of these patients is of very great clinical import as a probable index of duration of life, some of the patients, particularly those with the histologic characteristics of Hodgkin's paraneoplasia or of giant-follicle lymphosarcoma, will live a long time in reasonable comfort, whereas others will die in a short time whatever the treatment. Incidentally, treatment for each group is thoroughly and well described.

Jackson and Parker face the often discussed problem whether Hodgkin's disease is or is not to be regarded as a neoplasm by subdividing the cases into three types: Hodgkin's paraneoplasia, Hodgkin's granuloma and Hodgkin's sarcoma. In their own words "paraneoplasia bears little or no resemblance to a true tumor", regarding granuloma type "the fact that the Reed-Sternberg cells are frequently scattered, isolated and often separated widely by cells of other types favors an inflammatory process rather than a neoplasm," whereas "on the clinical side [many features] are all more characteristic of an infectious process than of a tumor", they state that "Hodgkin's sarcoma has all the characteristics of a true neoplasm." However, they

admit that in time one type of Hodgkin's disease can change to another

The "allied disorders" included by Jackson and Parker are considered to be neoplasms either malignant or potentially malignant. Of these giant-follicle lymphoma long may behave as a benign neoplasm.

This monograph, written by a clinician and a pathologist long interested in these conditions, will prove useful to both pathologists and clinicians. The reviewer commends it to both groups of potential readers as a source of valuable information.

## NOTICES

### NEW ENGLAND DIABETES ASSOCIATION

A joint meeting of the New England Diabetes Association with the Middlesex South, Middlesex North, Norfolk, Norfolk South and Suffolk district medical societies will be held in Sanders Theater, Cambridge, on Monday, December 6, at 8 00 p m.

#### PROGRAM

Introductory remarks by the chairman, Dr W Richard Ohler

The Purpose of Diabetes Week Dr Howard F Root, chairman of the Diabetes Detection Committee, American Diabetes Association

Important Physiologic Facts Dr DeWitt Stettin, Jr, of the Public Health Research Institute, New York

Clinical Management of Diabetes (each speaker will talk for ten minutes)

Diagnosis of Diabetes Dr Joseph W Rosenthal, Norfolk District

General Management of Diabetes Dr David Hurwitz, Norfolk District

Management of Diabetes during Acute Illnesses and Surgical Operations Dr James H Townsend, Middlesex South District

Treatment of Diabetic Acidosis Dr Reed Harwood, Norfolk District

Peripheral Vascular Disease Dr E Everett O'Neil, Norfolk District

Crippling Complications of Diabetes Dr Howard F Root, Suffolk District

All the speakers will answer questions submitted either in writing beforehand or from the floor, followed by an address on the subject "After Fifty Years" by Dr Elliott P Joslin, Suffolk District

Membership in the New England Diabetes Association is open to any physician in New England. Application may be made to the Secretary, 330 Mt Auburn Street, Cambridge

### JOSEPH H PRATT DIAGNOSTIC HOSPITAL

30 Bennet Street, Boston

Lecture Hall, 9-10 a m

#### MEDICAL CONFERENCE PROGRAM

Friday, December 3 — Congenital Neurologic Cases Drs Clarence W Houghton and Nils E Svibergson

Wednesday, December 8 — Pediatric Clinicopathological Conference Drs James M Baty and H E MacMahoo

Friday, December 10 — To be announced

Tuesday, December 14 — The Relation of Opacities of the Lens to General Medicine Dr Josef Igersheimer

Friday, December 17 — Albumin in the Treatment of Hypoproteinemia Dr Sam T Gibson

Tuesday, December 21 — Journal review

Friday, December 24 — Craniopharyngioma, Ophthalmic Type, due to Pituitary Tumors (Demonstration and Discussion of Cases Operated on by Transphenoidal Methods) Dr Oscar Hirsch

On Tuesday morning, December 7, from 9 to 10 o'clock and on Wednesday mornings, December 1, 15 and 22, from 9 to 10 o'clock, Dr S J Thannhauser will give medical clinics on hospital cases. On Thursday mornings from 9 to 10 o'clock clinics will be given by Dr William Dameshek. On Friday, December 10, a therapeutic conference will be held with

round-table discussion from 2 to 4 o'clock (Dr Robert P McCombs, moderator). On Friday, December 10, Dr Merrill Sosman will conduct an x-ray conference from 4 to 6 o'clock. On Saturday mornings from 9 to 10 o'clock surgical clinics will be given by Dr C Stuart Welch. Medical Rounds are conducted each weekday except Saturday by members of the hospital staff from 12 to 1.

All conferences will be discontinued from December 24, 1948, through January 3, 1949.

All exercises are open to the medical profession.

### HARVARD MEDICAL SOCIETY AND BOSTON CITY HOSPITAL HOUSE OFFICERS' ASSOCIATION

A meeting of the Harvard Medical Society and Boston City Hospital House Officers' Association will be held in the Dowling Amphitheater of the Boston City Hospital on Tuesday, December 14, at 8 p m.

#### PROGRAM

Case Report Chronic Renal Acidosis with Osteomalacia Dr Beverly T Towery

Observations on Aureomycin Drs Harvey S Collins, E Buist Wells and Maxwell Finland

Nontuberculous Spinal Epidural Infections Dr A Price Heusner

Clinical Physiology of Vitamin B<sub>12</sub> Dr William B Castle (based on work done in collaboration with Dr Lionel Berk)

Subsequent meetings will be held on January 11, February 8, March 8, April 12 and May 10, 1949.

### NATIONAL GASTROENTEROLOGICAL ASSOCIATION 1949 AWARD CONTEST

The National Gastroenterological Association announces an annual cash prize award contest for 1949. One hundred dollars and a certificate of merit will be given for the best unpublished contribution on Gastroenterology or allied subjects. Certificates will also be awarded physicians whose contributions are deemed worthy.

Contestants residing in the United States must be members of the American Medical Association. Those residing in foreign countries must be members of a similar organization in their own country. The winning contribution will be selected by a board of impartial judges, and the award is to be made at the annual convention banquet of the Association in October, 1949.

Certificates awarded to other physicians will be mailed to them. The decision of the judges will be final. The Association reserves the exclusive right of publishing the winning contribution, and those receiving certificates of merit, in its official publication, *The Review of Gastroenterology*.

All entries should be limited to 5000 words and should be typewritten in English, prepared in manuscript form and submitted in five copies accompanied by an entry letter; they should be received not later than April 1, 1949. Entries should be addressed to the National Gastroenterological Association, 1819 Broadway, New York 23, N Y.

### APPOINTMENTS IN VETERANS ADMINISTRATION TUBERCULOSIS HOSPITALS

One hundred full-time doctors are needed by the Veterans Administration for duty in its tuberculosis hospitals.

Applicants should address their inquiries to the Chief Medical Director, Veterans Administration, Washington 25, D C.

The openings are scattered throughout the nation among Veterans Administration hospitals specializing in the treatment of tuberculous veterans and in Veterans Administration general medical and surgical hospitals operating tuberculosis departments.

The salary scale for full-time doctors in the Department of Medicine and Surgery ranges between \$4479 and \$10,305 annually for jobs now open.

During the past year, 18,222 tuberculous veterans were admitted to Veterans Administration hospitals for treatment. Discharges during the same period totaled 18,701.

(Notices concluded on page xiii)

## NOTICES (Concluded from page 902)

## SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING  
THURSDAY, DECEMBER 9

## FRIDAY DECEMBER 10

- \*9:00-10:00 a.m. Subject and speaker to be announced Joseph H Pratt Diagnostic Hospital.  
 \*9:00 a.m.-12:00 m. Combined Medical and Surgical Staff Rounds Peter Bent Brigham Hospital.  
 \*12:00 m. Clinicopathological Conference Margaret Jewett Hall Mt. Auburn Hospital, Cambridge  
 \*12:00 m.-1:00 p.m. Clinicopathological Conference (Boston Floating Hospital) Joseph H Pratt Diagnostic Hospital

## MONDAY DECEMBER 13

- \*12:15-1:15 p.m. Clinicopathological Conference Main Amphitheater Peter Bent Brigham Hospital.

## TUESDAY DECEMBER 14

- \*9:00-10:00 a.m. The Relation of Opacities of the Lens to General Medicine. Dr Josef Igersheimer Joseph H. Pratt Diagnostic Hospital.  
 \*12:15-1:15 p.m. Clinicopathological Conference. Peter Bent Brigham Hospital  
 \*1:30-2:30 p.m. Pediatric Rounds Burnham Memorial Hospital for Children Massachusetts General Hospital  
 8:00 p.m. Harvard Medical Society and Boston City Hospital House Officers Association Dowling Amphitheater Boston City Hospital

## WEDNESDAY DECEMBER 15

- \*11:00 a.m.-12:00 m. Medical Rounds. Amphitheater Children's Hospital  
 \*12:00 m.-1:00 p.m. Clinicopathological Conference (Children's Hospital) Amphitheater Peter Bent Brigham Hospital  
 \*2:00-3:00 p.m. Combined Clinic by the Medical Surgical and Orthopedic Services Amphitheater, Children's Hospital

\*Open to the medical profession

- DECEMBER 3-24. Joseph H Pratt Diagnostic Hospital Medical Conference Program. Page 902  
 DECEMBER 4. American Federation for Clinical Research Page 644 issue of October 21  
 DECEMBER 4-9. American Academy of Dermatology and Syphilology Page 728 issue of November 4  
 DECEMBER 6. New England Diabetes Association Page 902  
 DECEMBER 6. New England Heart Association. Page 844 issue of November 25  
 DECEMBER 6-8. American Academy of Allergy Fifth Annual Meeting Chalfonte-Haddon Hall Hotel, Atlantic City New Jersey  
 DECEMBER 7-9. Southern Surgical Association Annual Meeting Page 543 issue of April 8  
 DECEMBER 9. Recent Advances in Thoracic Surgery Dr Joseph P Lynch Penckuck Association of Physicians. 8:30 p.m. Haverhill  
 DECEMBER 9 and 10. New York State Society of Anesthesiologists Page 34 issue of July 1  
 DECEMBER 14. Harvard Medical Society and Boston City Hospital House Officers Association Page 902  
 DECEMBER 14. New England Society of Anesthesiologists Page 844 issue of November 25

## Something New Is Offered Doctors for Their Patients . . .

For patients who require rest in a charming, gracious atmosphere. Situated 23 miles south of Boston — 19-acre estate. Chauffeur service to and from doctors' offices and for rides about the countryside. Described by reputable Boston physician as luxurious country club. Registered nurses in attendance. Rates on request.

### STETSON HALL

NORWELL, MASSACHUSETTS

HARRIET F FLAGG, R.N.

Director

Telephone Hanover 395

## AN EFFICIENT 24-HOUR TELEPHONE ANSWERING SERVICE

If your telephone is unattended during the day or night — the **PHYSICIANS SERVICE EXCHANGE** will answer all calls and relay any message desired.

Our office is equipped with Soundscribers and Gray-  
Electronic Transcribers. This enables physicians to dictate from their office or home telephone and have the transcription dictated promptly.

## PHYSICIANS SERVICE EXCHANGE

264 BEACON ST  
131 STATE ST

Copley 7-4040  
CApitol 7-0332

BOSTON  
BOSTON

### BAKER'S Combined Vitamins

5000 U.S.P. Units Vitamin A  
1000 U.S.P. Units Vitamin D  
5 mg B<sub>1</sub> Thiamin Chloride  
5 mg B<sub>2</sub> Riboflavin  
1 mg B<sub>6</sub> Pyridoxine  
5 mg Calcium Pantothenate  
50 mg Nicotin Amide  
75 mg Ascorbic Acid (Vit. C)  
5.67 mg Mixed Tocopherols (Vit. E)

### BAKER'S Liver and Iron

2 mg B<sub>1</sub> Thiamin Chloride  
2 mg B<sub>2</sub> Riboflavin  
0.5 mg B<sub>6</sub> Pyridoxine  
20 mg Nicotin Amide  
1.5 mg Calcium Pantothenate  
226.8 mg Liver Concentrate 120  
50 mg Yeast Dried U.S.P.  
60.38 mg Ferrons Sulfate Dried  
50 mg Red Bone Marrow Dried

\$3.00 per Hundred

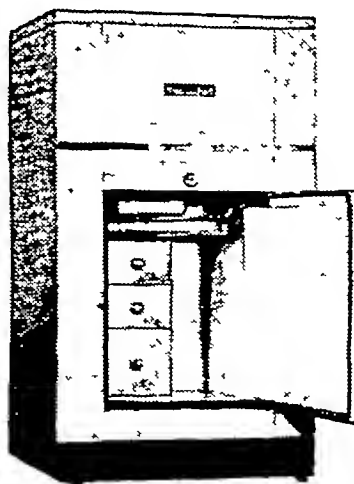
RETAIL PRICE

\$3.00 per Hundred

Available to druggists through their wholesaler

Chas. A. Baker Laboratories, Inc.  
BOSTON MASS

## LILLY BIOLOGICAL REFRIGERATOR



White enamel finish

Interior-white porcelain enamel

Internal space including drawer assembly 15" high x 12" wide x 12" deep

External overall dimensions 35 1/2" high x 19 3/4" wide x 19 3/4" deep

See it at our store or write for circular

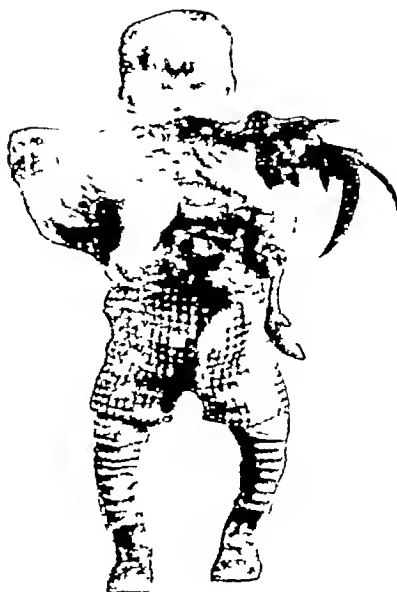
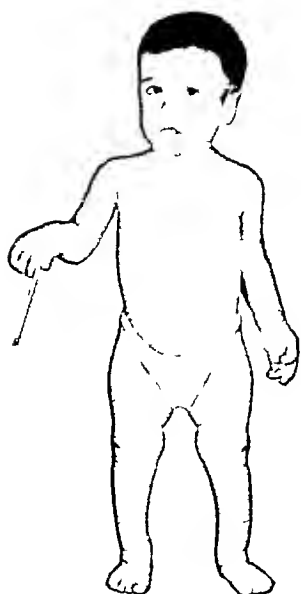
Immediate delivery

PRICE \$150

T. J. NOONAN COMPANY

911 BOYLSTON STREET

BOSTON 15



## IT DOES HAPPEN HERE

*Severe rickets still occurs—even in sunny climates*

Vitamin D has become such an accepted practice in infant feeding that it is easy to think that rickets has been eradicated. However, even deforming rickets is still seen, as witness the above three contemporary cases from three different sections of the United States, two of them having well above the average annual sunshine hours for the country. In no case had any antiricketic been given during the first two years of life. *It is apparent that sunlight did not prevent rickets.* In other cases of rickets, cod liver oil was given inadequately (drop dosage) and even this was continued only during the winter months.

*To combat rickets simply, inexpensively, effectively—*

## OLEUM PERCOMORPHUM

This highly potent source of natural vitamins A and D, if administered regularly from the first weeks of life, will not only prevent such visible stigmata of rickets as pictured above, but also many other less apparent skeletal defects that might interfere with good health. What parent would not gladly pay for this protection? And yet the average prophylactic dose of Oleum Percomorphum costs less than one cent a day. Moreover, since the dosage of this product is measured in drops, it is easy to administer Oleum Percomorphum and babies take it willingly. Thus there is assurance that vitamin D will be administered *regularly*.

### OLEUM PERCOMORPHUM WITH OTHER FISH-LIVER OILS AND VIOSTEROL

Potency, 60,000 vitamin A units and 8,500 vitamin D units per gram. Supplied in 10 cc and 50 cc bottles, and as capsules in bottles containing 50 and 250

MEAD JOHNSON & COMPANY, Evansville 21, Indiana, U. S. A

1751

2311

1941

# The New England Journal of Medicine

Copyright, 1948 by the Massachusetts Medical Society

Volume 239

DECEMBER 9, 1948

Number 24

## THE EFFECT OF INJURY TO THE SPINAL CORD AND CAUDA EQUINA ON THE SEXUAL POTENCY OF MEN\*

DONALD MUNRO, M D, † HERBERT W. HORNE, JR. M D ‡ AND CAPTAIN DAVID P. PAULL, M C A U S ‡

BOSTON AND FRAMINGHAM, MASSACHUSETTS

PATIENTS who are paralyzed as the result of an injury to the spinal cord or cauda equina have to face many difficult physical and psychologic problems. One of the most difficult of the psychologic ones is that which has to do with their loss of sexual ability. To discuss it at all with their doctors requires mutual understanding and confidence. Such confidence presupposes knowledge on the part of the physicians — that is knowledge of the effect of a cord injury on the various aspects of sexual and possibly married life. Unfortunately, such basic information is conspicuous by its absence. Doctors, therefore, either admit their ignorance or make up explanations and prognoses out of whole cloth.

Because of the confusion between what has been demonstrated in animals and deduced in man, all sorts of legends about the effect of spinal-cord injuries on the sexual act in man have come to be accepted. One hears, for example, that lesions of the conus will cause impotence, that transection at any level of the cord will always have the same effect, and that priapism has prognostic significance and the like. Impotence has not been distinguished from sterility, and this medical ignorance has become a matter of concern to prospective spouses. The fact appears to be that as far as we can find out, except as noted below, competent physiologic study of the effect on the sexual capacity of man of partial and transverse injuries of the spinal cord, as well as injuries of varying degree to the cauda, has not been made.

The concentration of paralytic patients with cord injuries at certain veterans' hospital centers offered a unique opportunity to study this aspect of the sterility problem in men provided that the

patients would co-operate. Such co-operation was forthcoming at Cushing Veterans Administration Hospital at Framingham, Massachusetts. This paper is a report of an investigation on the relation between spinal-cord and cauda-equina injuries and sexual potency that has been carried out on these volunteers. A paper on sterility will follow.

### NEUROANATOMY AND PHYSIOLOGY

Despite the traditions and misinterpretations that have sprung up over the years the description of the neuroanatomy and neurophysiology of the activities of the generative apparatus as given by Starling<sup>1</sup> and Sherrington<sup>2</sup> are the basis of all later work. So far as the male is concerned they point out that in animals the sexual reflexes of erection and ejaculation are independent of suprasegmental connections. Erection takes place reflexly as the result of the active dilatation of the vessels of the penis and contraction of the ischiocavernosus muscle, with resultant compression of the dorsal veins of the penis. The vasa deferentia and the seminal vesicles in the cat, for example, are described as being supplied by the sympathetic nerves via the inferior mesenteric and hypogastric plexuses. Starling<sup>1</sup> says that "stimulation of these nerves excites strong contraction of the whole musculature of the vasa deferentia and seminal vesicles, which may be strong enough to cause emission of semen from the penis." The sympathetic system is not the only source of neural impulses, however, because the ischiocavernosus and bulbocavernosus and constrictor urethrae muscles, which not only are involved in the erection of the penis but also assist in the emission of the semen, are supplied by somatic neurones through the internal pudic nerves. The bladder is supplied through the parasympathetic system. They give the origin of these various connections as being in the lumbar and sacral portions of the cord.

So far as man is concerned, Woolsey<sup>3</sup> says no more than that "Priapism is common in high (cord) lesions especially when severe." Frazier and Allen<sup>4</sup> have no comments on this subject. Head and Riddoch<sup>5</sup> also have nothing to say about this aspect

\*From the Paraplegia Service, Cushing Veterans Administration Hospital, Framingham, Massachusetts, and the Department of Neurosurgery, Boston City Hospital.

Presented at the annual meeting of the New England Surgical Society, New Haven, Connecticut, October 1, 1948.

The conclusions and opinions expressed herein are the authors' own and do not necessarily represent those of the Veterans Administration or the United States Army.

†Assistant professor of neurosurgery, Harvard Medical School, associate professor of neurosurgery, Boston University School of Medicine, chief, Department of Neurosurgery, Boston City Hospital.

‡Assistant resident, Free Hospital for Women, formerly resident in surgery, Cushing Veterans Administration Hospital.

§Resident in surgery, Cushing Veterans Administration Hospital.

of cord injuries, nor does Wilson<sup>6</sup> Grinker<sup>7</sup> makes the statement that "fracture (of the first lumbar vertebra) [*sic*] produces loss of sexual function" Fulton<sup>8</sup> follows Sherrington, and Cobb and Coleman<sup>9</sup> deal with the return of sexual function in patients that recovered from spinal-cord injuries only from the point of view of time Kuntz<sup>10</sup> writes that in man the testicles, seminal vesicles, vasa deferentia and epididymis all receive their innervation from the sympathetic system The prostate and prostatic urethra, as well as the corpora cavernosa penis, are innervated by both the sympathetic and the parasympathetic and the corpora cavernosa urethrae and the penile urethra through the communications with the internal pudic nerves in addition He also notes that the voluntary muscles employed in the act of ejaculation—that is, the compressor urethrae and ischiocavernosus and bulbocavernosus muscles—are supplied through the branches of the internal pudic nerves The preganglionic and visceral afferent sympathetic fibers are described as components of the tenth and higher thoracic (up to the sixth) nerves The parasympathetic and internal pudic central connections are said to be through the second, third and fourth sacral segments Kuntz states further

Our knowledge of the role of nerve impulses in the regulatory control of the functions of the male sex organs is based mainly on the findings of the early physiologists The results of animal experimentation however clearly indicate that reflex erection is mediated through centers in the lumbar and sacral segments of the spinal cord and another in the lumbar cord which mediates reflex ejaculation

In general, his conclusions are in agreement with those of Starling and Sherrington cited above, but he leaves the impression that he predicates an ejaculatory center in the lumbar portion of the cord in man He does note however, that "In man voluntary inhibition also plays an important role in sexual excitability and under normal conditions is the controlling factor in sexual behavior"

White and Smithwick<sup>11</sup> quote Kuntz and the older physiologists but in addition point out that Simeone<sup>12</sup> demonstrated in man that if those sympathetic nerves which, when stimulated, cause contraction of the vasa deferentia and the seminal vesicles were paralyzed viable spermatozoa no longer reached the seminal vesicles They also quote Learmonth<sup>13</sup> to the effect that after removal of the superior hypogastric plexus or injury to the first lumbar ganglions the power of ejaculation is lost although the operation does not impair the power of erection or the sensation of orgasm Thus, an abdominal sympathectomy would produce this result They state that in man the central site of the parasympathetic neuron cells is in the anterior horns of the second, third and fourth sacral segments and that the sympathetic preganglionic cells lie in the lower thoracic and upper lumbar levels of the intermediolateral column The somatic connec-

tions are through the anterior horns and the posterior and lateral columns of the second, third and fourth sacral segments

It may be concluded from this evidence that in animals the act of erection is reflex and accomplished by engorgement of vessels of the penis aided by contraction of certain periurethral muscles The nerves involved are the sympathetic and the somatic, and there is said to be a center for erection in the lumbar and sacral portions of the cord Ejaculation takes place reflexly as the result of contraction of the musculature of the vasa deferentia and seminal vesicles aided by voluntary contraction of periurethral muscles The nerves involved are the sympathetic and the somatic, and there is said to be a center for ejaculation in the lumbar portion of the cord The sympathetic connections for these two acts are through the lumbar portion of the cord

In conformity with these data the present opinion appears to be that in men erection takes place as the result of parasympathetic stimulation of the appropriate arterioles, with resultant engorgement of the corpora cavernosa and corpus spongiosum Associated with this there is compression of the efferent veins of these structures by at least the bulbocavernosus and ischiocavernosus muscles The reflex is initiated by either tactile stimuli locally or as the result of psychic stimuli The neural impulses pass both ways over the parasympathetic nerves and the somatic internal pudic nerves The central-nervous-system center lies in the second, third and fourth sacral segments "Ejaculation is not a necessary accompaniment of erection [It is] essentially a reflex reaction" In normal healthy persons the discharge of seminal fluid is elicited only by stimulation of the glans There is thought to be a summation of impulses, which occurs in the spinal cord "When such summation has reached the threshold level a sudden discharge of afferent impulses takes place which calls forth sudden contraction of the smooth musculature of the entire sexual apparatus resulting in the propulsion of seminal fluid into the urethra"<sup>10</sup> Afferent impulses reach the spinal cord over the internal pudic nerves, and efferent impulses travel over the sympathetic nervous system by way of the upper lumbar communicating rami and the hypogastric nerves The presence of seminal fluid in the urethra sets up another reflex with resulting contraction of the constrictor urethrae, bulbocavernosus and ischiocavernosus muscles—all striated and voluntary muscles innervated by the somatic internal pudic nerves The spinal-cord segments that are involved are the second, third and fourth sacral and the upper lumbar In the course of the ejaculatory act the prostate is stimulated, its secretion is added to the semen in the prostatic urethra, and the internal vesicle sphincter contracts, blocking off the bladder<sup>14</sup> Sexual orgasm is associated with

ejaculation and constitutes the sensations caused thereby. It is not known how or where these sensations arise. It need not be assumed that they reach the cerebral cortex. They do, however, give rise to reactions in other visceral organs and the excitation apparently spreads throughout the autonomic nervous system. They also give rise to somatic reflexes in addition to those activating the penurethral muscles and produce spastic contractions of the extensor muscles of the lower extremities.<sup>10</sup>

### MATERIAL

Eighty-four of the paraplegic and paraparetic patients at Cushing Veterans Administration Hospital volunteered for this investigation. Their ages ranged from twenty-one to forty years. In addition certain data on priapism collected over the years by one of us from a personal series of some 320 civilian injuries of the spinal cord and cauda equina have been included. Table 1 shows the distribution of the Veterans Administration cases by level and diagnosis. Seventy of these 84 patients were interviewed personally. Information regarding the other 14 was obtained by letter. Patients diagnosed as suffering from a transection have been divided into two groups, depending upon the accuracy of verification of the diagnosis. In those diagnosed as Anatomic-Visualized Transection (Tr-A) the injury has been actually seen at laminectomy to be one in which there is a complete separation of the cut ends of the cord. In those diagnosed as Clinical-Not Visualized Transection (Tr-C) either the cord injury has not been seen or, if seen, the continuity of the cord was found to be either grossly intact or maintained by intervening scar tissue. The character and length of the clinical course taken by the patients, however, have justified the diagnosis of transection. In both instances, only patients with a complete sensory and voluntary motor loss of function below the level of the cord injury are included as cord transections. Patients diagnosed as suffering from a Partial Cord Injury (P) are those in whom it has been possible to demonstrate some degree of retention of either sensation or voluntary motion, or both in the body and extremities below the level of maximal cord injury. The same diagnostic criteria have been applied to patients with cauda equina (CE) injuries.

The problems of erection, ejaculation and the patient's ability to impregnate his wife were studied in relation not only to the type and level of cord injury but also to how these functions had been affected by anterior dorsolumbar rhizotomy. The significance of certain analogous functions in the interpretation of loss or retention of sexual capacity has also been considered from the point of view of the innervation of the reproductive organs and has been investigated in terms of anal reflex and

type of bladder response to cystometric studies.<sup>15</sup> The figures for these various data are included in Tables 2 and 3.

### Effects of the Type of Cord and Cauda-Equina Injury

*On erections.* Sixty-two or 74 per cent, of the 84 patients had erections after injury. It made no difference so far as the presence of erections was concerned whether the spinal cord or cauda equina was transected or the seat of a partial injury only. One patient with a partial lesion at the level of the

TABLE 1 *Distribution of Cases by Diagnosis and Level of Injury*

DIAGNOSIS	LEVEL OF INJURY				TOTAL
	CERVICAL	THORACIC	LUMBO-SACRAL	CAUDA EQUINAL	
Transection					
Anatomic visualized	0	27	2	0	29
Clinical not visualized	1	14	4	1	20
Partial injury	5	1	11	6	23
Totals	6	54	17	7	84

fifth lumbar and first sacral segments and another with a transected cauda equina had no erections. Otherwise the level of injury had no effect on this phenomenon.

*On ejaculations.* Only 8 or 7 per cent of the 84 patients had ejaculations after injury. Only 1 patient with a verified anatomic transection of the cord or cauda equina had an ejaculation. Two patients with clinically diagnosed transection of the thoracic cord, however, as well as 4 patients with partial lesions of the cord and 1 with a partial lesion of the cauda equina did have ejaculations after injury. So far as our experience goes both a transection and a partial injury of the cord will diminish but not eliminate the possibility of ejaculations.

*On ability to impregnate.* Two patients succeeded in impregnating their respective wives after injury. One is reported in detail below. He unquestionably had a transection. There is still a total loss of all sensation and voluntary motion below the sixth thoracic dermatome, his bladder and bowel are reflex and he has involuntary flexor-adductor-extensor muscle spasms of both legs, his abdomen and his back. His clinical condition has not changed for three and three-fourths years. He is able to have intercourse, and has no sensation of orgasm but has an increase in the spasms of his legs and abdomen during ejaculation. He impregnated his wife nineteen months after his injury. The other patient who succeeded in impregnating his wife had a partial injury of the cord at the level of the fifth cervical dermatome. In addition a patient with an anatomic transection at the eleventh and twelfth dorsal segments claims to be able to have intercourse.

From these figures it can at least tentatively be concluded that erections occur after an injury to the cord or cauda equina, regardless of whether either is transected or the seat of only a partial injury, that it is possible for a patient with a transected cord to have ejaculations, that as far as this small series goes, he will have slightly less than 1 out of 10 chances of having ejaculations regardless of the kind of injury, and that neither a transection

be considered competent. For one thing, there are too many uncontrolled psychologic factors with unpredictable influences on such a function.

*On erections* An indication of the effect of this operation on erections can be obtained, however, by a comparison of the known occurrence of this function in patients with and without rhizotomy (Table 2). Twenty-nine, or 34 per cent, of the 84 patients in this series had had anterior rhizotomies,

TABLE 2 *Effect of Anterior Rhizotomy on Erections in Patients with Injuries at Various Levels of the Spinal Cord*

CLASSIFICATION	INJURY OF CERVICAL SEGMENTS				INJURY OF THORACIC SEGMENTS				INJURY OF LUMBOSACRAL SEGMENTS				INJURY OF CAUDA EQUINA				INJURIES AT ALL LEVELS				PERCENTAGE
	ANATOMIC	CLINICAL	PARTIAL	TOTAL	ANATOMIC	CLINICAL	PARTIAL	TOTAL	ANATOMIC	CLINICAL	PARTIAL	TOTAL	ANATOMIC	CLINICAL	PARTIAL	TOTAL	ANATOMIC	CLINICAL	PARTIAL	TOTAL	
Patients with anterior rhizotomy	0	0	0	0	16	6	7	29	0	0	0	0	0	0	0	0	16	6	7	29	34
Erections present	0	0	0	0	12	5	7	24	0	0	0	0	0	0	0	0	12	5	7	24	83
Erections absent	0	0	0	0	4	1	0	5	0	0	0	0	0	0	0	0	4	1	0	5	17
Patients with no rhizotomy	1	0	5	6	13	8	6	27	1	4	11	16	0	1	6	7	15	13	28	56	66
Erections present	1	0	5	6	7	6	5	18	0	2	5	7	0	0	5	5	8	8	20	36	64
Erections absent	0	0	0	0	6	2	1	9	1	2	6	9	0	1	1	2	7	5	8	20	36
Totals	1	0	5	6	29	14	13	56	1	4	11	16	0	1	6	7	31	19	35	85	

nor a partial injury of the cord is necessarily a bar to the patient's ability to impregnate his wife.

#### *Effect of Anterior Dorsolumbar Rhizotomy*

Some patients have claimed that the frequency of their erections has been altered for the worse after an anterior dorsolumbar rhizotomy. On the other hand, others have said that the operation has had no such effect, and one has unequivocally stated that whereas before operation he had been unable to produce an erection, erections not only occurred spontaneously but also could be elicited by local stimulation after operation. The operation if properly done divides all the lumbar together with the tenth, eleventh and twelfth thoracic and first sacral anterior roots. Since the division is carried out intrathecally the autonomic as well as the somatic connections made by those roots between the periphery and the central nervous system may be cut. On the other hand, the somatic and parasympathetic segmental nerve supply to the pelvic and reproductive organs is completely spared. It is anatomically possible for either of the above claims to be correct, provided that the observations are competent. In this instance, however, the observations by the patients cannot

22 having suffered from transections and 7 being classed as partial lesions of the cord. All the rhizotomies were done on patients with injuries to the thoracic portion of the cord. Twenty-four, or 83 per cent, had erections before and after operation. Five patients had erections before but not after a rhizotomy. In 3 marked uncontrollable oozing of blood accompanied in 2 by extensive adhesive arachnoiditis and difficulty in identifying the roots to be sectioned may be considered adequate cause for an abnormally extensive denervation with resultant loss of erections. No reason is apparent or can be found to account for the loss of erections in the other 2. Fifty-six, or 66 per cent, did not have a rhizotomy, and 36 (64 per cent) of these patients had erections. Failure to have an erection after rhizotomy, therefore, cannot be traced mathematically to the effect of the operation per se.

Of the 7 patients with partial transections who had had rhizotomies, 1 had been operated upon elsewhere. He had sensation but is said to have had no motion at any time below the level of injury, which was at the eleventh thoracic segment. One had sensation and motion below the cord-injury level at the fourth thoracic segment but

had such severe spasms that rhizotomy with its flaccid paralysis was preferred to the retention of motion with its necessary accompaniment of spasm. In another with an injury at the eighth thoracic segment the voluntary motion was limited to slight activity in the toes only. Sensation was present but reduced. The other 4 patients never had any voluntary motion below the level of the cord injury at any time. Sensation was present

*On ejaculation* The effect of anterior dorso-lumbar rhizotomy on the occurrence of ejaculations is less apparent. Eight of the 84 patients had ejaculations. Five of these had partial injuries at the fifth cervical, twelfth thoracic, second and fifth lumbar segments and the cauda equina, respectively, and 3 had transections at the second, sixth and eighth thoracic segments, respectively. None of these had had a rhizotomy. Twenty-eight

TABLE 3 *Effect of Spinal-Cord Injury on Various Functions*

CLASSIFICATION	INJURY OF CERVICAL SEGMENTS				INJURY OF THORACIC SEGMENTS				INJURY OF LUMBOSACRAL SEGMENTS				INJURY OF CAUDA EQUINA				INJURIES AT ALL LEVELS				PERCENTAGE
	ANATOMIC	CLINICAL	PARTIAL	TOTAL	ANATOMIC	CLINICAL	PARTIAL	TOTAL	ANATOMIC	CLINICAL	PARTIAL	TOTAL	ANATOMIC	CLINICAL	PARTIAL	TOTAL	ANATOMIC	CLINICAL	PARTIAL	TOTAL	
Patients with erections	1	0	5	6	21	11	12	44	0	2	5	7	0	0	5	5	22	13	27	62	74
Patients with ejaculations	0	0	1	1	1	2	1	4	0	0	2	2	0	0	1	1	1	2	3	8	7
Patients producing pregnancy	0	0	1	1	0	1	0	1	0	0	0	0	0	0	0	0	0	1	1	2	3
Patients with anal reflex	1	0	5	6	23	12	11	46	0	1	2	3	0	0	1	1	24	13	19	56	67
Patients without anal reflex	0	0	0	0	3	2	2	7	1	3	9	13	0	1	5	6	4	6	16	26	31
Atonic bladder	0	0	0	0	2	0	0	2	0	0	0	0	0	0	0	0	2	0	0	2	2
Autonomous bladder	0	0	0	0	3	2	2	7	1	3	9	13	0	1	5	6	4	6	16	26	31
Reflex bladder	1	0	5	6	21	12	11	44	0	1	2	3	0	0	0	0	22	13	16	51	44
Normal bladder	0	0	2	2	0	0	0	0	0	0	0	0	0	0	1	1	0	0	3	3	4

but impaired in these cases. The levels of the injuries were the first thoracic segment in 2 cases and the seventh and eighth thoracic segments in the other 2.

The levels of injury in the patients with transected cords who had erections were the second (1 case), second and third (1 case), third (2 cases), third, fourth and fifth (1 case), fourth (1 case), fifth (1 case), sixth (2 cases), sixth and seventh (1 case), seventh and eighth (1 case), eighth (3 cases), ninth (2 cases), ninth and tenth (1 case), tenth (1 case) and twelfth (1 case) thoracic segments. Two others — both transections, one at the tenth and the other at the tenth and eleventh thoracic segments — did not have erections either before or after rhizotomy. One patient with a transection at the fifth dorsal segment had no erections after a second rhizotomy.

It should be noted that there were examples of loss of both motion and sensation and loss of motion with retention of sensation among the patients who had erections after rhizotomy and that virtually all the thoracic segments of the cord were involved. It appears that the proper performance of an anterior dorsolumbar rhizotomy will not affect the occurrence of erections.

other patients had rhizotomies but have not had ejaculations at any time either before or after the operation. They include the 22 thoracic transections and the 7 partial lesions described in detail above. It is impossible to decide on this evidence whether an anterior dorsolumbar rhizotomy, if properly performed, will or will not prevent ejaculations. What evidence there is seems to favor the view that the operation will not affect their occurrence.

*On pregnancy* Neither of the patients that had produced a pregnancy had had a rhizotomy.

SEGMENTAL INNERVATION OF THE MALE ORGANS OF GENERATION

“Reflex erection in animals is mediated through centers in the lumbar and sacral segments of the spinal cord and ejaculation through another in the lumbar cord.”<sup>10</sup> In man the demonstration of an anal reflex establishes the integrity of the internal pudic nerves — a somatic connection — and their sensory and motor distribution. The presence of a reflex bladder confirms this and also demonstrates the integrity of the parasympathetic plexuses and their central and peripheral connections. These neural pathways are known to have their central

connections in the sacral portion of the cord. It is impossible on the available evidence to be certain of the functions mediated by the sympathetic connections to the pelvic and genital organs in man even though there is increasing evidence that, in some patients at least, disorganization of sympathetic responses throughout the body is connected with distention of the bladder.<sup>16</sup> These neural pathways are known to have their central connections in the lumbar portion of the cord. If the above statements hold true and experimental evidence in animals can be applied to man, erections in human beings should occur whenever the lumbar and sacral segments and their somatic and anatomic connections can be shown to be uninjured. They should be absent when the reverse is true—that is, when the anal reflex is absent, and the bladder is atonic or autonomous or the sphincter atonic.

Six cervical, 40 thoracic (29 transections and 11 partial injuries) and 2 lumbar injuries (1 transection at the second and 1 partial injury at the first lumbar segment) had an anal reflex and either normal or reflex bladders (Table 3). All these patients had erections. On the other hand, 4 patients with transections at the third, sixth and seventh, tenth and tenth and eleventh thoracic segments, 1 with a partial injury at the first lumbar segment and 1 with a partial cauda-equina injury also had anal reflexes and reflex (5) or autonomous (1) bladders but did not have erections. It is thus apparent that with intact somatic and parasympathetic neural connections between the pelvic and reproductive organs and the sacral segments erections were present in 48 and did not occur in 6 cases. Moreover, despite evidence of both transection and partial injury to the thoracic and lumbar segments of the cord erections did occur.

Eleven patients who did not have an anal reflex and had atonic (1) or autonomous (10) bladders had erections as follows: 1 with a partial injury at the twelfth thoracic segment, 1 with a transection at the first lumbar segment, 4 with partial injuries at the first, second, third and fifth lumbar segments, and 5 with partial lesions of the cauda equina. Thus in 11 cases in which the evidence is unquestionably in favor of at least partial denervation of the pelvic and reproductive organs by major damage to their central connections, including virtually all the lumbar segments as well as the cauda equina, erections were nevertheless present. Twelve other patients—3 with transections at the fifth and sixth, sixth and eleventh thoracic segments, respectively, 1 with a partial injury at the twelfth thoracic segment, 3 with transections at the first thoracic segment, and 5 with partial injuries at the twelfth thoracic and first lumbar, first, second and third lumbar and fifth lumbar and first sacral segments gave evidence of interrupted parasympathetic and

somatic connections in that they had no anal reflex and atonic (1) and autonomous (11) bladders. They also had no erections. Attention is again called to the 28 patients with transections of the thoracic segment and the 7 with partial injuries of the thoracic segments who had rhizotomies. In all the patients with transections the pelvic and reproductive organs were cut off not only from all suprasegmental connections but also from the motor side of the lumbar cord. All but 1 of these patients had an anal reflex, and all but 3 (2 autonomous and 1 chemical cystitis) reflex bladders. All but 5 had erections. The same observation held true in the partial injuries so far as the anal reflex and the bladder went. Moreover, sensation in the body and extremities below the upper level of cord injury was present to some extent. All these patients had erections. On this evidence, therefore, it appears that in man erections may or may not occur in the presence of intact somatic and parasympathetic segmental connections between the central nervous system and the pelvic and reproductive organs. Furthermore, an intact lumbar cord and its motor connections are not necessary for their production. Clinical absence of such connections as evidenced by an absent anal reflex and an atonic or autonomous bladder is not necessarily a bar to the presence of erections.

The same criteria can be used to measure the integrity of these neural connections in relation to the occurrence of ejaculations. As noted above, ejaculations were absent in all but 8 cases. One patient with a partial lesion of the fifth cervical segment, 3 with transecting lesions of the second, sixth and eighth thoracic segments, 1 with a partial lesion of the twelfth thoracic segment, 2 with partial lesions of the second and fifth lumbar segments, and 1 with a partial lesion of the cauda equina had ejaculations. None had had a rhizotomy. The patient with the cervical lesion and the 3 with thoracic transections had reflex, but all the rest had autonomous bladders. Six of these patients had had an anal reflex, which was absent in the others. The patients with partial injury at the fifth cervical and transection at the sixth thoracic segment impregnated their wives. Patients with injuries similar in level and pathology and with both absent and present anal reflexes, as well as both reflex and autonomous bladders and with and without rhizotomies, did not have ejaculations. If it is true that to have an ejaculation the periurethral muscles must be innervated and at least reflexly active by way of the internal pudic nerves and if there is no other strictly anatomic factor involved, only patients with totally destructive lesions of the sacral or at most the lumbosacral segments of the cord or with transecting or totally destructive lesions of the cauda equina should be unable to have ejaculations. Thus, none of these patients in this series

who had ejaculations would necessarily be deprived of that ability (since they had only partial lesions) It is impossible to be certain in any given cord injury, however, how far below the level of maximum damage the lesion has extended A level at the first lumbar segment, for example, may have produced changes that are undemonstrable clinically at any point down to the tip of the conus Such a hypothesis would account for the fact that 2 patients with signs of transection at the tenth and eleventh thoracic segments, respectively, and 1 with a partial lesion at the twelfth thoracic segment had absent anal reflexes, autonomous bladders and no ejaculations At least one of them (at the eleventh thoracic segment) was known to have an extensive atrophy of all the cord below the level of transection On the other hand, 2 patients with verified transections at the sixth and seventh and tenth and eleventh thoracic segments, as well as 1 with a clinical transection at the tenth thoracic segment, also had no ejaculations but *did* have an anal reflex and reflex bladders It appears that, unlike the function in animals, the ability to have an ejaculation in man does not rest solely on an intact upper lumbar segment of the cord

PRIAPISM

Priapism "persistent abnormal erection of the penis, usually without sexual desire"<sup>17</sup> There is a medical tradition — undocumented to be sure — that priapism may be expected constantly to accompany severe cervical cord injuries In times past, this relation has been considered to be of diagnostic significance An analysis of 320 injuries of the spinal cord and cauda equina demonstrates that these beliefs are not in accordance with the facts A note regarding the presence of priapism was made in 221 male patients of the total series of 320 There were 122 injuries of the cervical segments, 46 of the thoracic, 21 of the lumbosacral and 34 of the cauda equina Priapism was present in 22 or 10 per cent. It was most common in the cervical group, appearing in 17 cases, or 14 per cent It was also present in all the other groups as follows thoracic, 3 out of 46, or 6.5 per cent, lumbosacral, 1 out of 21, or 5 per cent, and cauda equina, 1 out of 34, or 3 per cent It is undoubtedly of pathologic significance when it does occur It is apparent from these figures that priapism may occur in association with a spinal-cord or cauda-equina injury at any level It occurs most frequently as an accompaniment of cord injuries of the cervical segment but not frequently enough to be of any diagnostic significance

CASE REPORT

Because of its importance to other paraplegic patients the following account of a paraplegic patient's successful impregnation of his wife is included The details have been furnished by the

couple, and the text that follows has been reviewed by them and has their approval

This patient, now 27 years of age, was injured in October, 1944, by a bomb fragment, which struck him in the region of the sixth and seventh thoracic vertebrae As a result he developed a complete motor and sensory paralysis below the level of the xiphoid A laminectomy was performed in September, 1945, and the cord was described in the report of this operation as being discolored and closely adherent to the surrounding scarred dura but without obvious anatomic transection There has been no return of function since the injury

Before and after this laminectomy he had moderately severe leg and abdominal spasm, for which rhizotomy had been recommended and refused

Three months after the injury his urethral catheter, which he had worn till then, was removed He has been able to void since then by manual compression of the bladder but maintains nevertheless, varying amounts of residual urine A transurethral resection of the internal sphincter was advised but refused

About 1 month after injury he began to have spontaneous erections lasting from 1 to 20 minutes They had no relation to cerebral activity The patient then discovered that erections could be caused by local stimulation of the penis About 10 months after injury he attempted masturbation for the first time After this stimulation he obtained a brownish-red ejaculate A week later he repeated the procedure with essentially the same result Since then ejaculations have been described as being normal in appearance, substance and quantity During ejaculation, the patient's spasms increase momentarily, but no other sensation occurs

He was married to a nurse, aged 25 years, in May, 1946 Intercourse was timed to correspond with his wife's periods of intermenstrual pain (Mittelschmerz) His wife's last menstrual period prior to delivery began on May 31, 1946, and she was delivered of a normal, full-term child on March 1, 1947

DISCUSSION

When the material that has been collected as the result of this study (Table 4) is applied to the few observations hitherto made on man and to the deduc-

TABLE 4 Effect of Injuries at Various Levels on Erections and Ejaculations

	TRANSECTIONS ONLY			
	T1*	Yes	No	
Erections present in patients with injury between	T6	Yes	No	Conus
Ejaculations present in patients with injury between	T2	Yes	No	Conus
Erections present in patients with injury between	ALL CASES			L5
	C4	Yes	No	
Ejaculations present in patients with injury between	C4	Yes	No	Cauda equina
	C4	No		Cauda equina

\*The letters and figures refer to spinal-cord segments.

tions made from animal experiments, it is evident that except for certain details the mechanism of erection and ejaculation as described by Kuntz is correct.

Erections

It is apparent from our series and from earlier studies of bladder innervation that erection takes place on a purely segmental-reflex basis and that suprasegmental connections are unnecessary In paraplegic patients the afferent sensory impulses that initiate the reflex are caused by tactile stimula-

tion of the glans and travel to the second, third and fourth sacral segments by way of the internal pudic nerves. Efferent impulses leave these same segments by way of the parasympathetic supply and cause dilatation of the arterioles of the penis, with distention and congestion of the corpora cavernosa and spongiosum. In addition, efferent impulses leave the same segments over the internal pudic nerves to cause contraction of the periurethral muscles, with resultant compression of the venous drainage channels of the penis.

Our series indicates that destruction of the sacral segment of the cord or transection and destruction of the cauda equina and the pelvic parasympathetic plexuses are the only neurologic, anatomic lesions that will prevent the occurrence of erections. Associated with such absence will be an autonomous bladder, an absent anal reflex and possibly atonic urethral sphincters. Erections occur in the presence of all other cord injuries, whether partial or transecting, and regardless of the level involved.

### *Ejaculations*

Our series indicates that ejaculation is basically a complex purely spinal segmental reflex function. Suprasegmental connections are not necessary for the act. Our findings differ from those of Kuntz and others in that we believe our evidence indicates that destruction or maintenance of the low thoracic and high lumbar sympathetic central connections is the important link in this particular neurologic chain. In this connection we have demonstrated that ejaculations were absent in 28 low thoracic and upper lumbar transections between the sixth thoracic and third lumbar segments. Moreover, of those patients in whom ejaculations were present the injury, except in 1 patient with a transection at the eighth thoracic segment, was outside this area. Two patients, 1 with a transection of the sacral segment and another with a transection of the cauda equina, as well as a patient with a partial lesion at the fifth lumbar segment, had no ejaculations. Otherwise identical cord injuries produced ejaculations in 1 case but not in another.

We interpret these data to mean that to prevent ejaculations the cord damage must be between the sixth thoracic and third lumbar segments and must be extensive within these limits. Since it may be accepted as fact that the impulses that control the first part of the ejaculatory act travel over the sympathetic nervous system, we believe that it is not so much the cord damage in general that acts as a preventive but rather its location and extent within the cord. In support of this contention, in part at least, we call attention to the fact that although no patient with a transection who had had ejaculations had had an anterior dorsolumbar rhizotomy, there were 54 patients who had not had a rhizotomy, as well as 28 who had, that had no ejaculations either before or after the operation.

Such rhizotomies divide all efferent sympathetic connections from the eleventh dorsal through the first sacral segment, and may effectively prevent ejaculation. On the other hand, the tremendous overlap of the sympathetic supply is well known and might serve to maintain neurologic connections between the central nervous system and the smooth musculature of the seminal vesicles, the vasa deferentia and the ejaculatory ducts in spite of such widespread sympathetic denervation.

The second step in ejaculation is also basically reflex, is initiated, according to Kuntz and others, by the sensory impulses set up by the presence of semen in the posterior urethra and sets off efferent impulses, which innervate the periurethral muscles and which result in the actual ejaculation of the semen from the meatus. These afferent and efferent impulses travel over the internal pudic nerves by way of the second, third and fourth sacral segments. As would be expected, the patients with transections of the sacral segments and the cauda equina had no ejaculations.

Our evidence indicates that ejaculations will be prevented by a destructive lesion of the sacral segments of the cord or a transecting lesion of the cauda equina. If the damage is extensive enough and properly placed in the cord ejaculation will also be prevented by either transecting or partial injuries of the cord between the sixth thoracic and third lumbar segments, depending upon the degree of destruction of the sympathetic components in this area of the cord. Complete detachment of the sympathetic system from the anterior aspect of the cord between the eleventh thoracic and first sacral segments may or may not prevent ejaculation, the evidence being inconclusive at present. There is no "center" for ejaculation in the lumbar portion of the cord or anywhere else.

### *The Orgasm*

We have no data on the occurrence of an orgasm in connection with ejaculation except in the case reported above in detail. This suggests that a thoracic transection will do away with the sensation of orgasm and that orgasm of the male is not essential for successful impregnation.

### *Sterility*

To impregnate successfully, the semen must have an adequate count of viable motile spermatozoa. The question arises whether or not spinal-cord injuries affect this aspect of the problem. It is known that the spermatozoa are stored in the seminal vesicles, having been transferred there by the ciliary action of the vas deferens. It is not known whether muscular contractions are necessary in addition. In any event, it appears to be true that any strictly neural activity that takes place does so by way of the sympathetic system, which is known to supply the vasa, the vesicles, the prostate and ejaculatory

ducts. A more detailed study of this aspect of the problem will follow in a later paper.

### CONCLUSIONS

It seems reasonable to conclude until more extensive studies can be made that, unless he has a destructive lesion of the sacral cord, a transection of the cauda equina or injury to the cord between the sixth thoracic and third lumbar segments extensive enough to interrupt completely the thoracolumbar sympathetic outflow, a patient can and should be potent—that is, he should be able to have erections and to ejaculate—and that unless other abnormalities prevent it, he will be fertile and capable of producing pregnancy.

### REFERENCES

- 1 Starling E. H. Muscular mechanisms of generative apparatus. In *Textbook of Physiology*, Edited by E. A. Schaefer. 2 vol. New York Macmillan 1900 Vol 2 P 347
- 2 Sherrington, C. S. Spinal cord. In *Textbook of Physiology*, Edited by E. A. Schaefer. New York Macmillan 1900 Vol 2 P 765
- 3 Woolsey G. Surgery of spine. In *Surgery Its principles and practice* Vol 2, 920 pp Philadelphia W. B. Saunders Co 1915 Pp 816-883
- 4 Frazier C. H. and Allen H. R. *Surgery of the Spine and Spinal Cord*. 971 pp New York D. Appleton & Co 1915
- 5 Head H. et al. *Studies in Neurology*. 2 vol London Oxford University Press 1920 Vol 2 P 467
- 6 Wilson S. A. *Neurology*. Edited by A. Ninian Bruce. 2 vol 1838 pp Baltimore Williams & Wilkins 1940
- 7 Ginker R. R. *Neurology*. 979 pp Baltimore Charles C Thomas 1944 P 778
- 8 Fulton J. F. *Physiology of the Nervous System*. Second edition 614 pp New York Oxford University Press 1945
- 9 Cobb S. and Coleman C. C. Course of recovery following trauma of spinal cord. *Arch Surg* 3 132-139 1921
- 10 Kuntz A. *The Autonomic Nervous System*. Third edition 687 pp Philadelphia Lea & Febiger 1945
- 11 White J. C. and Smithwick R. H. *The Autonomic Nervous System Anatomy, Physiology and surgical application*. Second edition 469 pp New York Macmillan 1941
- 12 Simeone F. A. Neuromuscular mechanism in ductus epididymis and its impairment by sympathetic denervation. *Am J Physiol* 103 382-391 1932
- 13 Learmonth J. R. Cited by White and Smithwick.<sup>11</sup>
- 14 Lowsley O. S. and Karwin T. J. *Clinical Urology*. Second edition 2 vol 1791 pp Baltimore Williams and Wilkins Co., 1944
- 15 Munro D. Rehabilitation of patients totally paralyzed below waist with special reference to making them ambulatory and capable of earning their living. II. Control of urination. *Ver Eng J Med* 234 207-216 1946 III. Tidal drainage cystometry and bladder training. *Ibid* 236 225-235 1947
- 16 Thompson C. E. and Witham, A. C. Paroxysmal hypertension in spinal-cord injuries. *Ver Eng J Med* 239 291-294 1948
- 17 Dorland, W. A. *The American Illustrated Medical Dictionary*. Twenty-first edition 1660 pp Philadelphia W. B. Saunders Co 1947 P 1115

## OBSERVATIONS ON THE ETIOLOGIC RELATIONSHIP OF ACHYLIA GASTRICA TO PERNICIOUS ANEMIA\*

### X Activity of Vitamin B<sub>12</sub> as Food (Extrinsic) Factor

LIONEL BERK, M.D.,† WILLIAM B. CASTLE, M.D.,‡ ARNOLD D. WELCH, M.D.,§ ROBERT W. HEINLE, M.D.,||  
RUDOLF ANKER, Ph.D. || AND MARTIN EPSTEIN, M.D.\*\*

BOSTON, MASSACHUSETTS, AND CLEVELAND, OHIO

IT HAS been shown that various foods—for example, beef skeletal muscle,<sup>1</sup> milk<sup>2</sup> and eggs<sup>3</sup>—contain a heat-stable, unidentified substance,<sup>4</sup> the so-called extrinsic factor. When such a source of extrinsic factor as beef muscle is ingested by a patient with pernicious anemia, untreated or in relapse, it produces little or no hematopoietic effect unless normal human gastric juice is also administered, either simultaneously or at least within six hours.<sup>5</sup> The very small amount of the gastric secretion of the patient with pernicious anemia thus apparently supplies little or none of the heat-labile

substance, possibly an enzyme,<sup>6-8</sup> that is responsible for the activity of the so-called intrinsic factor of normal human gastric juice when administered with beef muscle. Gastric juice when given without opportunity for contact with beef muscle or with components of an unrestricted diet possesses no hematopoietic power.<sup>5</sup> Despite claims to the contrary,<sup>9</sup> incubation of mixtures of beef muscle and gastric juice does not produce the heat-stable, antipernicious-anemia principle of liver *in vitro*.<sup>6</sup> Although there is reason to believe that contact between beef muscle and gastric juice at or near a neutral reaction within the intestinal tract is required for hematopoiesis,<sup>6</sup> attempts to concentrate hematopoietic substances from incubated mixtures of beef muscle and gastric juice have given inconsistent results at best. These observations are compatible with the theory that the patient with pernicious anemia requires intrinsic factor to utilize extrinsic factor at some stage in the production of the antipernicious-anemia principle of liver, but that a direct reaction between extrinsic and intrinsic factors does not necessarily occur.

Extrinsic factor is presently recognizable only by virtue of its hematopoietic potency upon oral administration in pernicious anemia with normal

\*From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School, and the Departments of Pharmacology and Medicine, School of Medicine, Western Reserve University, and the University Hospitals.  
The expenses of this investigation were in part defrayed by the J. K. Lilly gift to Harvard Medical School and by a grant from the United States Public Health Service to Western Reserve University.

†Deceased; formerly research fellow in medicine, Harvard Medical School, and research fellow, Thorndike Memorial Laboratory, Boston City Hospital.

‡Professor of medicine, Harvard Medical School, director, Second and Fourth Medical Services (Harvard), and director, Thorndike Memorial Laboratory, Boston City Hospital.

§Professor of pharmacology, School of Medicine, Western Reserve University.

||Associate professor of medicine, School of Medicine, Western Reserve University.

\*\*Research fellow in pharmacology, School of Medicine, Western Reserve University.

\*\*Chief resident in medicine, University Hospitals, Cleveland, Ohio.

human gastric juice. Consequently, we have assumed as a working hypothesis that the greatly increased hematopoietic activity in pernicious anemia of liver<sup>10</sup> and of relatively crude liver extracts<sup>11</sup> when ingested with normal human gastric juice indicated the presence of both the extrinsic factor and the antipernicious-anemia principle. Recently, however, we have found that refined liver extracts when given by mouth are also potentiated in their hematopoietic activity by gastric juice, as shown by the following observation, which as conducted according to the methods referred to below.

A patient with pernicious anemia and an initial red-cell count of 2,540,000 was given 1 cc of solution of liver extract, purified (Lederle), containing

neutralized normal human gastric juice to each patient. The methods of dietary control, of obtaining normal human gastric juice and of blood study employed in these observations have previously been described,<sup>1, 5</sup> as has the interpretation of successive reticulocyte responses.<sup>15</sup> Particular attention was paid to administering the gastric juice at times as widely separated as possible from meals to minimize possible contact between the patient's food and the gastric juice. As an additional control on any hematopoietic effect of the gastric juice on the food, 3 patients (Cases 102, 103 and 104) received gastric juice during the first period twelve hours before each dose of vitamin B<sub>12</sub>.

As shown in Table 1, in each case a reticulocyte response was observed during Period II. Except in

TABLE 1 *Potentialization of Hematopoietic Activity of Orally Administered Vitamin B<sub>12</sub> by Normal Human Gastric Juice*

CASE No	TEN-DAY PERIOD No	RED CELL COUNT		RETICULOCYTE PEAK		DAILY THERAPY*
		INITIAL $\times 10^6$	FINAL $\times 10^6$	%	day	
101	I	1.56	1.91	5.7	8	5 gamma of vitamin B <sub>12</sub> † at 8 p m
	II	1.82	2.72	9.3	7	5 gamma of vitamin B <sub>12</sub> and 150 cc. of gastric juice at 8 p m
102	I	1.79	1.74	2.5	10	5 gamma of vitamin B <sub>12</sub> † at 8 a m. at 8 p m. 125 cc. of gastric juice
	II	1.65	2.45	16.7	7	5 gamma of vitamin B <sub>12</sub> and 150 cc. of gastric juice at 8 p m.
103	I	1.62	2.12	none	none	5 gamma of vitamin B <sub>12</sub> † at 8 a m. at 8 p m. 150 cc. of gastric juice
	II	1.90	2.54	3.8	8	5 gamma of vitamin B <sub>12</sub> and 150 cc. of gastric juice at 8 p m.
104	I	2.16	1.93	none	none	5 gamma of vitamin B <sub>12</sub> † at 9 a m. at 9 p m. 125 cc. of gastric juice
	II	2.14	2.10	3.8	10	5 gamma of vitamin B <sub>12</sub> and 125 cc. of gastric juice at 9 p m.
	III	1.91	2.57	14.0	8	5 gamma of vitamin B <sub>12</sub> intramuscularly

\*Given orally unless otherwise indicated.

†Suspended in 125 or 150 cc of physiologic saline solution.

15 USP units (injectable), daily by mouth for ten days. A reticulocyte peak of 3.4 per cent was attained on the seventh day. During a second consecutive ten-day period, the simultaneous administration of normal human gastric juice with the same amount of liver extract produced a second reticulocyte peak of 6.6 per cent at an initial red-cell level of 2,980,000. In other patients it was shown that hydrolysis of liver extracts with dilute sulfuric acid, which apparently destroyed most of the antipernicious-anemia principle, also prevented the material from being potentiated by normal human gastric juice.

With the isolation<sup>12</sup> of crystalline vitamin B<sub>12</sub>, which behaves so far as is now known like the classic antipernicious-anemia principle of liver,<sup>13, 14</sup> the effect of normal human gastric juice on the activity of the pure substance when orally administered could for the first time be tested. Accordingly, 5 microgm of vitamin B<sub>12</sub>\* dissolved in 125 or 150 cc of physiologic saline solution was given daily by mouth during a first ten-day period to 4 patients with untreated pernicious anemia. Immediately thereafter in a second ten-day period, the same amount of vitamin B<sub>12</sub> was given by mouth simultaneously with 125 or 150 cc of previously

Case 104, this was accompanied by a significant increase of red cells and indicates the greater hematopoietic effect of vitamin B<sub>12</sub> given simultaneously with normal human gastric juice. The reticulocyte peaks were not marked in Period II of Cases 103 and 104. However, no hematopoietic effect whatever was noted during Period I, and significant clinical improvement did not begin until the reticulocyte response appeared in Period II of the observations on these 2 patients. In Case 104, during Period III, 5 gamma of vitamin B<sub>12</sub> was given intramuscularly daily. This resulted in a striking second reticulocyte response.

## CONCLUSIONS

These observations indicate that the hematopoietic activity in pernicious anemia of orally administered vitamin B<sub>12</sub> is potentiated by the simultaneous administration of normal human gastric juice but, as with liver extracts, is not so great as the activity of the vitamin B<sub>12</sub> when given parenterally. It is suggested, therefore, that the food (extrinsic) factor may be identical with or closely related chemically to the antipernicious-anemia principle of liver, which is itself presumably identical with vitamin B<sub>12</sub>. It is further suggested that the gastric

\*Kindly supplied for clinical use by Dr. Augustus Gibson of Merck and Company Incorporated Rahway, New Jersey.

(intrinsic) factor is necessary for the optimal utilization of the relatively small amounts of vitamin B<sub>12</sub> or of chemically related substances present in various foods

Preliminary microbiologic findings with the use of *Lactobacillus leichmanni* (A T C C 4797) in an untreated patient with pernicious anemia suggest that the fecal elimination of vitamin B<sub>12</sub> is of such magnitude that either the vitamin derived from the food, or more probably that synthesized by intestinal bacteria, is not absorbed in sufficient amounts to abolish the deficiency (Since this manuscript was submitted for publication Bethell and his associates<sup>16</sup> have reported the results of microbiologic observations demonstrating large daily fecal excretions of vitamin B<sub>12</sub> in 4 cases of untreated pernicious anemia, and from this fact have drawn similar conclusions) Other observations suggest that material soluble in 70 per cent alcoholic extracts of beef muscle, a classic source of extrinsic factor, when prepared in a form suitable for parenteral administration, possesses both microbiologic activity as vitamin B<sub>12</sub> and hematopoietic activity upon intravenous injection in pernicious anemia. It is therefore possible that the function of the intrinsic factor of normal human gastric juice is to facilitate the absorption by the intestine of vitamin B<sub>12</sub> or of chemically related compounds in the food, rather than to react with the extrinsic factor as hitherto assumed

#### REFERENCES

- 1 Castle W B, and Townsend, W C. Observations on etiologic relationship of achylia gastrica to pernicious anemia. II. Effect of administration to patients with pernicious anemia of beef muscle after incubation with normal human gastric juice. *Am J M Sc* 178 764-777 1929
- 2 Miller F R and Pritchard W H. Presence in milk of extrinsic factor of Castle. *Proc Soc Exper Biol. & Med.* 37 149-152 1937
- 3 Singer K. Eiertherapie der perniziösen Anämie. *Wien. klin. Wchnschr* 45 1063 1932
- 4 Castle W B et al. Extrinsic factor in pernicious anemia. Ineffectiveness of purified casein and of identified components of vitamin B complex. *Science* 100 81 83 1944
- 5 Castle W B and Ham T H. Observations on etiologic relationship of achylia gastrica to pernicious anemia. V. Further evidence for essential participation of extrinsic factor in hematopoietic responses to mixtures of beef muscle and gastric juice and to hog stomach mucosa. *J A M A* 107 1456-1463 1936
- 6 Castle W B, Heath C W, Strauss M B and Heinle R W. Observations on etiologic relationship of achylia gastrica to pernicious anemia. VI. Site of interaction of food (extrinsic) and gastric (intrinsic) factors. Failure of *in vitro* incubation to produce thermostable hematopoietic principle. *Am J M Sc* 194 618-625 1957
- 7 Gessler C, J, Dexter S O, Adams M A and Taylor F H L. Observations on etiologic relationship of achylia gastrica to pernicious anemia. VIII. Further studies of proteolytic activity of normal human gastric juice *in vitro* and limitations of method in pernicious anemia. *J Clin Investigation* 19 225 251 1940
- 8 Agren G and Waldenström, J. Intrinsic factor activity of highly purified preparations of aminopolypeptidase. *Acta med Scandinav* 119 167-179 1944
- 9 Klein L and Wilkinson J F. Investigations on nature of haemopoietin, anti-anemic substance in hog's stomach. II. Production of thermostable haemopoietically active substance similar to or identical with anti-anemic principle of liver by action of thermostable haemopoietin on beef. *Biochem J* 28 1684-1692 1934
- 10 Reimann F and Fritsch F. Die Wirksamkeitssteigerung der Leber nach Behandlung mit Magensaft. II. Untersuchungen zur Leberwirkung bei der Anämia perniciosa. *Ztschr f klin Med* 126 469-484 1934
- 11 Fouts P J, Helmer O M and Zerfas L G. Quantitative studies on increased potency of liver extract by incubation with normal human gastric juice. *Ann. Int. Med.* 8 790-797 1935
- 12 Ricketts E L, Brink N G, Komposz F R, Wood, T R and Falkers K. Crystalline vitamin B<sub>12</sub>. *Science* 107 396 1948
- 13 West, R. Activity of vitamin B<sub>12</sub> in Addisonian pernicious anemia. *Science* 107 398 1948
- 14 Berk L, Denny-Brown D, Finland M L, and Castle W B. Effectiveness of vitamin B<sub>12</sub> in combined system disease: rapid regression of neurologic manifestations and absence of allergic reactions in patient sensitive to injectable liver extracts. *Ann Eng J Med* 239 328-330 1948
- 15 Minot G R and Castle W B. Interpretation of reticulocyte reactions: their value in determining potency of therapeutic materials especially in pernicious anaemia. *Lancet* 2 319-330 1935
- 16 Bethell F H, Meyers M C and Neligh R B. Vitamin B<sub>12</sub> in pernicious anemia and puerperal macrocytic anemia. *J Lab & Clin Med* 33 1477 1948

#### DIPHThERITIC MYOCARDITIS\*

NORMAN H BOYER, M D,† AND LOUIS WEINSTEIN, M D‡

BOSTON

DIPHThERIA has shown a striking rise in incidence over the entire world in the last five years. Although the rate of occurrence in the United States as a whole has remained at a static level during this period, some parts of the country have experienced a disturbing increase. In Massachusetts, for example, the number of cases has risen from 123 in 1941 to 439 in 1946 and 440 in 1947. This change, together with the prevalence of the disease in the armed forces in various areas of the world during the war, has aroused again an interest in the study of this infection. The purpose of this report is to re-emphasize the important effects of diphtheria on the heart as determined by electrocardiographic examination.

\*From the Haynes Memorial and the Evans Memorial, Massachusetts Memorial Hospitals, and the Department of Medicine, Boston University School of Medicine.

†Assistant professor of medicine, Boston University School of Medicine, visiting physician, Medical Service, Massachusetts Memorial Hospitals, Physician-in-charge, Cardiac Clinic, Massachusetts Memorial Hospitals.

‡Assistant professor of medicine, Boston University School of Medicine, instructor in infectious diseases, Harvard Medical School, physician and chief of service, Haynes Memorial and assistant member, Robert Dawson Evans Memorial, Massachusetts Memorial Hospitals.

The cases of diphtheria reported below occurred mainly in 1946 and 1947, some patients observed in the preceding two years and a few admitted in the early part of 1948 are included. During this period 140 patients with diphtheria were admitted to the Haynes Memorial Hospital (the Infectious Disease Department of the Massachusetts Memorial Hospitals), electrocardiograms were taken at periodic intervals in all cases. Casual electrocardiographic examination through the course of the disease was shown to be wholly inadequate because it was observed that changes might occur in the first few days of the disease or not until after several weeks and were not infrequently very transient. It became evident that, to demonstrate short-lived variations from the normal, electrocardiograms had to be made almost daily from the time of admission to the hospital until convalescence was well established. This point deserves special emphasis because without fre-

quently repeated studies a true estimate of the occurrence of diphtheritic myocarditis cannot be made. That such a practice is not widely adopted is borne out in the report of Kay and Livingood<sup>1</sup> on the cardiac complications of diphtheria of the skin. These investigators recommended that tracings be taken in mild cases about every two weeks until three weeks after the cutaneous lesions have begun to heal and every week or ten days until about seven weeks after the onset of the lesions in patients with severe cutaneous diphtheria.

In the beginning, our failure to appreciate the need for frequent electrocardiograms necessitated the elimination of 47 patients from our series because of too few tracings. Arbitrarily, five records

aberrations of the ST segments or T waves. Usually several, or all, of these abnormalities occurred simultaneously or appeared in successive records on the same patient. Particular care was taken to exclude any unusual findings that might reasonably be attributed to tachycardia during the early toxic phase of diphtheria or to serum reactions.

Figure 1 illustrates Grade 1 changes in 3 patients. These consist of lowering or flattening of the T waves with sagging of the ST segments, although they may occur in all leads, they were considered significant only when present in Leads 1 and 4.

Figure 2 shows Grade 2 alterations in 2 cases. In the first (G C), the ST segments were displaced, and there was slight prolongation of the PR inter-

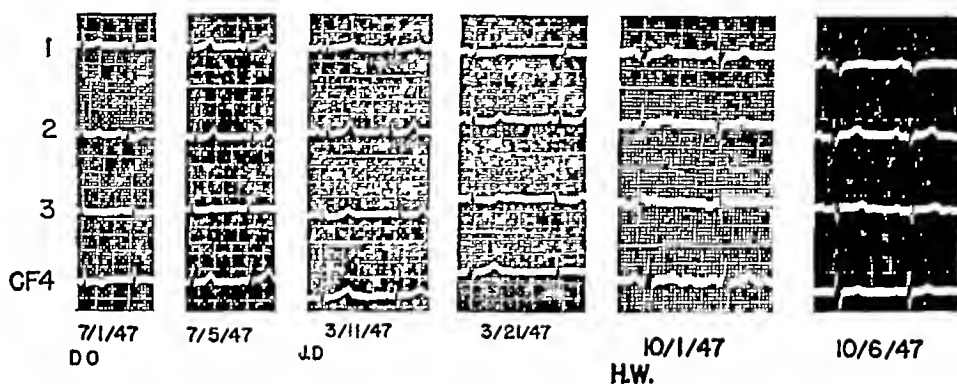


FIGURE 1 Grade 1 Changes

*D O*, a twenty-three-year-old woman, was admitted to the hospital on the third day of disease. She received 50,000 units of antitoxin. On the sixth day of illness the ST segments showed slight sagging. By the fourteenth day changes in the T waves had become maximal and are shown over the date "7/1/47". Four days later the record was normal and remained so. There were no other signs of cardiac involvement.

*J D*, a fifteen-year-old boy, was admitted to the hospital on the tenth day of disease, he received 20,000 units of antitoxin. The record on the fourteenth day of disease was considered within normal limits. On the eighteenth day ST-segment changes appeared and were maximal on the twenty-fifth day. The electrocardiogram was slightly abnormal at discharge on the fifty-third day. There were no other signs of cardiac involvement.

*H W*, a forty-eight-year-old woman, was admitted to the hospital on the fourth day of disease. She was given 20,000 units of antitoxin. The record on the fifth day of the disease was considered normal. Minor T-wave changes appeared on the ninth day and had become maximal on the twelfth day. Changes persisted until the twenty-fourth day. No other signs of cardiac involvement appeared.

taken during the course of the illness were considered the minimum adequate number, although it is almost certain that in some cases this was wholly inadequate for discovering transient changes. The cases were unselected, so that both severe and mild ones were included.

The degree of electrocardiographic abnormality was graded from 1 to 4. Grade 1 consisted of prolongation of the PR or QT intervals, or slight alterations in the ST segment or T wave. Grade 2 variations were either more marked or consisted of a combination of those classified as Grade 1. Grade 3 was made up of records showing the same changes as those in Grade 2 (but more intense), whereas the designation of Grade 4 was reserved for cases of complete auriculoventricular block, bundle-branch block, ventricular tachycardia or very marked

val. This was the only case of reciprocal displacement of the ST segments. In all the others the ST segments were directed downward in all the affected leads.

Figure 2 exemplifies the characteristic change in the ST segments and T wave, which is very similar to that produced by digitals. In addition there are "splintering" without widening of the QRS complex and development of deep S waves in Leads 2 and 3.

The electrocardiograms characteristic of Grade 3 are presented in Figure 3. The earliest detectable abnormality, prolongation of the QT interval, appeared on the seventh day of the disease. This was soon followed by progressive sagging of the ST segments and an increasing degree of inversion of the T waves in Leads 1, 2 and CF<sub>4</sub>, which per-

sisted until the patient's death on the forty-seventh day after the onset of diphtheria. Aside from some increase in heart size, there were no signs of cardiac involvement, such as murmurs or gallop, and no congestive phenomena. Autopsy showed very marked generalized fibrosis, but, by that time, all the inflammatory cellular reaction had subsided.

Figure 4 is an example of Grade 4 since it demonstrates complete auriculoventricular block, there are also marked ST-segment and T-wave changes. This patient died of bronchopneumonia on the forty-seventh day. The record taken on the day before death showed considerable improvement. Histologic examination of the myocardium revealed widespread fibrosis, however.

Grade 4 electrocardiograms of 4 patients are illustrated in Figure 5. These tracings reveal the most severe abnormalities — namely, ventricular tachycardia, complete auriculoventricular block, and widened QRS complexes. The widened QRS complexes in patients R H and R G may have been due either to bundle-branch block or to origin of the impulse somewhere below the junctional tissue. The only patient who developed auricular

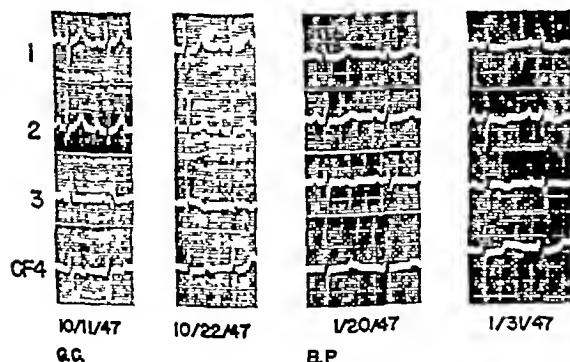


FIGURE 2 Grade 2 Changes

G C, a five-year-old girl, was admitted to the hospital on the third day of disease. She received 20,000 units of antitoxin. The record labeled "10/11/47" was taken on the fourth day of disease and was normal. Maximal ST changes were recorded on October 22. Two days later the ST segments had returned to normal, but the QT interval was prolonged. A record on October 30 was normal. There were no other signs of cardiac involvement.

B P, an eleven-year-old girl was admitted to the hospital on the sixth day of disease. She was given 50,000 units of antitoxin. The first record to be made (marked "1/20/47") was on the eleventh day of disease. The QT interval was prolonged, but otherwise the record was normal. Two days later ST-segment changes appeared and became maximal. The record became normal on the thirty-eighth day of disease. From the twenty-first to the twenty-third day gallop rhythm, an apical systolic murmur and frequent premature beats were present.

fibrillation (preceded by flutter) was G C. She also had complete auriculoventricular block since the ventricular rate was 115 and regular. The voltage of the QRS complexes decreased markedly from that found in earlier records, and comparatively deep S waves appeared in Lead I.

Table 1 indicates the relative frequency of electrocardiographic abnormalities during the course of diphtheria. Seventeen (18.2 per cent) of the 93 patients showed normal records throughout. It should be noted, however, that the average number of records per patient in this group was only seven, and only 4 of the 17 patients had more than eight. In view of the transient nature of the changes with myocardial involvement, it seems probable that, had more tracings been made, significant variations

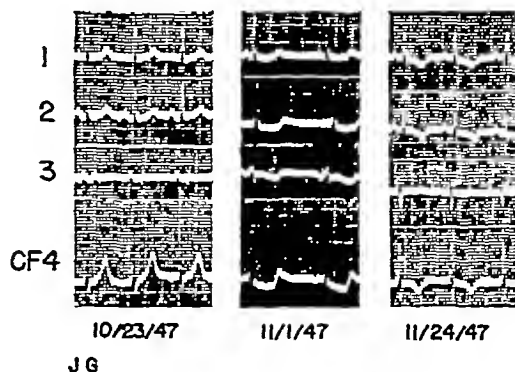


FIGURE 3 Grade 3 Changes

J G, a fifty-two-year-old man, was admitted to the hospital on the fourth day of disease. He received 100,000 units of antitoxin. The record dated "10/23/47" was made on the fifth day of disease and was normal. Two days later the QT interval was prolonged, and auricular premature beats appeared. Progressive ST-segment changes appeared and reached their maximum on November 1 — shown above. As the ST segment changes regressed progressive T-wave inversion appeared, reaching maximum inversion on November 24. These changes persisted until death on the forty-seventh day of disease. The heart size was increased on both physical and x-ray examination, but there were no other signs of cardiac involvement. Concomitantly widespread polyneuropathy appeared, and, terminally, signs of bronchopneumonia. Histologic examination showed extremely marked, generalized fibrosis and some muscle fragmentation, but no acute degeneration or inflammatory cellular reaction. The coronary arteries revealed slight intimal thickening but were patent throughout.

would have been detected in cases in which no cardiac dysfunction was apparent.

An almost equal number of patients (16.3 per cent) showed electrocardiographic findings that were neither clearly normal nor abnormal. The main difficulty lay in the interpretation of T-wave changes in Lead CF<sub>4</sub>. Since only one chest lead was taken, alterations in the T waves from day to day could often be attributed to difference in the position of the exploring electrode. Arbitrary standards were adopted as follows: an inverted T wave in Lead CF<sub>4</sub> was accepted as normal if the R/S ratio was less than 1. If the R exceeded the S wave by 50 per cent or more an inverted T wave was considered abnormal. Records that did not fall into either of these categories were considered borderline. Questionable T-wave changes in Lead CF<sub>4</sub> accounted for 9 of the 15 borderline cases. In the remainder the QT interval, ST segments or T

waves showed changes that were probably, although not certainly, significant

Sixty-one patients (65.5 per cent) showed incontestable abnormalities, of these, the majority (65.5 per cent) were slight (Grade 1) and usually transient

The relative frequency of individual abnormalities is illustrated in Table 2. Multiple deviations from the normal were more usual than isolated

(12.5 per cent) who had no laboratory evidence of myocarditis were twenty years of age or older, whereas 30 (50 per cent) of those with abnormal records were over twenty years of age. As well as could be ascertained from the small number of cases in each of the grades of myocardial disease, age did not seem to determine the degree of electrocardiographic aberration.

On the whole the onset of electrocardiographic abnormalities was earlier than has been usually thought, the average being eleven and a half days after the inception of the diphtheria. These figures include patients with abnormal records on admission, the day of admission being counted as the day the electrocardiogram became abnormal. Since 34 per cent were abnormal on admission, with an average duration of disease of nine and three-fourths days, it is apparent that the true average time of onset is less than the above figure indicates. The exact time of the first occurrence of myocardial disease was not known in about a third of the patients, since the electrocardiograms were abnormal on entry into the hospital. The earliest abnormal record was encountered on the third, and the latest on the forty-seventh day of the disease.

The interval between the onset of diphtheria and the institution of antitoxin therapy was not greatly different in the various groups (Table 4). The average delay was only a little greater for patients with abnormal electrocardiograms, but was especially notable in those who developed Grade 4 changes. However, of the 9 patients in the latter category, 2 were not admitted to the hospital until the seventeenth and twenty-first days respectively, these cases weight the average of the group heavily.

The development and evolution of electrocardiographic abnormalities did not appear to be related to the type of organism (Table 5). Gravis strains predominated in patients with Grade 4 findings, the small number of cases makes such an observation of dubious significance, however.

The over-all mortality (Table 6) was 14.4 per cent for the series. There were no deaths among the patients who had normal or borderline electrocardiograms. The number of deaths rose steadily with increase in intensity of the electrocardiographic aberrations, being 5 per cent in the patients with Grade 1, 14 per cent in those with Grade 2, 40 per cent in those with Grade 3 and 78 per cent in those with Grade 4 changes.

#### DISCUSSION

Significant electrocardiographic abnormalities appeared to be much more common in the cases of diphtheria in this series than in those reported in other studies. The usual incidence of myocarditis has been thought to be between 10 and 20 per cent.<sup>2,3</sup> Begg,<sup>4</sup> however, found changes in the electrocardiographic records in 84 per cent of 103 selected cases of severe diphtheria. This figure is

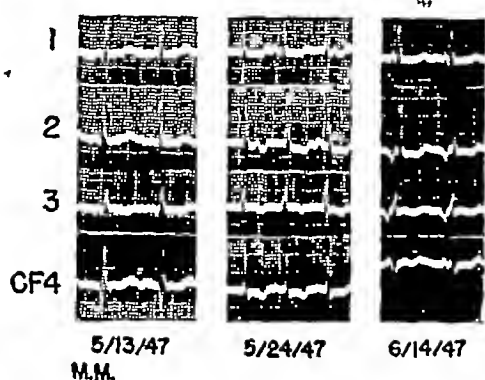


FIGURE 4. Grade 4 Changes

*M.M.*, a fifty-five-year-old woman, was admitted to the hospital on the seventh day of disease. She was given 100,000 units of antitoxin. The record dated "5/13/47" was made the day after admission—the eighth day of disease—and showed prolongation of the QT interval (the precordial lead was reversed). ST-T changes and complete auriculoventricular block appeared in the next few days and remained constant until June 3, when the block disappeared and ST-T reverted toward normal. On the day before death the record dated "6/14/47" was made, showing considerable change toward normal. There were no other signs of cardiac involvement. On the thirty-seventh day of disease polyneuritis developed, with regurgitation of food and inability to swallow. Aspiration pneumonia followed, and death occurred on the forty-seventh day. At autopsy the myocardium showed diffuse fibrosis.

ones, although variations in the ST segment or T waves, or both, not infrequently occurred alone. It is noteworthy that 1 patient, who showed Grade 4 changes (ventricular tachycardia) for a short period, had only minor electrographic findings before and after the period of rapid pulse. This was the only one of the group of patients with myocarditis of the most severe degree who survived.

Data regarding the relation of age to the occurrence of abnormal electrocardiograms are presented in Table 3. About a third of the patients were twenty years of age or over, and two thirds were younger. The average age of those showing significant findings was two and a half times that of those with normal records. Furthermore, the age range was much narrower for those with normal or borderline tracings. The oldest patient with a normal electrocardiogram was thirty years of age, the oldest with borderline variations was thirty-three years, and the oldest with distinct abnormalities seventy-two years old. Only 4 of those

in close agreement with that obtained in our group, which included both severe and mild cases. Frequent electrocardiograms appeared to provide the only certain means of detecting myocarditis,

of 3 patients displayed no abnormalities at any time.

The pathological characteristics of fatal diphtheritic myocarditis have recently been reviewed

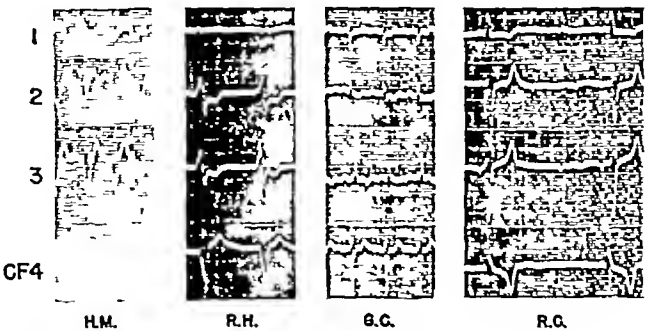


FIGURE 5 Grade 4 Changes

*H. M.*, an eight-year-old boy, was admitted to the hospital in the third week of disease with palatal paralysis and gallop rhythm. The electrocardiogram on admission showed complete auriculoventricular block, with a ventricular rate of 80 and marked ST-T changes. Just before death the record demonstrated ventricular tachycardia.

*R. H.*, an eleven-year-old boy, was admitted to the hospital on the seventeenth day of disease. He was given 10,000 units of antitoxin. Ventricular tachycardia was present on admission. On the day of death the above record was obtained.

*G. C.*, a nine-year-old girl, was admitted to the hospital on the fifth day of disease. She received 60,000 units of antitoxin. The electrocardiogram on the day after admission showed ventricular tachycardia, which persisted for four days. On the next day complete auriculoventricular block, with a ventricular rate of 110 and marked ST changes but with normal QRS complexes, was present. On the following day auricular flutter appeared, followed shortly by auricular fibrillation. After five days the auricular fibrillation disappeared and was replaced by complete auriculoventricular block and progressive QRS changes up to the time of death on the thirty-fifth day.

*R. C.*, a twelve-year-old boy, was admitted to the hospital on the fifth day of disease. He was given 40,000 units of antitoxin. On admission the heart was enlarged, and the rate was 35 per minute. Complete auriculoventricular block and widened QRS complexes were present.

since reliable physical signs of heart disease were never present in patients with the lesser grades of deviation from the normal and those with a high degree of electrocardiographic abnormality often revealed surprisingly little on examination of the cardiovascular system.

As has been stated above, it is possible that many of the normal or borderline cases did not belong

by Gore.<sup>5</sup> The essential features are muscle degeneration and cellular infiltration in the early and diffuse fibrosis with loss of muscle fibers in the later

TABLE 1 Electrocardiographic Findings among Patients with Diphtheria

ELECTROCARDIOGRAM	NO OF CASES	PER CENTAGE
Normal	17	18.2
Borderline	15	16.3
Abnormal	61	65.5
Grade 1 changes	40	65.5
Grade 2 changes	7	11.4
Grade 3 changes	5	8.5
Grade 4 changes	9	14.6

in these groups because they had only the minimum of five records. That some patients may escape detectable myocarditis is indicated, however, by the fact that thirteen to fifteen tracings in each

TABLE 2 Incidence of Abnormal Electrocardiographic Tracings

ABNORMALITY	SINGLE	COMBINED
Prolonged PR interval	1	7
Auriculoventricular dissociation	0	4
Abnormal ST-T	12	17
Abnormal T wave	15	10
Aberration of QRS complex	0	4
Bundle branch block	0	3
Right axis deviation	0	4
Frequent ectopic beats	0	10
Auricular	0	5
Ventricular	0	5
Prolonged QT interval	3	6
Abnormal P wave	0	5
Ventricular tachycardia	1	5
Auriculoventricular nodal rhythm	0	6
Auricular flutter	0	1
Auricular fibrillation	0	1
Auricular standstill	0	2
Unidentified rhythm	0	2

stages. Progressive fibrosis begins after the third week.<sup>6</sup> Clinicopathological correlation in our cases revealed the following facts. There were no deaths in the group with normal or borderline records.

In those with Grade 1 changes there were 2 deaths, only 1 of which came to autopsy. This patient died of pneumonia due to *Klebsiella pneumoniae* fourteen days after having become ill with diphtheria, autopsy revealed only slight to moderate myocar-

shown in Figure 3. Autopsies were performed in 6 of the 8 fatal cases classified as Grade 4. All showed a high degree of myocardial damage, either acute degenerative or fibrotic, depending upon the duration of the illness.

The view that diphtheritic myocarditis may give rise to difficulty years after recovery has been expressed<sup>5, 6</sup> and denied<sup>7</sup>. The demonstration of marked changes in the heart muscles in fatal cases makes it difficult to escape the conclusion that patients who do not die but who have electrocardiographic abnormalities of relatively the same degree as some of those who expire have lost a fair portion of their myocardium. Even if, for the sake of discussion, the minor degrees of departure from

TABLE 3 Relation of Age to Electrocardiographic Abnormalities

ELECTROCARDIOGRAM	AVERAGE AGE	RANGE*
	yr	yr
Normal	11.3	3-30
Borderline	12.8	3-33
Abnormal	27.4	3-72
Grade 1	30.3	4-65
Grade 2	25.9	5-72
Grade 3	21.2	3-57
Grade 4	19.5	3-65

\*Of these patients 64.3 per cent were below twenty years of age and 35.7 per cent were over twenty years of age.

ditis. One death occurred among the patients showing Grade 2 abnormalities. This patient expired on the fourth day of a severe tracheobronchial diphtheria, and autopsy revealed no significant findings.

TABLE 4 Average Delay before Treatment

ELECTROCARDIOGRAM	AVERAGE DELAY days
Normal	4.0
Borderline	3.8
Abnormal	5.2
Grade 1	4.8
Grade 2	4.4
Grade 3	4.5
Grade 4	7.6

in the heart. It is possible that the electrocardiographic findings were due to anoxia and tachycardia or that anatomic changes had not had time to develop. There were 2 deaths among the patients

TABLE 5 Types of Organism in Relation to Electrocardiograms

ELECTROCARDIOGRAM	MITIS TYPE %	GRAVIS TYPE %	NO TYPE %
Normal	52.9	47.1	0
Borderline	53.3	13.4	33.3
Abnormal	47.5	44.2	8.3
Grade 1	50.0	42.5	7.5
Grade 2	71.4	28.6	0.0
Grade 3	40.0	40.0	20.0
Grade 4	22.2	66.6	11.2

with Grade 3 changes — 1 on the forty-first and the other on the forty-ninth day of the disease. Both patients showed marked fibrosis of the myocardium at autopsy. The electrocardiograms of the patient who died on the forty-ninth day are

TABLE 6 Mortality

ELECTROCARDIOGRAM	NO OF CASES	DEATHS	MORTALITY %
Normal	17	0	—
Borderline	15	0	—
Abnormal	61	13	14.4
Grade 1	40	2	5.0
Grade 2	7	1	14.0
Grade 3	5	2	40.0
Grade 4	9	8	78.0

the normal are considered to be due to reversible processes (the one autopsy in the Grade 1 group refutes this), and if the patients that make up Grade 4 are given a hopeless prognosis for survival past the acute stage of the disease, there still remain the Grade 2 and 3 groups, over three fourths of whom live. Pathological examination of the fatal cases in Grades 3 and 4 revealed severe cardiac damage. Reversibility of the electrocardiographic changes cannot be considered as indicating a return to normal of the myocardium. Figure 4 presents the records of a patient who died of bronchopneumonia on the forty-seventh day of diphtheria. The electrocardiogram taken just before death showed reversion toward normal, and yet at autopsy there was a severe degree of myocardial fibrosis. Despite the marked destruction of muscle fibers the abnormalities had decreased from Grade 4 with complete auriculoventricular block to Grade 2, or perhaps even Grade 1, at the time of death.

Although the evidence indicates that recovery is complete enough in the young patient, it seems illogical to assume that such hearts have a normal reserve for later life, should hypertension or coronary-artery disease make its appearance. The fifteen-year to twenty-year follow-up study of 100 cases reported by Thompson, Golden and White<sup>7</sup> has the objection that the subjects, ranging in age from sixteen to forty-six years, were still young. The obvious drawback in older persons is, of course, that any abnormality may be attributed to coronary-artery disease alone.

The fact that the electrocardiogram returns to normal despite loss of muscle substance and fibrosis is a good demonstration if any more are necessary, of the limitations of the method.

The management of diphtheritic myocarditis revolves mainly about constant and skilled nursing care and maximum rest of the heart. Both quinine and digitalis have theoretical disadvantages, and their place in the therapy of this disease is not clearly defined. The length of time for which the patient should remain completely inactive is a controversial point. Some clinicians believe that bed rest should be continued until the electrocardiogram has become normal again. Since this may require four to six months or longer, it seems unnecessary to insist on rest in bed for a long period particularly since antitoxin and penicillin rid the patient of the injurious agent rapidly and scar formation in the myocardium is usually well established after the third week.<sup>5</sup> In cases in which the electrocardiographic abnormalities have not disappeared completely, it is probably wise to prohibit severe or prolonged effort for several months.

#### SUMMARY

Of 93 patients with diphtheria who had had at least 5 electrocardiograms during the course of the disease, 61 showed abnormal tracings. The remainder were about equally divided between equivocal or borderline changes and normal records.

The degree of abnormality was classified as Grade 1 through 4. Grade 1 changes were found in 40, Grade 2 in 7, Grade 3 in 5, and Grade 4 in 9 patients.

Although the mortality rose sharply with increasing degrees of abnormality, the pathological data available indicated that the anatomic lesions in the heart varied quantitatively rather than qualitatively and that even the lesser degrees of electrocardiographic change were associated with irreversible myocardial lesions.

Neither the type of organism nor delay in antitoxin therapy appeared of any importance in determining the development or degree of electrocardiographic abnormality. The determining factors appeared to be the extent and severity of the local diphtheritic lesion.

Information obtained from autopsied cases showing all types and degrees of normal electrocardiographic patterns indicated that recovery is probably associated with loss of muscle substance and is therefore, never complete. This apparently holds true even in the face of a return of the electrocardiogram to normal.

#### REFERENCES

1. Kay, C. F. and Livingood, C. S. Myocardial complications of cutaneous diphtheria. *Am. Heart J.* 31:744-756, 1946.
2. McCulloch, H. Studies on effect of diphtheria on heart. *Am. J. Dis. Child.* 20:89-112, 1920.
3. Burkhardt, E. A., Egleston, C., and Smith, L. W. Electrocardiographic changes and peripheral nerve palsies in toxic diphtheria. *Am. J. W. Sc.* 195:301-315, 1958.
4. Begg, N. D. Diphtheritic myocardium: electrocardiographic study. *Lancet* 1:857-860, 1957.
5. Gore, I. Myocardial changes in fatal diphtheria: summary of observations in 221 cases. *Am. J. W. Sc.* 218:257-266, 1948.
6. Butler, S. and Levine, S. A. Diphtheria as cause of late heart-block. *Am. Heart J.* 5:392-398, 1950.
7. Thompson, W. P., Golden, G. E., and White, P. D. Heart fifteen to twenty years after severe diphtheria. *Am. Heart J.* 13:534-541, 1937.

In those with Grade 1 changes there were 2 deaths, only 1 of which came to autopsy. This patient died of pneumonia due to *Klebsiella pneumoniae* fourteen days after having become ill with diphtheria, and autopsy revealed only slight to moderate myocar-

TABLE 3 *Relation of Age to Electrocardiographic Abnormalities*

ELECTROCARDIOGRAM	AVERAGE AGE	RANGE*
	yr	yr
Normal	11 3	3-30
Borderline	12 8	3-33
Abnormal	27 4	3-72
Grade 1	30 3	4-65
Grade 2	25 9	5-72
Grade 3	21 2	3-57
Grade 4	19 5	3-65

\*Of these patients 64.3 per cent were below twenty years of age and 35.7 per cent were over twenty years of age.

ditis. One death occurred among the patients showing Grade 2 abnormalities. This patient expired on the fourth day of a severe tracheobronchial diphtheria, and autopsy revealed no significant findings.

TABLE 4 *Average Delay before Treatment*

ELECTROCARDIOGRAM	AVERAGE DELAY days
Normal	4 0
Borderline	3 8
Abnormal	5 2
Grade 1	4 8
Grade 2	4 4
Grade 3	4 5
Grade 4	7 6

in the heart. It is possible that the electrocardiographic findings were due to anoxia and tachycardia or that anatomic changes had not had time to develop. There were 2 deaths among the patients

TABLE 5 *Types of Organism in Relation to Electrocardiograms*

ELECTROCARDIOGRAM	MITIS TYPE %	GRAVIS TYPE %	NO TYPE %
Normal	52 9	47 1	0
Borderline	53 3	13 4	33 3
Abnormal	47 5	44 2	8 3
Grade 1	50 0	42 5	7 5
Grade 2	71 4	28 6	0 0
Grade 3	40 0	40 0	20 0
Grade 4	22 2	66 6	11 2

with Grade 3 changes — 1 on the forty-first, and the other on the forty-ninth day of the disease. Both patients showed marked fibrosis of the myocardium at autopsy. The electrocardiograms of the patient who died on the forty-ninth day are

shown in Figure 3. Autopsies were performed in 6 of the 8 fatal cases classified as Grade 4. All showed a high degree of myocardial damage, either acute degenerative or fibrotic, depending upon the duration of the illness.

The view that diphtheritic myocarditis may give rise to difficulty years after recovery has been expressed<sup>5, 6</sup> and denied<sup>7</sup>. The demonstration of marked changes in the heart muscles in fatal cases makes it difficult to escape the conclusion that patients who do not die but who have electrocardiographic abnormalities of relatively the same degree as some of those who expire have lost a fair portion of their myocardium. Even if, for the sake of discussion, the minor degrees of departure from

TABLE 6 *Mortality*

ELECTROCARDIOGRAM	NO OF CASES	DEATHS	MORTALITY %
Normal	17	0	—
Borderline	15	0	—
Abnormal	61	13	14.4
Grade 1	40	2	5.0
Grade 2	7	1	14.0
Grade 3	7	2	40.0
Grade 4	9	8	78.0

the normal are considered to be due to reversible processes (the one autopsy in the Grade 1 group refutes this), and if the patients that make up Grade 4 are given a hopeless prognosis for survival past the acute stage of the disease, there still remain the Grade 2 and 3 groups, over three fourths of whom live. Pathological examination of the fatal cases in Grades 3 and 4 revealed severe cardiac damage. Reversibility of the electrocardiographic changes cannot be considered as indicating a return to normal of the myocardium. Figure 4 presents the records of a patient who died of bronchopneumonia on the forty-seventh day of diphtheria. The electrocardiogram taken just before death showed reversion toward normal, and yet at autopsy there was a severe degree of myocardial fibrosis. Despite the marked destruction of muscle fibers the abnormalities had decreased from Grade 4 with complete auriculoventricular block to Grade 2, or perhaps even Grade 1, at the time of death.

Although the evidence indicates that recovery is complete enough in the young patient, it seems illogical to assume that such hearts have a normal reserve for later life, should hypertension or coronary-artery disease make its appearance. The fifteen-year to twenty-year follow-up study of 100 cases reported by Thompson, Golden and White<sup>7</sup> has the objection that the subjects, ranging in age from sixteen to forty-six years, were still young. The obvious drawback in older persons is, of course, that any abnormality may be attributed to coronary-artery disease alone.

The fact that the electrocardiogram returns to normal despite loss of muscle substance and fibrosis is a good demonstration, if any more are necessary, of the limitations of the method.

The management of diphtheritic myocarditis revolves mainly about constant and skilled nursing care and maximum rest of the heart. Both quinidine and digitalis have theoretical disadvantages and their place in the therapy of this disease is not clearly defined. The length of time for which the patient should remain completely inactive is a controversial point. Some clinicians believe that bed rest should be continued until the electrocardiogram has become normal again. Since this may require four to six months or longer, it seems unnecessary to insist on rest in bed for a long period particularly since antitoxin and penicillin rid the patient of the injurious agent rapidly and scar formation in the myocardium is usually well established after the third week.<sup>5</sup> In cases in which the electrocardiographic abnormalities have not disappeared completely, it is probably wise to prohibit severe or prolonged effort for several months.

#### SUMMARY

Of 93 patients with diphtheria who had had at least 5 electrocardiograms during the course of the disease, 61 showed abnormal tracings. The remainder were about equally divided between equivocal or borderline changes and normal records.

The degree of abnormality was classified as Grade 1 through 4. Grade 1 changes were found in 40, Grade 2 in 7, Grade 3 in 5, and Grade 4 in 9 patients.

Although the mortality rose sharply with increasing degrees of abnormality, the pathological data available indicated that the anatomic lesions in the heart varied quantitatively rather than qualitatively and that even the lesser degrees of electrocardiographic change were associated with irreversible myocardial lesions.

Neither the type of organism nor delay in antitoxin therapy appeared of any importance in determining the development or degree of electrocardiographic abnormality. The determining factors appeared to be the extent and severity of the local diphtheritic lesion.

Information obtained from autopsied cases showing all types and degrees of normal electrocardiographic patterns indicated that recovery is probably associated with loss of muscle substance and is therefore, never complete. This apparently holds true even in the face of a return of the electrocardiogram to normal.

#### REFERENCES

1. Kay C. F. and Livingood, C. S. Myocardial complications of cutaneous diphtheria. *Am Heart J* 31:744-756 1946.
2. McCulloch H. Studies on effect of diphtheria on heart. *Am J Dis Child* 20:89-112, 1920.
3. Burkhardt, E. A. Eggeston, C., and Smith L. W. Electrocardiographic changes and peripheral nerve palsies in toxic diphtheria. *Am J M Sc* 195:01-15 1948.
4. Begg N. D. Diphtheritic myocarditis: electrocardiographic study. *Lancet* 1:857-860 1957.
5. Gore I. Myocardial changes in fatal diphtheria: summary of observations in 221 cases. *Am J M Sc* 215:257-266 1948.
6. Butler S. and Levine S. A. Diphtheria as cause of late heart-block. *Am Heart J* 5:592-598 1950.
7. Thompson W. P. Golden G. E. and White P. D. Heart fifteen to twenty years after severe diphtheria. *Am Heart J* 13:534-541 1937.

# THE TREATMENT OF RUPTURED LIVER WITH ABSORBABLE HEMOSTATICS\*

## Report of Three Cases

GEORGE W. PAPEN, M.D.,† AND STANLEY MIKAL, M.D.‡

BOSTON

**S**URGERY of the liver has lagged behind surgical operations on the other abdominal viscera, mainly because of the difficulty of controlling hemorrhage. However, with the recent development of absorbable hemostatic substances in the form of sponges and packs, control of hemorrhage from the liver can be obtained. The purpose of this paper is to present 3 cases of traumatic rupture of the liver in which hemorrhage was controlled with oxycel and gelfoam.

### HISTORICAL REVIEW

In 1888 Langenbuch,<sup>1</sup> with mass ligatures, controlled severe liver hemorrhage following partial resection.

Kousnetzoff and Penski,<sup>2</sup> in 1896, devised a special needle for liver suture. The needle was large, curved, wedge-shaped and blunt tipped. It was passed through the liver with a continuous suture. The suture was subsequently cut up into single mattress sutures and tied. If any large vessels continued to bleed from the cut liver surface they were circumstitched and ligated.

Ceccherelli and Bianchi,<sup>3</sup> in 1894, reported on the use of decalcified bone plates in controlling hemorrhage from the liver. They placed the bone plates on the upper and lower surfaces of the liver and secured them with through-and-through sutures. In a similar manner, Payer used magnesium plates, and Segale ivory rods.<sup>4</sup>

Terrier and Auvray,<sup>5</sup> in 1898, used a continuous-chain-suture technic for hepatic hemostasis, with good results.

In 1902 Beck<sup>6</sup> employed a Nélaton rubber catheter for elastic compression around the cut surface of the liver, together with iodoform gauze as a tampon. The catheter and gauze were brought out through the abdominal wound and removed in four to six days. Later, in the same year, he reported the use of split bands of abdominal wall consisting of fascia, peritoneum and muscle, which were attached to the abdominal wall at one end, the other being used as suture material.

Kocher,<sup>7</sup> in 1902, applied crushing stomach clamps to the cut liver edge. The clamps were brought out through the abdominal wound and removed in forty-eight hours.

In 1905, Cullen<sup>8, 9</sup> used an overlapping-mattress-suture technic with a modified Kousnetzoff needle for controlling hepatic hemorrhage.

Gillette<sup>10</sup> passed five or six sutures of catgut through the entire liver substance, brought them through the chest wall around a rib and tied the sutures on the skin. In 1905 he reported 2 such cases with recovery.

Boljarski,<sup>11</sup> in 1910, used isolated omentum and catgut sutures for control of liver bleeding.

Cushing<sup>12</sup> used striated muscle in neurosurgery as a hemostatic plug and later applied it to liver biopsies, reporting the results in 1911. Striated muscle controlled hemorrhage because thrombokinase liberated by the damaged muscle aided in blood clotting and also the muscle plug by its bulk caused hemostatic compression of the liver sinuses.

In 1915 Grey<sup>13</sup> used sheep's fibrin in small blocks for hemostasis, and Harvey, in 1918,<sup>14</sup> used beef fibrin in small sheets for similar purposes.

Seegers and his co-workers<sup>15, 16</sup> discovered thrombin in 1938 and used it as a hemostatic agent in human beings and animals in the following year.

Ingraham et al.,<sup>17-21</sup> in 1944, used human fibrinogen foam and fibrin foam for hemostasis in neurosurgery and showed the value of these substances in general surgery. They found these products absorbable, nonirritating and more effective in combination with thrombin.

In 1943 Frantz<sup>22</sup> employed oxidized cellulose (oxycel) to arrest hemorrhage from brain, liver, kidney and spleen in animals. The oxidized cellulose was prepared from gauze or cotton and subjected to an oxidation process, which produced cellulosic acid. Hemostasis was a result of the action of this acid, and no advantage was obtained by the use of thrombin with oxycel because thrombin became inactive in an acid medium. The oxycel turned black on contact with blood and was completely absorbed in three or four weeks. It was probably absorbed by phagocytosis and by dissolution as small particles into the blood stream, which were excreted subsequently by the kidneys. Tissue reaction to the oxycel was minimal.<sup>22-25</sup>

Light and Prentice,<sup>26, 27</sup> in 1945, used a gelatin sponge (gelfoam) for hemostasis in surgery. The gelatin sponge was made from ordinary commercial gelatin by the introduction of air into a gelatin solution to obtain a porosity. This sponge was then heated in an oven until dry. The hemostatic

\*From the First Surgical Service, Boston City Hospital and the Department of Surgery, Tufts College Medical School.

†Clinical professor of surgery, Tufts College Medical School; surgeon-in-chief, First Surgical Service, Boston City Hospital.

‡Senior assistant resident, First Surgical Service, Boston City Hospital.

action of the gelatin sponge was twofold: it acted as a tampon and also liberated thromboplastin from damaged platelets that entered its foam structure and became traumatized by contact with the walls of its interstices. Gelfoam was hemostatic when used with or without thrombin and was absorbed in fifteen to twenty-four days with minimal tissue reaction.

Levitski<sup>25</sup> chose a hemostol plug for hemostasis. The hemostol plug was made from relatively fresh coagulated human plasma. He used 100 parts of citrated plasma from blood three to five days old and added 5 parts of calcium chloride to coagulate the plasma. The coagulated plasma was transferred to a sponge, and the serum squeezed out of it. The hemostol plug was inserted into the liver wound for three to five minutes, after which hemostasis and adherence took place. This plug of coagulated human plasma was completely absorbed, and the tissue reaction to it negligible.

In 1946, Lowry<sup>29</sup> used synthetic adhesive tape in treating wounds of the liver. After resecting sections of rabbit livers, he applied two strips of Scotch tape, in the form of an envelope, to the liver. The entrapped clot acted as a plug and controlled the hemorrhage. Small localized encapsulated abscesses or caseous residues surrounded by fibrous tissue were usually found at the end of a month of such treatment.

Jenkins,<sup>30, 31</sup> in 1947, applied gelfoam by a blanket technic to control wounds from the liver in animals; he also applied it to the aorta by a cuff technic and to the vena cava and the heart by a patch technic.

#### INCIDENCE

Thöle<sup>32</sup> collected 752 cases of liver injury and found that a third were due to internal injuries (patient run over by wheel, blow to abdomen and so forth), whereas two thirds were penetrating injuries, such as stab and gunshot wounds. Of Krieg's<sup>33</sup> 60 cases, 83 per cent were of the penetrating type, and only 17 per cent of the subcutaneous type. Anderson<sup>34</sup> found that the liver was injured in 10 per cent of all open wounds of the abdomen, and in 19.5 per cent of internal abdominal injuries. During World War II, Fox<sup>35</sup> reviewed 270 thoraco-abdominal wounds in an American combat hospital in Italy and reported 27 per cent involvement of the liver. The liver was drained in 18 per cent, packed with gauze in 9.7 per cent, sutured in 2.8 per cent and packed with muscle in 1.6 per cent. Of these cases, subphrenic abscesses developed in 6 per cent, intrahepatic abscesses in 1 per cent, subhepatic abscesses in 4 per cent, and biliary peritonitis in 0.7 per cent.

#### MORTALITY

Among 829 patients with wounds of the liver in World War II, Madding<sup>36</sup> reported a mortality of 27 per cent, regardless of the type of treatment.

According to Boljarski,<sup>37</sup> the mortality for penetrating wounds was 30 per cent, whereas that for internal injuries was 88 per cent.

Thöle<sup>32</sup> found the operative mortality in penetrating and internal injuries of the liver to be 39 per cent during the first six hours after injury, 50 per cent after six to twelve hours, 67 per cent after twelve to twenty-four hours and 86 per cent after twenty-four hours.

Boljarski's<sup>37</sup> figures likewise indicate the value of early operation. He reported an operative mortality of 15 per cent during the first three hours after injury and one of 50 per cent twenty-four hours after injury.

Death during the first seventy-two hours after hepatic trauma is usually due to hemorrhage and shock. After the fourth day, it is due to biliary septic peritonitis. Hemorrhage from liver rupture or penetration is severe because the hepatic veins are thin walled, contain very little elastic tissue and have no valves. Bleeding is also prolonged because of the massaging effect of the diaphragm and the admixture of bile with blood, which delays clotting.

#### AMOUNT OF LIVER NECESSARY FOR LIFE

Mann<sup>38</sup> (1927) removed as much as 50 per cent of liver tissue in animals without any serious impairment of liver function. He also demonstrated that liver tissue has remarkable powers of regeneration and recuperation. Ireneus and Puestow,<sup>39</sup> in 1944 removed as much as 90 per cent of liver tissue in dogs in successive intervals with survival. They also showed that the functional reserve of liver is unimpaired after massive blood loss from partially hepatectomized animals. In 1947 Martin<sup>40</sup> disclosed that in dogs the usual functional liver tests, such as bromsulfalein excretion, galactose tolerance, prothrombin time and alkaline phosphatase are not affected to any appreciable extent after massive trauma to the liver when as much as 50 per cent of the liver was damaged.

#### CLASSIFICATION OF LIVER TRAUMA

Liver trauma may be classified according to cause or effect. The classifications of Vance<sup>41</sup> are as follows: percutaneous or penetrating (stab or gunshot wounds), and internal or nonpenetrating (blow or wheel compressing abdomen). Movnihan<sup>42</sup> lists the following as the results of pathologic conditions: rupture of the liver, with laceration of Glisson's capsule, subcapsular hemorrhage, and central rupture with hematoma formation and subsequent development of an abscess or cyst.

#### CASE REPORTS

**CASE 1 (B.C.H. 1258525).** D.L., a 19-year-old boy, was admitted to the hospital on August 26, 1947, with a history of having fallen from a horse-drawn wagon, whose wheels ran over his chest. The patient complained of pain in the right lower lateral portion of the chest wall, right shoulder and right upper quadrant.

# THE TREATMENT OF RUPTURED LIVER WITH ABSORBABLE HEMOSTATICS\*

## Report of Three Cases

GEORGE W. PAPEN, M.D.,† AND STANLEY MIKAL, M.D.‡

BOSTON

**S**URGERY of the liver has lagged behind surgical operations on the other abdominal viscera, mainly because of the difficulty of controlling hemorrhage. However, with the recent development of absorbable hemostatic substances in the form of sponges and packs, control of hemorrhage from the liver can be obtained. The purpose of this paper is to present 3 cases of traumatic rupture of the liver in which hemorrhage was controlled with oxycel and gelfoam.

### HISTORICAL REVIEW

In 1888 Langenbuch,<sup>1</sup> with mass ligatures, controlled severe liver hemorrhage following partial resection.

Kousnetzoff and Penski,<sup>2</sup> in 1896, devised a special needle for liver suture. The needle was large, curved, wedge-shaped and blunt tipped. It was passed through the liver with a continuous suture. The suture was subsequently cut up into single mattress sutures and tied. If any large vessels continued to bleed from the cut liver surface they were circumstitched and ligated.

Ceccherelli and Bianchi,<sup>3</sup> in 1894, reported on the use of decalcified bone plates in controlling hemorrhage from the liver. They placed the bone plates on the upper and lower surfaces of the liver and secured them with through-and-through sutures. In a similar manner, Payer used magnesium plates, and Segale ivory rods.<sup>4</sup>

Terrier and Auvray,<sup>5</sup> in 1898, used a continuous-chain-suture technic for hepatic hemostasis, with good results.

In 1902 Beck<sup>6</sup> employed a Nélaton rubber catheter for elastic compression around the cut surface of the liver, together with iodoform gauze as a tampon. The catheter and gauze were brought out through the abdominal wound and removed in four to six days. Later, in the same year, he reported the use of split bands of abdominal wall consisting of fascia, peritoneum and muscle, which were attached to the abdominal wall at one end, the other being used as suture material.

Kocher,<sup>7</sup> in 1902, applied crushing stomach clamps to the cut liver edge. The clamps were brought out through the abdominal wound and removed in forty-eight hours.

In 1905, Cullen<sup>8,9</sup> used an overlapping-mattress-suture technic with a modified Kousnetzoff needle for controlling hepatic hemorrhage.

Gillette<sup>10</sup> passed five or six sutures of catgut through the entire liver substance, brought them through the chest wall around a rib and tied the sutures on the skin. In 1905 he reported 2 such cases with recovery.

Boljarski,<sup>11</sup> in 1910, used isolated omentum and catgut sutures for control of liver bleeding.

Cushing<sup>12</sup> used striated muscle in neurosurgery as a hemostatic plug and later applied it to liver biopsies, reporting the results in 1911. Striated muscle controlled hemorrhage because thrombokinase liberated by the damaged muscle aided in blood clotting and also the muscle plug by its bulk caused hemostatic compression of the liver sinuses.

In 1915 Grey<sup>13</sup> used sheep's fibrin in small blocks for hemostasis, and Harvey, in 1918,<sup>14</sup> used beef fibrin in small sheets for similar purposes.

Seegers and his co-workers<sup>15,16</sup> discovered thrombin in 1938 and used it as a hemostatic agent in human beings and animals in the following year.

Ingraham et al.,<sup>17-21</sup> in 1944, used human fibrinogen foam and fibrin foam for hemostasis in neurosurgery and showed the value of these substances in general surgery. They found these products absorbable, nonirritating and more effective in combination with thrombin.

In 1943 Frantz<sup>22</sup> employed oxidized cellulose (oxycel) to arrest hemorrhage from brain, liver, kidney and spleen in animals. The oxidized cellulose was prepared from gauze or cotton and subjected to an oxidation process, which produced cellulosic acid. Hemostasis was a result of the action of this acid, and no advantage was obtained by the use of thrombin with oxycel because thrombin became inactive in an acid medium. The oxycel turned black on contact with blood and was completely absorbed in three or four weeks. It was probably absorbed by phagocytosis and by dissolution as small particles into the blood stream, which were excreted subsequently by the kidneys. Tissue reaction to the oxycel was minimal.<sup>22-25</sup>

Light and Prentice,<sup>26,27</sup> in 1945, used a gelatin sponge (gelfoam) for hemostasis in surgery. The gelatin sponge was made from ordinary commercial gelatin by the introduction of air into a gelatin solution to obtain a porosity. This sponge was then heated in an oven until dry. The hemostatic

\*From the First Surgical Service, Boston City Hospital and the Department of Surgery, Tufts College Medical School.

†Clinical professor of surgery, Tufts College Medical School, surgeon-in-chief, First Surgical Service, Boston City Hospital.

‡Senior assistant resident, First Surgical Service, Boston City Hospital.

showing the value of absorbable hemostatics in ruptured livers in human beings. In all cases relatively complete hemostasis was obtained three to five minutes after the laceration had been packed with oxycel and gelfoam and gentle pressure applied. No delayed secondary liver hemorrhage ensued postoperatively. Pulmonary complications such as atelectasis and hydrothorax were common sequelae, and thoracentesis was frequently resorted to. In Case 1, in which the peritoneal cavity was drained, a temporary biliary fistula and subhepatic abscess developed, and thoracotomy with rib resection was required. Postoperative biliary peritonitis or fistula never developed when the abdomen was closed without drainage. Hence, primary closure of the abdomen without drainage is advocated instead of that with drainage.

These cases present relatively simple technics of obtaining hemostasis in bleeding livers. The patient in Case 1 was treated by simple packing and compression of the lacerated liver with oxycel and gelfoam, the patient in Case 2 by loose suture of the oxycel to the liver capsule, and the patient in Case 3 by packing of the lacerated liver with oxycel and suturing of the capsule of the liver to the diaphragm and abdominal wall to prevent the suction effect of the diaphragm on the liver. All three of these methods proved satisfactory in the control of hepatic hemorrhage.

It may be added that though the abdominal approach was used in these cases, some surgeons would choose the thoracic method because of the greater exposure of the dome of the liver obtained. However, when there is trauma to an abdomen, a hollow organ as well as a solid organ may be ruptured. To differentiate hollow-organ perforation and solid-organ rupture is often difficult, and the two frequently occur simultaneously. Hence, if jejunum, ileum or colon is perforated and the liver ruptured, an abdominal approach will give better exposure to these structures situated in the middle or lower portion of the abdomen. If greater exposure of the superior surface of the liver is required, a combined abdominothoracic incision is indicated.

### SUMMARY

A brief history of control of liver hemorrhage in surgery is presented, and 3 cases of traumatic rupture of the liver in human beings successfully treated with oxycel and gelfoam are reported.

The treatment recommended for large or jagged lacerations of the liver is packing of the laceration with absorbable hemostatic sponges (gelfoam, oxycel, fibrin foam or fibrinogen foam).

These hemostatic packs may be held in place by simple pressure, suture to the liver capsule or suture of the liver capsule to the diaphragm and abdominal wall.

Closure of the abdomen without drainage is advocated because it lessens the chance of external infection along the drainage pathway.

### REFERENCES

- Langenbuch C. Ein Fall von Resection eines linksseitigen Schnurlappens der Leber. *Heilung*. *Berl klin Wchnschr* 25:37, 1888.
- Konsanetzoff M. and Penski J. Sur la resection partielle du foie. *Rev de chir* 16 501-521 and 954 1896.
- Ceccherelli and Bianchi. Cited by Shelden and Johnston.<sup>4</sup>
- Shelden W M. and Johnston F. Traumatic rupture of liver. *Arch Eng J Med* 213 961 965 1935.
- Ternier F. and Auvray M. Les tumeurs du foie au point de vue chirurgical. *Étude sur la resection du foie*. *Rev de chir* 18 403-422 1898.
- Beck, C. Surgery of liver. *J A M A* 38 1053-1068 1902.
- Kocher T. *Chirurgische Operationslehre*. Fourth edition. 628 pp. Jena. Gustav Fischer 1902 P 348.
- Cullen T S. Large carcinomatous tumor of liver. removal seventeen months after nephrectomy for carcinoma of left kidney. Temporary recovery. *J A M A* 44 1239-1247 1905.
- Idem. Surgery of liver. series of liver cases in which it was necessary to remove segment of liver or to suture torn areas. *Surg Gynec & Obst* 4 573-584 1907.
- Gillette W J. Surgery of liver. *Surg Gynec & Obst* 1 361, 1905.
- Boljarski, N. Über Leberverletzungen in klinischer und experimenteller Hinsicht, unter besonderer Berücksichtigung der isolierten Netzplastr. *Arch. f. klin. Chir* 93 507-547 1910.
- Cushing H. Control of bleeding in operations for brain tumors with description of silver "clips" for occlusion of vessels inaccessible to ligature. *Ann Surg* 54 1-19 1911.
- Grey E G. Fibrin as haemostatic in cerebral surgery. *Surg Gynec & Obst* 21 452-454 1915.
- Harvey S C. Fibrin paper as haemostatic agent. *Ann Surg* 68 66-70 1918.
- Seegers W H. Brinkhous K. M., Smith H. P., and Warner E. D. Purification of thrombin. *J Biol Chem* 126 91-95 1938.
- Seegers W H. Warner E. D. Brinkhous K. M. and Smith H. P. Use of purified thrombin as hemostatic agent. *Science* 89 86 1939.
- Ingram, F. D. and Bailey O T. Clinical use of products of human plasma fractionation. III. Use of products of fibrinogen and thrombin in surgery. *J A M A* 126 680-685 1944.
- Idem. Use of products prepared from human fibrinogen and human thrombin in neurosurgery. fibrin foams as hemostatic agents. fibrin films in repair of dural defects and in prevention of meningocerebral adhesions. *J Neurosurg* 1 23 39 1944.
- Ingram, F. D. Bailey O T. and Nulsen F. Studies on fibrin foam as hemostatic agent in neurosurgery with special reference to its comparison with muscle. *J Neurosurg* 1 171-181 1944.
- Bailey O T. and Ingram, F. D. Use of fibrin foam as hemostatic agent in neurosurgery. XXX. Clinical and pathological studies. *J Clin Investigation* 23 591 596 1944.
- Bailey O T. Ingram F. D. Swenson O. Lowrey J J. and Bering E A. Jr. Human fibrin foam with thrombin as hemostatic agent in general surgery. experimental study and clinical use. *Surgery* 18 347-369 1945.
- Frantz, V K. Absorbable cotton paper and gauze (oxidized cellulose). *Ann. Surg* 118 116-126 1943.
- Frantz, V K. Clarke H. T. and Lattes R. Hemostasis with absorbable gauze (oxidized cellulose). *Ann Surg* 120 181-198 1944.
- Frantz, V K. New methods of hemostasis. *S. Clin. North America* 25 338 349 1945.
- Frantz, V K. and Lattes R. Oxidized cellulose-absorbable gauze (cellulosic acid). *J A M A* 129 798-801 1945.
- Light, R. U. and Prentice H. Gelatin sponge. surgical investigation of new matrix used in conjunction with thrombin in hemostasis. *Arch. Surg* 51 69 77 1945.
- Idem. Surgical investigation of new absorbable sponge derived from gelatin for use in hemostasis. *J Neurosurg* 2 435-455 1945.
- Levitski B P. Hemostasis of wounds of liver. *Am. Rev. Soviet Med* 3 336-338 1946.
- Lowry M. L. Synthetic adhesives in treatment of wounds of liver and other surgical conditions. preliminary report. *Arch. Surg* 52 160-171 1946.
- Jenkins H. P. and Janda R. Studies on use of gelatin sponge or foam as hemostatic agent in experimental liver resections and injuries to large veins. *Ann Surg* 124 952 961 1946.
- Idem. Control of hemorrhage by gelatin sponge. *J Internat. Coll. Surgeons* 10 521-528 1947.
- Thöle F W H. *Ferletzungen der Leber und der Gallenwege* 218 pp. Stuttgart F. Enke 1912 (Vol 4 in *Neue Deutsche Chirurgie* 1912-1941).
- Krieg E C. Hepatic trauma. analysis of sixty cases. *Arch. Surg* 32 907-914 1936.
- Andersson L. Kasuistischer Beitrag zur Kenntnis der subkutanen Leber- und Gallengangverletzungen. *Acta. chir. Scandinav* 59 380-414 1925-26.
- Fox D B. Thoracoabdominal wounds. review of 270 cases. *Surg., Gynec & Obst* 82 64-70 1946.
- Madding G F., Lawrence K. B. and Kennedy P A. War wounds of liver. *Bull U S Army M Dept* 5:579 583 1946.
- Boljarski, N. Über Leberverletzungen auf Grund eines Materials von 109 Fällen. *Beitr. z. klin. Chir* 89 587-593 1914.
- Mann, F. C. Effects of complete and partial removal of liver. *Medicine* 6 419 511 1927.
- Ireneus C., Jr., and Prestow C. B. Effect of massive experimental hemorrhage on hepatic function in dogs. *Arch. Surg* 49 100-103 1944.
- Martin, J D., Jr. Wounds of liver. *Ann Surg* 125 756-767 1947.
- Vance B M. Subcutaneous injuries of abdominal viscera. anatomic and clinical characteristics. *Arch. Surg* 16 631-679 1928.
- Moynihan B. *Abdominal Operations*. Fourth edition. 2 vol. Philadelphia W B Saunders Company 1926. Vol 2 P 237.

Physical examination showed that the patient was in shock, but alert and responsive. There was dullness with decreased breath sounds at the right base, and the ninth, tenth and eleventh ribs in the right midaxillary line were tender. The heart sounds were feeble and rapid. The right upper quadrant was tender but nonspastic. There was slight tenderness in both lower quadrants. The liver edge was tender but not displaced below the right costal margin.

The blood pressure was 40/30, the pulse 125, and the respirations 50.

The patient was given 1500 cc. of 5 per cent glucose in physiologic saline solution, 500 cc. of whole blood and 2 units of plasma; the blood pressure rose to 110/80 1 hour after admission. Gas-gangrene and tetanus antitoxin was also given prophylactically. X-ray examination of the chest and abdomen was negative for pneumoperitoneum, pneumothorax and hemothorax. The red-cell count was 3,500,000, with a hemoglobin of 7.5 gm. and a white-cell count of 25,000. The urine was normal. Abdominal exploration was decided upon, the preoperative diagnosis being rupture of the liver.

Under spinal anesthesia the peritoneal cavity was entered, and at least 1500 cc. of free blood was aspirated. A large, 10-cm., stellate-shaped laceration was found on the dome of the right lobe of the liver. The lacerated liver was packed with two squares of gelfoam and three strips of oxycel, and hemostasis was obtained. Two drains were placed in the peritoneal cavity, one in the subhepatic and the other in the suprahepatic space. The abdomen was closed in layers with No. 1 chromic catgut and No. 28 steel-wire stay sutures.

The patient was placed on gastric suction for 3 days. An x-ray film of the chest on the 4th postoperative day revealed fluid in the lower right pleural cavity. On the 5th postoperative day the drains were removed, and he was allowed out of bed. The right side of the chest was tapped, and 1000 cc. of serosanguineous fluid was obtained on the 15th postoperative day. A repeated chest tap 4 days later yielded 150 cc. of foul-smelling pus, from which a hemolytic *Staphylococcus aureus* and *Proteus vulgaris* were cultured.

A diagnosis of subphrenic abscess was made, and on the seventeenth day a thoracotomy was performed, 200 cc. of pus being evacuated from the right subphrenic space. Culture of the thoracotomy fluid revealed *Pseudomonas aeruginosa* and enterococci. The thoracotomy drain was removed 1 week later. The patient received penicillin for approximately 1½ months and was discharged 50 days after admission with a slight amount of purulent drainage from the chest wound.

**CASE 2 (BCH 1267897)** B M, a 26-year-old man, was admitted to the hospital on November 25, 1947, with a history of having been struck by an automobile and dragged approximately 50 feet. He complained of moderately severe right-sided chest pain. This pain was aggravated by deep breathing and was relieved when the patient lay on the right side.

Physical examination showed a conscious and co-operative man who was in shock. There was decreased expansion of the right lung, but the lung fields were clear to percussion and auscultation. The heart sounds were distant and thready. Both upper abdominal quadrants were tender, but there was no muscle spasm. Intestinal peristalsis was audible.

The blood pressure was 60/0, the radial pulse was absent, and the respirations were 36.

X-ray examination revealed no pneumothorax, hemothorax or pneumoperitoneum. Examination of the blood disclosed a red-cell count of 4,010,000, with a hemoglobin of 13.5 gm., and a white-cell count of 20,000. The urine was normal. Plasma, whole blood and gas-gangrene and tetanus antitoxin were given. The blood pressure rose to 100/60. The preoperative diagnosis was rupture of the liver. Abdominal exploration was decided upon.

An upper right-rectus-muscle-splitting incision was made in the abdomen under spinal anesthesia, and whole blood was transfused into the veins of an arm and leg simultaneously. The peritoneum was opened, and about 2 liters of free blood was found in the peritoneal cavity and aspirated. Large jagged lacerations were found in the domes of the right and left lobes of the liver. Oxycel gauze was packed into these lacerations and sutured loosely to the liver with No. 0 chromic catgut. The abdominal wall was closed in layers with No. 1 chromic catgut and four silk stay sutures without drainage.

The patient remained on intestinal suction for 5 days and was sustained on 3000 cc. of fluids administered intravenously

each day. The patient was able to walk on the 2nd postoperative day. X-ray examination showed some haziness present in the left-lower-lung field on the day after operation, but this rapidly cleared by the 10th day. All sutures were removed on the 11th postoperative day. The patient received penicillin intramuscularly for 12 days and was discharged as improved 15 days after admission.

**CASE 3 (BCH 1276872)** N S, a 27-year-old Negress, was admitted to the hospital on February 27, 1948, after having been struck by an automobile. The patient was in shock and complained of severe constant pains in the right shoulder, right lateral portion of the chest and right upper quadrant. These pains were aggravated by breathing.

Physical examination showed the patient to be alert, oriented and co-operative but apprehensive. The skin was cold, clammy and ashen gray. There was splinting of the right side of the chest. The right leaf of the diaphragm was elevated, and the right tenth, eleventh and twelfth ribs in the midaxillary line were tender. The chest revealed no pneumothorax or hemothorax. The heart sounds were weak and rapid. The liver edge was felt 2 fingerbreadths below the right costal margin and was very tender. There was marked tenderness in the right upper quadrant with bilateral rectus-muscle spasm. Intestinal peristalsis was absent. At the junction of the middle and upper thirds of the right leg there was a bony deformity with crepitation, indicating a fracture site.

The blood pressure was 60/40, the pulse 120 to 150, and the respirations 50.

Examination of the blood disclosed a red-cell count of 3,470,000, with a hemoglobin of 10.5 gm., and a white-cell count of 22,150. A specimen of urine was negative for blood.

The patient was given 1500 cc. of 5 per cent glucose in physiologic saline solution, 300 cc. of plasma and 300 cc. of whole blood. The blood pressure rose to 110/70, and the pulse dropped to 112. The right lower quadrant was tapped with a spinal needle, and free blood was obtained from the peritoneal cavity. Because of the patient's response to shock therapy 7 hours after admission, abdominal exploration was decided upon, the preoperative diagnosis being rupture of the liver and questionable rupture of a hollow viscus.

Under spinal anesthesia, while blood was being transfused into one arm and leg, an upper-right-rectus-muscle-splitting incision was made in the abdomen. When the peritoneum was incised, about 1 liter of blood poured out from the peritoneal cavity. The blood was sucked out from the liver and a 12.7-cm. stellate laceration was palpated on the dome of the right lobe of the liver. The stellate laceration was sponged out with dry gauze and packed with four strips of oxycel gauze and held with moderate pressure until hemostasis occurred. The liver capsule was subsequently sutured to the inferior surface of the diaphragm and a portion of the anterior abdominal wall to prevent a suction effect of the diaphragm on the liver. The abdomen was closed without drainage, No. 1 chromic catgut being used as suture material and No. 28 steel wire for stays.

On the third postoperative day the fractured right lower leg was reduced under spinal anesthesia and set in a mid-thigh-to-toes plaster cast. On the 5th postoperative day chest films revealed development of fluid in the right-lower-lung field. The skin sutures and steel stays were removed on the 8th and 11th days after operation. The right side of the chest was tapped on the 26th postoperative day, and serous fluid obtained. Culture of this fluid was negative. Repeated check of x-ray films of the chest revealed clearing of the fluid in the right base. Two months after operation, the cast on the right leg was removed, and a brace applied. The patient received penicillin intramuscularly for 6½ weeks and was ambulatory after the 11th postoperative day. She was discharged 67 days after admission as improved.

## DISCUSSION

The use of absorbable hemostatics in liver surgery is a new procedure. Very little is known of their application to human beings, since most of the literature deals with their use in animals. The cases presented above may be of significance in

It is the consensus of those working in this field that in only a small group of patients are quantitative tests of pulmonary function, particularly divided functions, necessary, but that in the borderline cases they are of tremendous practical help.

Cournand and Richards<sup>19</sup> have reviewed the subject of pulmonary insufficiency and adapted many of the previous laboratory studies to the purposes of clinical medicine. Drawing on their own experience and that of others, they have distinguished between the ventilatory and respiratory aspects of pulmonary function with symptoms of dyspnea and cyanosis respectively. Dyspnea is usually dependent upon a mechanical fault, which in turn may result in a physicochemical imbalance. The two factors may be combined, and they may or may not have cardiocirculatory complications. In the study of ventilatory insufficiency, Cournand and Richards have recommended the following maximum breathing capacity, — that is, maximum voluntary ventilation per unit of time (normally, 154 liters per minute for male and 100 liters per minute for female patients), breathing requirement, and breathing reserve, which equals maximum breathing capacity minus the actual ventilation per minute in any given physical state. The authors have considered the ratio of breathing reserve to maximum breathing capacity a useful index of pulmonary function that could be correlated with observed dyspnea in their cases. Their own experience and that of others suggested that a decrease in arterial oxygen saturation and a decrease in the rate of oxygen removal from the inspired air (ventilatory equivalent) were the most useful indicators of respiratory insufficiency. In a group of 31 thoracoplasty patients, it was apparent that by far the greater part of the subject's loss of pulmonary function existed prior to operation. Of some practical interest was the fact that when the reserve was less than 85 per cent of maximum breathing capacity, a difficult postoperative course was likely. In a review of the published experience of many authors,<sup>20-23</sup> it is apparent that maximum breathing capacity

is the clinical cornerstone of external spirometric methods, replacing the time-honored but

unreliable vital capacity, bronchspirometry, or internal spirometry, has had extensive clinical application, chiefly in the field of collapse therapy.<sup>24-26</sup> Here, the limitations imposed by "stenosis breathing" have

rendered interpretation of results difficult. Norris, Long and Oppenheimer<sup>26</sup> have recently attempted to minimize this factor by using a single-lumen endobronchial catheter to replace the double-lumen catheter of Zavod<sup>27</sup> or Gebauer,<sup>28</sup> which, in turn, replaced the bronchoscopic method of Jacobaeus. The differential uptake of oxygen, usually in conjunction with the ventilatory function of each lung has been the basis of most studies. The analogy

to split renal-function studies is obvious, but the validity of interpretation is not so clear.

Vaccarezza et al<sup>29</sup> have recently described 15 cases of marked discrepancy between clinicoradiologic and bronchspirometric findings. The difficulties of determining function on the basis of the x-ray film are obvious, but it is of interest that the authors accept the laboratory data as their frame of reference when it is apparent, on review of the protocols submitted, that artifacts, particularly those arising from bronchial secretions blocking the airway, may have greatly modified results. In so complex a function as respiration, quantitative measurements must be interpreted with caution. Wright and Woodruff<sup>30</sup> have discussed the complexities of bronchspirometry and have demonstrated many of the variables involved in its clinical application. Wright<sup>31</sup> has recently reported a case of chronic tuberculous empyema in which, after decortication and expansion of the lung, there was only slight increase in ventilation of that lung, and the development of incomplete arterial oxygen saturation. This case is of interest as a qualitative measure of physiologic loss to offset a radiologic gain.

Pulmonary edema has been the subject of a monograph by Drinker,<sup>32</sup> who defends the thesis that pulmonary edema and related phenomena depend more upon alterations and permeability of lung capillaries than upon complicated pressure relations in the pulmonary circulation. Anoxia a cause of increased capillary permeability throughout the body, is considered to be equally effective in the lungs, but the capillary membrane is dependent upon the oxygen of the alveolar air rather than upon that in the blood stream. By blocking the alveoli, "anoxia begets anoxia" as, in shallow breathing, anoxemia, by depressing the respiratory center, leads to further anoxemia.

Eaton<sup>33</sup> has approached the problem of pulmonary edema consequent upon acute blood loss. He had noted an increase in pulmonary lymph flow and histologic evidence of edema in dogs suffering acute loss of 25 per cent of blood volume from the femoral artery. Experimentally, a disproportionate rise of pulmonary-artery pressure seemed to be a significant change in a cycle of progressive circulatory imbalance, which included low systemic arterial pressure and elevated peripheral venous pressure. This fact was interpreted as evidence of an obstruction to normal circulation existing in the lung or the left side of the heart, or both. From this point of departure, efforts were made to measure "pulmonary moisture" under experimental conditions of hemorrhage and replacement. It became obvious that replacement by intravenous saline solution of blood lost led to more consistent and greater increases in "pulmonary moisture" than did replacement by blood. The clinical application of this is apparent.

## MEDICAL PROGRESS

### THORACIC SURGERY

J GORDON SCANNELL, M D \*

BOSTON

THIS report concerns the following aspects of advances in thoracic surgery anatomy of the lung, physiologic considerations, chest injuries, cancer of the lung, tuberculosis, coccidioidomycosis, suppurative disease, bronchiectasis, the esophagus, congenital atresia, and miscellaneous considerations

#### ANATOMY OF THE LUNG

In recent years, significant progress has been made in precise descriptive anatomy of the lung. Advances have been made along two broad lines: accurate topographic description of the bronchopulmonary segment, and reduction of the complexities of bronchovascular anatomy to a reasonable schedule.

Although there is quite general agreement among anatomists and surgeons regarding the disposition of the segments, there is less agreement about their terminology. Boyden,<sup>1</sup> has accepted the nomenclature of Jackson and Huber<sup>2</sup> as the most accurate and simplified currently available. This terminology is based upon the position of the segment within the lobe, rather than upon its relation to the chest wall or adjacent structures. British authors—Brock,<sup>3</sup> Foster-Carter,<sup>4</sup> Appleton<sup>5</sup> and others—have inclined toward the latter view. Brock has published an extremely useful volume on the anatomy of the bronchial tree, which, together with the papers of Jackson and Huber (1943), and Boyden (1945), covers the subject admirably. Boyden<sup>6-10</sup> has also embarked upon a thorough quantitative study of bronchial variations and related bronchovascular patterns.

By way of summary the following schedule of the bronchopulmonary segments is appended, Huber's terminology, Boyden's system of enumeration and, parenthetically, Brock's nomenclature being used.

#### Right Upper Lobe

- 1 Apical (*apical*)
- 2 Anterior (*pectoral*)
- 3 Posterior (*subapical*)

#### Right Middle Lobe

- 4 Lateral (*lateral*)
- 5 Medial (*medial*)

#### Left Upper Lobe

- 1 + 3 Apical-posterior  
(*apical-subapical*)
- 2 Anterior (*pectoral*)
- 4 Superior lingular
- 5 Inferior lingular

#### Right Lower Lobe

- 6 Superior (*apical*)
- 7 Medial basal (*cardiac*)
- 8 Anterior basal (*anterior basal*)
- 9 Lateral basal (*middle basal*)
- 10 Posterior basal (*posterior basal*)

#### Left Lower Lobe

- 6 Superior (*apical*)
- 7 + 8 Anteromedial  
basal (*anterior basal*)
- 9 Lateral basal (*middle basal*)
- 10 Posterior basal (*posterior basal*)

As technical experience with excision of the lung has increased, the need for precise knowledge of the associated vascular arrangement within the lung has become apparent. The surgical contributions of Churchill and Belsey,<sup>11</sup> Kent and Blades<sup>12</sup> and Miskall and Cornell<sup>14</sup> are well known. Recently, Overholt<sup>15</sup> has discussed the subject in surgical detail relative to segmental resection. Regarding bronchovascular anatomy, the studies of Boyden and his associates<sup>6-7</sup> and also of Appleton<sup>16</sup> are of great importance. Complex by necessity, they are available reference material for future clinical developments. In Boyden's work the prevailing bronchovascular pattern and common variations therefrom are discussed in detail and suitably illustrated. The segmental nature of the pulmonary arterial supply, corresponding in general to the bronchial segments, but with considerable variation at the level of the hilus, has been confirmed. The veins, on the other hand, have been shown to be intersegmental. The major clinical application of these studies has been in the technics of segmental resection.

Liebow et al.<sup>17</sup> have reported an excellent and relatively simple method of preparing lungs by the injection of various colored plastics. Particularly in the study of abnormalities of bronchial-artery supply, as well as the production of exquisite anatomic specimens, the method should be of great value. Cauldwell and his associates<sup>18</sup> have described the complexities of the bronchial-artery supply on the basis of 150 cadaver dissections. There is obviously a rich collateral circulation at the level of the lobar bronchus, and great variation in both origin and distribution of the main bronchial-artery trunks.

#### PHYSIOLOGIC CONSIDERATIONS

The measurement of pulmonary function, either total or of each lung separately, continues to have its greatest clinical application in collapse therapy.

\*Instructor in surgery Harvard Medical School assistant in surgery Massachusetts General Hospital

and partial obstruction of the airway. They have postulated a somatovisceral reflex, accounting, in part at least, for changes in the underlying lung following painful injuries to the chest wall. Experimental support is found in the work of deTakats et al,<sup>46</sup> who noted, in the dog, bronchial spasm and increased bronchosecretory activity after trauma to the chest wall, as well as after experimental pulmonary embolization and intra-abdominal manipulation. Daniel and Cate<sup>47</sup> have produced "wet lung" in anesthetized dogs by blunt trauma and tangential bullet wounds of the thoracic cage. Effects of this trauma could be intensified by intravenous infusions of saline, which also produced "wet lung" in dogs breathing low concentrations of oxygen. The effects of excision of large portions of the pulmonary sympathetic supply upon the development of generalized "wetness" were not conclusive, but suggested that the condition was, in part, a reflex phenomenon. Interference with respiratory motion and decrease in effective cough have seemed to many to offer adequate explanation of the pulmonary moisture and collapse following thoracic injury, and reason enough to employ intercostal block in their relief.

To render oxygen administration effective, Army technical bulletins<sup>48</sup> have been explicit in recommending the free and prompt use of tracheal suction or bronchoscopic aspiration. Samson and Brewer<sup>49</sup> have recently reviewed their experiences in this regard and outlined practical suggestions to improve inadequate tracheal-bronchial drainage following trauma to the chest. The technics of tracheal aspiration and the importance of forced cough after the airways have been cleared are carefully explained.

One of the definite departures from prewar practice has been in the treatment of hemothorax. On the theoretical ground of controlling continuing bleeding from a lacerated lung, aspiration of blood with air replacement had been recommended. During the war, however, it was found that continuing intrapleural hemorrhage was rarely of pulmonary origin, that prompt re-expansion of the lung was desirable and that prompt needle aspiration of massive hemothorax, the blood obtained being used for autotransfusion if necessary, should be carried out. The use of whole blood in chest wounds, when it is of obvious importance to restore the oxygen-carrying capacity, as well as the volume of circulating blood, was established.

The late effects of intrapleural bleeding with clotted hemothorax or chronic hematoma of the pleural space were responsible for one of the more dramatic surgical developments of the war—namely, pulmonary decortication. Samson and Burford<sup>50</sup> have presented an excellent general review of the subject and have given a detailed account of the technic of operation. They have emphasized the fact that the fundamental lesion

is not of the pleura itself but of a false membrane overlying the pleura. The aim of the procedure is early restitution of pulmonary function, and the avoidance of the late, crippling effect of extensive fibrothorax. They, in common with most authors who have written on this subject, limit their procedure chiefly to the visceral pleura and are not concerned with the parietal peel. In the uninfected clotted hemothorax, decortication was carried out four to six weeks after trauma if there appeared, by x-ray examination, to be lateral pulmonary compression of 50 per cent or more, if there were obvious limitations of chest expansion and if there was clinically significant shortness of breath. It was believed that prior to three weeks after injury, the peel was not sufficiently tough to permit satisfactory removal, and that after that time fibrous changes were found in the lung. In cases of infected hemothorax, the time of operation was advanced to about two weeks after trauma. Signs of increasing toxicity, mounting fever or rapid increase in the size of the hemothorax were considered presumptive evidence of infection. In 125 cases in which operation was performed, there were no deaths and no serious sepsis, and less than 25 per cent of patients had residual empyemas, the great majority of which were small and basal in location. The authors estimated that approximately 1500 early decortications had been done in the armed forces with an operative mortality of less than 2 per cent.

Tuttle, Langston and Crowley<sup>51</sup> have also reported essentially similar experiences with early decortication for chronic traumatic hemothorax and have described in detail the pathological changes encountered in this condition. Of 89 cases of uninfected (not grossly infected), and 51 grossly infected hemothoraces, a total of 140 cases, the results were good in 77.1 per cent, fair in 18.6 per cent and poor in 4.3 per cent, there were no deaths. Their criterion for "good" was exacting—namely, that the lung after the operative procedure expanded completely in forty-eight hours. A "fair" result meant that the ultimate result was good, but somewhat delayed. In the cases of infected organizing hemothorax (51 cases), primary healing of the empyema occurred in 49.1 per cent, eventual healing in 45.1 per cent and chronic empyema in 5.8 per cent. Penicillin was not always available during the course of this study and was used in 77 of the 140 patients. It is of interest that all 25 patients who experienced primary closure of the empyema space after decortication received penicillin. Sanger<sup>52</sup> has argued that perhaps the importance of penicillin has been overrated in decortication for empyema, admitting, however, that it has given the surgeon courage to proceed in the presence of severe infection. He believed that the mechanical removal of the culture medium upon which the organisms could grow and the re-expansion of the

Collateral ventilation has been restudied by Baarsma and Dirken<sup>34</sup> spirometrically, confirming, in rabbits, the previous work of Van Allen and his associates in dogs. The Dutch authors have also extended their studies to man.<sup>35</sup> In a limited series of observations, using an occluding catheter with an inflatable cuff, no collateral ventilation was apparent on occlusion of a lobar bronchus, but definite collateral ventilation was demonstrated upon occlusion of a segmental bronchus in the lower lobe. Lindskog (who contributed much to the early studies in this field) and Alley<sup>36</sup> have recently observed in dogs that the intravenous administration of histamine results in the abrupt cessation of collateral respiration that persists for variable periods of minutes. This effect is abolished by prior administration of benadryl. It seems important to extend these observations to other agents in common clinical use and to changes in the physiologic state of the patient.

Perhaps the physiologic advances that have the greatest bearing on thoracic surgery have been consequent upon the recent development of the cardiac-catheterization technic. First introduced by Forssman in 1929, much of its recent development is attributable to the efforts of Courmand and his associates.<sup>37</sup> Furthermore, effective teamwork between physiologist and surgeon has been particularly apparent in the combined efforts of Bing et al.<sup>38</sup> on the one hand and Blalock and his co-workers on the other. McMichael,<sup>39</sup> in Great Britain, and Dexter and his associates,<sup>40</sup> in Boston, have also contributed significantly to the subject. The use of the method is by no means limited to these few centers, and the literature on the subject is extensive.

The earliest of recent efforts were directed toward accurate measurement of cardiac output utilizing the Fick principle, which, stated simply, is that cardiac output equals oxygen intake divided by arteriovenous oxygen difference. Heretofore, inaccuracies had arisen from the inability to obtain true mixed venous blood. By sampling directly from the auricle, the ventricle or the pulmonary artery this source of inaccuracy could be obviated.<sup>37</sup> By further development of the Fick principle, direction and amount of flow in abnormal circulatory shunts could be estimated.<sup>38-40</sup> By study of pressure changes in the ventricles, pulmonary arteries, peripheral arteries and other portions of the circulatory system, more accurate study of hemodynamics is now possible, and precision methods of the experimental laboratory can be applied to clinical problems. Changes in the pulmonary circulation under physiologic and pathologic conditions are at present under the closest scrutiny.<sup>38-40-41-43</sup>

Although cardiac catheterization has been a relatively safe procedure, there are hazards attendant upon its use. Cardiac irregularities during catheterization are not uncommon, there is always

the hazard of air embolism in the presence of a right to left shunt, and intimal damage though presumably rare, remains a possibility. However with proper indications, there can be little doubt of the clinical and experimental value of the method.

### CHEST INJURIES

In the war the principles underlying the management of serious injuries to the chest were tested against a tremendous volume of experience. Many concepts, proved valid after much extensive trial, are directly applicable to the severe chest injuries encountered in civilian practice and in the casualties of heavy industry and high-velocity automobiles.

Churchill<sup>44</sup> has presented, in general terms, the management of thoracic casualties in the military theater to which he was consultant. He has emphasized the importance of distinguishing two phases of chest trauma: the serious disturbance of cardio-respiratory physiology that demands prompt and intelligent treatment, and the problem of infection, which requires fully as intelligent but less urgent attention. More specifically, he suggests, "the urgent physiologic disturbances that attend wounds of the chest can be controlled by needle aspiration of air and blood, aspiration of blood and mucus from the tracheobronchial tree, novocaine injection of intercostal spaces, insertion of a catheter with a flutter valve for pressure pneumothorax, oxygen therapy and transfusions, and débridement of sucking wounds with hemostasis of intercostal vessels and approximation of deep structures of the chest wall to close the pleural opening." In the emergency treatment of such wounds, however, an occlusive dressing of petrolatum gauze and adhesive strapping was not only adequate but also preferable to an airtight closure in that it could act as an escape valve in case a persistent bronchial leak were present.

Of the measures detailed above, some have important application to trauma as seen in civilian life. Significant among these is the use of intercostal block for the relief of pain, as opposed to the time-honored but physiologically unsound, overgenerous use of morphine and tight adhesive strapping. The latter should be reserved for minor rib fractures, and possibly also for a few cases of paradoxical motion of the chest wall resulting from anterior and posterior fractures of the ribs. In such cases, when the paradoxical motion is of an intolerable degree, open operation may be necessary. By permitting the patient to cough effectively and breathe actively, intercostal block is instrumental in maintaining a clear airway so essential to the patient. Some authors, notably Burford and Burbank,<sup>45</sup> on the basis of considerable first-hand experience with thoracic casualties, have argued that the "wet lung of trauma" may depend on more than mechanical interference with the chest bellows.

histology of fragments in the sputum, with careful study of the characteristics of the individual cells.

More recently, there has been widespread interest in the cytologic study of sputum by the Papanicolaou technic or its modifications. At the recent Quebec meeting of thoracic surgeons, Watson et al.<sup>66</sup> reported their experience in the study of pulmonary neoplastic disease. In 400 cases studied at The Memorial Hospital, 236 patients had carcinoma, and of these, 141 (60 per cent) had positive sputums. False-positive reactions occurred in 4 of an over-all group of 1200 cases. In 3 cases the specimen came from a patient subsequently found to have bronchiectasis, and the confusing cells were probably fragments of papillomatous growths of the bronchial mucosa such as have been previously described.

In 1946 Herbut and Clerf<sup>67</sup> reported 83 cases studied, in which 38 patients had carcinoma — 30 with positive sputums, or 79 per cent positive reactions. No false-positive tests were reported. These authors stressed the desirability of studying bronchial washings obtained at time of bronchoscopy by saline irrigation and aspiration of specific limbs of the bronchial tree, rather than sputum, which is more dilute and whose source is less specific. A preliminary survey of the experience with pulmonary cases at the Massachusetts General Hospital yields the following figures.<sup>68</sup> In a total of 157 cases studied in 1946, 56 patients were shown to have carcinoma of the lung. One hundred and nineteen had sputum studies, with false-negative reactions in 37.9 per cent and false-positive reactions in 6.0 per cent. In 81 cases cytologic examination of bronchial washings was performed, with 56 per cent false-negative and 1.8 per cent false-positive tests. In the following year, 123 cases were studied with either or both methods. Fifty-four patients had cancer. Examinations of the sputum were performed in 74 cases, with 25.7 per cent false-negative and no false-positive reactions. In 60 cases of bronchial aspiration there were false-negative tests in 66.0 per cent and no false-positive tests. Strieder<sup>69</sup> reports the experience at the Boston City and the Massachusetts Memorial Hospitals, as follows: in 170 cases studied bronchoscopically, 48 patients had carcinoma proved histologically, and 6 had unequivocal clinical evidence of carcinoma. Positive smears were obtained in 40, or 74 per cent of the 54 cases. False-positive reactions occurred in 3 cases, or 1.8 per cent. Bronchoscopy was positive in 29 of the 54 cases, or 54 per cent.

A review of the reported experience at large makes it apparent that theoretically and in practice, cytologic examination of the sputum will give a higher percentage of positive results than bronchoscopic biopsy. Added to the other data obtained in a given case, it may be an important bit of evidence, when positive, on which the decision to operate may be based. Particularly in the early and ob-

scure case, it may be of great value in strengthening the surgeon's hand. It is also apparent that the incidence of false-negative reactions is sufficiently high so that a negative examination cannot be strongly considered in ruling out carcinoma — 18 per cent in Wandall's<sup>65</sup> series, 43 per cent in that of Gower,<sup>64</sup> 21 per cent in that of Herbut and Clerf,<sup>67</sup> 36 per cent in that of Graham,<sup>68</sup> 40 per cent in that of Watson et al.,<sup>66</sup> and 26 per cent in that of Strieder.<sup>69</sup>

Other than the introduction of cytologic methods, little has been added to the diagnostic devices of the expert consultant in carcinoma of the lung. The value of bronchoscopy is well known, but Churchill's<sup>62</sup> statement should be emphasized:

The purpose of bronchoscopy extends beyond the removal of a fragment of tissue to confirm the histologic diagnosis. Unless the examination is carried out by an operator who is accustomed to make his observations in terms of the feasibility of a surgical attack on the lesion, the bronchoscopy may have to be repeated by one who is

Bronchography is rarely indicated in diagnosis of cancer of the lung, and except under unusual circumstances may complicate further x-ray studies and clinical management of the case. It should be emphasized that x-ray study implies a real responsibility of the roentgenologist in assisting in the management of the patient, and not merely the routine chest film. Were it not for the great number of cases in which the observation is not made until late, it would seem superfluous to recall the importance of a careful palpation of the neck for metastases to lymph nodes. Simple biopsy of these may not only lead to the diagnosis but also determine the whole plan of management and save the patient prolonged hospitalization, often at considerable distance from home.

In summarizing the problem of early diagnosis and the management of the patient, Churchill<sup>62</sup> writes as follows:

This review of the responsibilities of the expert consultant makes it obvious that he should have at his command a number of diagnostic techniques that range from careful case history taking and physical examination, to thoracotomy for biopsy of a doubtful lesion. These responsibilities must be faced in logical sequence and carried through without delay. On the other hand, the consultant may indulge in certain assumptions relative to his responsibility that are not altogether warranted. Attention is called to these because they may retard the development of that close relationship between practitioner and specialist that is desired to promote progress in cancer control. They also directly influence the extent to which the patient will respond to the educational efforts that urge him to consult a physician in regard to early symptoms.

One of these assumptions is that the expert must invariably exclude any possibility of cancer, however remote, by resorting to major diagnostic techniques without regard to whether the clinical problem under consideration indicates their use. Another false assumption is that a presumptive clinical diagnosis always must be extended to histological confirmation despite the fact that the course of management is obviously not going to be altered by the reading of the microscopic slides. Finally, in deciding on the course that the management of an advanced case is to take, surgical exploration is oftentimes proposed as the

incarcerated lung were of more importance than chemotherapy, which, however, seemed to be of greatest effect in preventing invasive infection. As a result it now appears not only possible but also, in many cases, advisable to convert a localizing empyema into a generalized pleural contamination to re-expand the lung, thereby reversing the field completely so far as the classic treatment of empyema is concerned.

One of the casualties of the war has been the sanctity of the diaphragmatic barrier. For many years the transthoracic route to the structures of the upper abdomen has been employed, but not with the zeal and general enthusiasm that is now apparent.<sup>53</sup> It seems reasonable to suppose that the wide experience with thoracoabdominal wounds in the recent conflict has done much to break down the old pattern of thought, which divided the body neatly at the midriff. Space does not permit a review of the many excellent reports of experience in large thoracic centers and general hospitals in the Army and Navy.<sup>54-60</sup> In a sense, these reports are the source material from which broader concepts of the management of serious thoracic injury have been derived.

Blades<sup>61</sup> has recently summarized the opinion of many others that the advances in the treatment of chest injuries during the war were largely the result of judicious timing and selection of surgical procedure rather than technical improvement. In summary of the application to civilian emergencies of lessons learned from the military, he has emphasized the use of whole blood in the treatment of shock, the dangers of excessive use of morphine, the control of chest pain by paravertebral block, the treatment of "traumatic wet lung" by paravertebral block, oxygen and tracheobronchial aspiration, the early aspiration of hemothorax to effect complete re-expansion of the lung and conservation of cardiopulmonary function, and, finally, decortication in cases of clotted hemothorax based on indications established in the war.

## CANCER OF THE LUNG

### *Earlier Diagnosis*

Churchill<sup>62</sup> has recently reviewed the problem of cancer of the lung and re-emphasized the need of earlier diagnosis, pointing out that it is doubtful if more radical treatment can be devised that will materially improve results. The limits of operability — so far as the patient's chance of surviving major surgery are concerned — have been extended, so that resectability rates are steadily being revised upward. It is important to remember, however, that the rates are a measure not only of the individual courage and skill of the operator but also of the process of selection of cases before the patient reaches the surgeon. There is therefore

great need for intelligent teamwork between practitioner and expert consultant.

For various reasons, detection by means of survey films shows only moderate promise. Men between forty and sixty, the age group that suffers the highest incidence of pulmonary cancer, are the most difficult to include in any survey. Furthermore, except for the few silent peripheral lesions, x-ray changes are usually dependent upon bronchial encroachment, which produces symptoms sufficient to send the patient to the doctor.

The symptoms of cancer of the lung are well known and need no repetition here, except to recall that they may be so commonplace as to escape the serious attention of the patient or his physician. As many have emphasized, the important points in a review of symptoms are change in cough habits, persistent, unexplained or rationalized x-ray shadow, persistent streaking of the sputum — corresponding to the constant trickle from a gastrointestinal cancer that gives rise to occult blood in the stool, and the cold that "hangs on."

One of the more important recent advances in the diagnosis of cancer of the lung has been the increasing use of cytologic studies of the sputum or of bronchial secretions. Many papers dealing with the technics of such studies are available. As in any precise laboratory maneuver, great attention must be paid to the details of collecting and preparing the material, and considerable mature judgment must be exercised in interpretation of specimens. Although examination of the sputum for tumor cells had been done sporadically for many years, the first widespread and successful clinical application of the method was reported by Dudgeon and Wrigley<sup>63</sup> in 1935. They found 43 positive sputums in 56 cases of proved carcinoma of the lung — that is, false-negative tests in 23 per cent of their cases. In 2 of 102 cases the sputum was reported positive, but these cases were ultimately proved to be of inflammatory nature — false-positive reactions, therefore, in 2 per cent of cases. In 1943 Gower,<sup>64</sup> at the London Hospital, reported a series of 93 patients suffering from pulmonary disease of whom 63 were proved to have carcinoma. Of these, 36 (57 per cent) had a positive sputum — false-negative reactions, therefore, in 43 per cent. The number of false-positive tests was not stated. Wandall, in 1944,<sup>65</sup> reported extensive experience culled from the hospitals of Copenhagen. One hundred and ninety-three patients with pulmonary disease were studied, 120 of whom were proved to have carcinomas of the respiratory tract, of which 100 were carcinomas of the lung. Of the 120, there were positive sputums in 98 (82 per cent), or 18 per cent false-negative reactions. Of the 193 cases, there were 32 per cent false-positive tests in cases of chronic pneumonia and tuberculosis. Wandall's series and those reported above were based on the

- 61 Blades B Injuries of chest. *J A M A* 135 812-814 1947  
 62 Churchill E. D Primary carcinoma of lung *J A M A* 137 455-461 1948  
 63 Dudgeon L. S., and Wrigley C. H. On demonstration of particles of malignant growth in sputum by means of wet film method *J Laryng & Otol* 50 752-762 1935  
 64 Gower F J S Carcinoma of lung value of sputum examination in diagnosis *Brit. J Surg* 30 193-200 1943

- 65 Wandall H. H. *A Study on Neoplastic Cells in the Sputum* 128 pp Copenhagen Nyt Nordisk Forlag Arnold Busck, 1944  
 66 Watson W L. Personal communication  
 67 Herbert P A and Clerf L. H. Bronchogenic carcinoma diagnosis by cytologic study of bronchoscopically removed secretions *J A M A* 130 1005-1012 1946  
 68 Graham R. M. Personal communication  
 69 Strieder J W. Personal communication

## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

TRACY B MALLORY M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

EDITH E PARRIS, *Assistant Editor*

### CASE 34501

#### PRESENTATION OF CASE

*First admission* A thirteen-year-old girl entered the hospital complaining of pain in back of the left knee and in the hips

The symptoms were first noted one and a half years prior to admission, following strenuous activity or occasionally after prolonged sitting in one position. The pain was usually relieved by resting the leg. X-ray films were taken at the time of onset of the pain and were reported as normal. However, repeat films six months later revealed undescribed changes. The patient was then placed in a spica cast for three months, followed by a nonweight-bearing cast for an additional six months. Neither the cast nor the brace effected much change in the symptoms, which continued as before. The pain was not too well localized but seemed to be mostly in the left groin and popliteal space. At first the pain was periodic and related to activity, but later became more or less continuous and was not affected by exercise or relieved by rest. Aspirin usually brought relief, which lasted about four hours. The patient ran a low-grade afternoon fever (temperature of 99.4 to 99.6°F), but there were no chills, night sweats or cough.

The past and family histories were entirely irrelevant.

Physical examination showed a well developed and well nourished girl. Examination was entirely negative except for the left leg and hip. The legs were equal in length, but there was atrophy of the left thigh and calf. The hip was held in 20° permanent flexion. Rotation in extension was about two thirds

normal. Abduction and adduction were very slightly limited. On flexion the hip went into 30°



FIGURE 1

of permanent external rotation and into 20° of abduction at right-angle flexion.

The temperature was 99.8°F, the pulse 90, and the respirations 20. The blood pressure was 110 systolic, 65 diastolic.

Examination of the blood showed a hemoglobin of 14 gm and a white-cell count of 10,900, with 59 per cent neutrophils, 30 per cent lymphocytes, 10 per cent monocytes and 1 per cent eosinophils. The

"only chance" and as such, one that cannot be denied the patient. In their quest for scientific exactitude the members of the profession must not confuse scientific precision with which certain parts of the evidence can be formulated, with the broad responsibility of weighing evidence as a whole. Courts of law may exact severe or even capital punishment if the evidence as a whole is judged valid "beyond any reasonable doubt." It is the responsibility of the consultant in conference with the family medical advisor to determine whether the "only chance" offered by surgical treatment is in truth a reasonable chance, or whether the cancer is surgically "out of bounds" beyond any reasonable doubt.

(To be concluded)

## REFERENCES

- 1 Boyden, E. A. Intrabronchial and related segmental anatomy of lung. *Surgery* 18:706-731, 1945
- 2 Jackson C. L. and Huber J. F. Correlated applied anatomy of bronchial tree and lungs with system of nomenclature. *Dis of Chest* 9:319-326, 1943
- 3 Brock R. C. *The Anatomy of the Bronchial Tree with Special Reference to the Surgery of Lung Abscesses*. 96 pp. London: Oxford University Press, 1946
- 4 Foster-Carter A. F. Anatomy of bronchial tree. *Brit J Tuberc* 36:19-39, 1942
- 5 Appleton A. B. Segments and blood vessels of lungs. *Lancet* 2:592-594, 1944
- 6 Boyden, E. A. and Hartmann J. F. Analysis of variations in bronchopulmonary segments of left upper lobe of fifty lungs. *Am J Anat* 79:321-360, 1946
- 7 Boyden E. A. and Scannell J. G. Analysis of variations in bronchovascular pattern of right upper lobe of fifty lungs. *Am J Anat* 82:27-73, 1948
- 8 Scannell J. G. Study of variations of bronchopulmonary segments in left upper lobe. *J Thoracic Surg* 16:530-537, 1947
- 9 Scannell J. G. and Boyden E. A. Study of variations of bronchopulmonary segments of right upper lobe. *J Thoracic Surg* 17:232-237, 1948
- 10 Smith F. R. and Boyden E. A. Unpublished data
- 11 Churchill, E. D. and Belsey R. Segmental pneumonectomy in bronchiectasis: lingula segment of left upper lobe. *Ann Surg* 109:481-499, 1939
- 12 Kent, E. M. and Blades B. Anatomic approach to pulmonary resection. *Ann Surg* 116:782-794, 1942
- 13 *Idem*. Surgical anatomy of pulmonary lobes. *J Thoracic Surg* 12:18-30, 1942
- 14 Miscall L. and Cornell C. M. Surgical anatomy of bronchi and vessels. *J Thoracic Surg* 12:526-543, 1943
- 15 Overholt, R. H. and Langer L. New technique for pulmonary segmental resection: its application in treatment of bronchiectasis. *Surg Gynec & Obst* 84:257-268, 1947
- 16 Appleton A. B. Arteries and veins of lungs. I. Right upper lobe. *J Anat* 79:97-120, 1945
- 17 Liebow A. A. Hales M. R. Lindskog G. E. and Bloomer W. E. Plastic demonstrations of pulmonary pathology. *Bull Internat A Med Museums* 27:116-129, 1947
- 18 Cauldwell E. W. Siekert, R. G. Linsinger R. E. and Anson B. J. Bronchial arteries: anatomic study of 150 human cadavers. *Surg Gynec & Obst* 86:395-412, 1948
- 19 Courmand A. and Richards D. W. Jr. Pulmonary insufficiency: discussion of physiological classification and presentation of clinical tests. *Am Rev Tuberc* 44:26-41, 1941
- 20 Harden, K. A. Payne H. M. Weaver M. P. and Laurey J. R. Cardiorespiratory testing in tuberculosis. *Am Rev Tuberc* 50:234-243, 1944
- 21 Warming F. C. Jr. Ventilatory function: experiences with simple practical procedure for its evaluation in patients with pulmonary tuberculosis. *Am Rev Tuberc* 51:432-454, 1945
- 22 Leiner G. C. Spirometric and bronchospirometric studies in thoracoplasty. *Am Rev Tuberc* 53:195-214, 1946
- 23 Ornstein, G. G. Herman M. Friedman M. and Friedlander E. Pulmonary function tests. Description of method for measuring diffusion of oxygen and carbon dioxide in lungs. *Am Rev Tuberc* 53:306-332, 1946
- 24 Jacobsens H. C. Bronchospirometry: review of present experiences and some further investigations. *J Thoracic Surg* 7:235-261, 1938
- 25 Frenckner P. and Björkman S. Bronchospirometry and its clinical application with short account of bronchial catheterization. *Proc Roy Soc Med* 30:477-492, 1936
- 26 Norris C. M., Long J. and Oppenheimer M. J. Bronchospirography: apparatus and technique. *J Thoracic Surg* 17:357-365, 1948
- 27 Pinner M., Leiner G. C. and Zavod W. A. Bronchospirometry. *Ann Int Med* 22:704-718, 1945
- 28 Gebauer P. W. Catheter for bronchospirography. *J Thoracic Surg* 8:674-682, 1939
- 29 Vaccarezza R. F., Lanari A., and Souhrie A. Discrepancies between clinical radiological and bronchospirometric findings. *Am Rev Tuberc* 55:128-143, 1947
- 30 Wright, G. W., and Woodruff W. Bronchospirography: ventilation and oxygen absorption of normal and diseased lungs during nitrogen respiration in opposite lung. *J Thoracic Surg* 11:278-287, 1942
- 31 Wright G. W., Yee L. B., Filley G. F., and Stranahan A. Physiological observations concerning decortication of lungs. Paper presented at meeting of American Association for Thoracic Surgery, 1948
- 32 Drinker C. K. *Pulmonary Edema and Inflammation. An analysis of processes involved in the formation and removal of pulmonary transudate and exudates*. 106 pp. Cambridge: Harvard University Press, 1945
- 33 Eaton R. M. Pulmonary edema: experimental observations on dogs following acute peripheral blood loss. *J Thoracic Surg* 16:668-694, 1947
- 34 Baarsma, P. R. and Dirken M. N. J. Collateral ventilation. *J Thoracic Surg* 17:238-251, 1948
- 35 Baarsma P. R., Dirken M. N. J. and Haizenga E. Collateral ventilation in man. *J Thoracic Surg* 17:252-263, 1948
- 36 Lindskog G. E. and Alley R. D. Pharmacologic factors influencing collateral respiration. Paper presented at meeting of American Surgical Association, 1948
- 37 Courmand A. Measurement of cardiac output in man using right heart catheterization: description of technique, discussion of validity and of place in study of circulation. *Federation Proc* 4:207-212, 1945
- 38 Bing R. J., Vandam L. D., and Gray F. D. Jr. Physiological studies in congenital heart disease. I. Procedures. *Bull Johns Hopkins Hosp* 80:107-120, 1947. II. Results of preoperative studies in patients with tetralogy of Fallot. *Ibid* 80:121-141, 1947. III. Results obtained in five cases of Eisenmenger's complex. *Ibid* 80:323-347, 1947. IV. Measurements of circulation in five selected cases. *Ibid* 81:192-215, 1947
- 39 McMichael J. Notes on cardiac output methods. *Federation Proc* 4:212-214, 1945
- 40 Dexter L. et al. Studies of congenital heart disease. I. Technique of venous catheterization as diagnostic performance. *J Clin Investigation* 26:547-553, 1947. II. Pressure and oxygen content of blood in right auricle, right ventricle and pulmonary artery in control patients with observations on oxygen saturation and source of pulmonary "capillary" blood. *Ibid* 26:554-560, 1947. III. Venous catheterization as diagnostic aid in patent ductus arteriosus, tetralogy of Fallot, ventricular septal defect. *Ibid* 26:561-576, 1947
- 41 Courmand A., Hemmelstein A., Riley R. L., and Lester C. W. Follow-up study of cardiopulmonary function in four young individuals after pneumonectomy. *J Thoracic Surg* 16:30-49, 1947
- 42 Bloomfield R. A., Lawson H. D., Courmand A., Breed E. S., and Richards D. W. Jr. Recording of right heart pressures in normal subjects and in patients with chronic pulmonary disease and various types of cardio-circulatory disease. *J Clin Investigation* 25:639-664, 1946
- 43 Hickam J. B. and Cargill W. H. Effect of exercise on cardiac output and pulmonary arterial pressure in normal persons and in patients with cardiovascular disease and pulmonary emphysema. *J Clin Investigation* 27:10-23, 1948
- 44 Churchill E. D. Trends and practices in thoracic surgery in Mediterranean Theater. *J Thoracic Surg* 13:307-315, 1944
- 45 Burford T. H. and Burbank, B. Traumatic wet lung: observations on certain physiologic fundamentals of thoracic trauma. *J Thoracic Surg* 14:415-424, 1945
- 46 deTakats G., Fenn G. K., and Jenkinson E. L. Reflex pulmonary atelectasis. *J A M A* 120:686-690, 1942
- 47 Daniel R. A. Jr. and Cate W. R. Jr. "Wet lung"—experimental study. *Ann Surg* 127:836-857, 1948
- 48 Notes on care of battle casualties. *T B Med* 147. War Dept., Washington D. C. March, 1945
- 49 Samson P. C. and Brewer L. A. III. Principles of improving inadequate tracheobronchial drainage following trauma to chest: further problems in treatment of wet lung. *J Thoracic Surg* 15:162-172, 1946
- 50 Samson P. C. and Burford T. H. Total pulmonary decortication: its evolution and present concepts of indications and operative technique. *J Thoracic Surg* 16:127-145, 1947
- 51 Tuttle W. M., Langston H. T., and Crowley R. T. Treatment of organizing hemothorax by pulmonary decortication. *J Thoracic Surg* 16:117-126, 1947
- 52 Sanger P. W. Decortication in acute empyema thoracis. *Surg Gynec & Obst* 82:71-80, 1946
- 53 Carter B. N. Combined thoracoabdominal approach with particular reference to its employment in splenectomy. *Surg Gynec & Obst* 84:1019-1028, 1947
- 54 Harken D. E. Review of activities of thoracic center for III and IV hospital groups, 160th General Hospital European Theater of Operations, June 10, 1944 to Jan 1, 1945. *J Thoracic Surg* 15:31-43, 1946
- 55 Burbank C. B., Falor W. H., and Jones H. W. Jr. Three hundred seventy-four acute war wounds of thorax. *Surgery* 21:730-738, 1947
- 56 Mackler, S. A. Experience with thoracic and thoracoabdominal wounds in evacuation hospital. *J Thoracic Surg* 16:538-570, 1947
- 57 Martin J. D. Jr. War wounds of chest. *Surgery* 21:381-389, 1947
- 58 Montgomery, H., Halbersleben D., and Carr F. B. Puncture wounds of chest. *J Thoracic Surg* 16:407-415, 1947
- 59 Miscall L. and Harrison A. W. Thoracic surgery in hospital center. *Ann Surg* 125:142-311, 1947
- 60 Snyder J. M. and Tropea F. Jr. War injuries of chest: report of series of 678 cases. *Surgery* 22:780-800, 1947

ture, which was not present. Lesions that we should consider seriously are osteoid osteoma and eosinophilic granuloma. I do not believe that I can completely exclude them. Osteoid osteoma causes constant pain such as this, with insidious onset, often worse at night and almost always relieved by aspirin. So from the history that is a possibility. By x-ray examination, it cannot be completely excluded, but the films are certainly not characteristic of osteoid osteoma. There is usually much greater sclerosis of the bone as well as an area of decreased density. With good x-ray technic we can almost always demonstrate a small nidus in the center, which I do not see. Do you see it, Dr. McCort?

DR. MCCORT: No, I certainly do not see it.

DR. BARR: If a central nidus is not present, I think it is unlikely to be osteoid osteoma. I have not seen such a lesion without a nidus.

I have seen a few cases of eosinophilic granuloma but have never made that diagnosis preoperatively. I think this could have been an eosinophilic granuloma. The pain was consistent. There is usually a bone-destroying lesion, and that is about as much as I can say about it.

The mechanical things that we usually consider I think can be ruled out. We have a lesion within the neck of the femur, and I think we can rule out slipped epiphysis and Legg's disease and so forth. We then come definitely to infection, and the picture does fit an infectious process. The patient had continuous pain, possibly an elevation in temperature, rather continuously, and a little change in differential count and in the monocyctic and lymphocytic ratio. Bone infections can go on for months or years with very little change in the appearance of the bone. If so, this obviously was a low-grade infection, and we have to consider the two main groups — a Brodie abscess or tuberculous infection of bone. I do not see how one can differentiate satisfactorily. A Brodie abscess usually produces more sclerosis than this, but I have seen *Staphylococcus aureus* infection of bone with practically no bone reaction about it, having been present a long time. Nevertheless, I lean a little toward tuberculosis. The tuberculin test was positive, and there was a very slowly progressive lesion in the central portion of the neck of the femur. I shall make a diagnosis of a low-grade infectious process, possibly tuberculosis.

DR. MARIAN ROPES: When I saw the patient before operation I had no idea what she had. I thought of the possibilities that Dr. Barr has mentioned, I did think she had definitely a synovitis and believed that the physical findings were consistent with that. I thought then and even at operation, when the synovial tissue in the hip was involved, that she had hemorrhagic villonodular synovitis with extension into the bone, although it was different from the average case that has been seen here at least. Beyond that I had no idea.

## CLINICAL DIAGNOSIS

Osteoid osteoma?  
Tuberculosis?  
Villonodular synovitis?

## DR. BARR'S DIAGNOSIS

Low-grade infectious process, possibly tuberculosis

## ANATOMICAL DIAGNOSES

*Osteoid osteoma*  
Acute synovitis

## PATHOLOGICAL DISCUSSION

DR. MALLORY: On the second occasion the hip joint was explored, and besides a diffuse synovitis, with considerable hypertrophy of the synovia, a localized lesion was found in the bone that appeared to penetrate the cortex in one or two spots. This was curetted out, and the material from the operation was divided into two lots, as we usually do with arthritic material, and the portion that we received showed nothing. We then asked the Arthritic Service to give us the other half, in which we found a characteristic osteoid osteoma. This is the first one we have seen in which the lesion had penetrated through the cortex of the bone, they are almost invariably subcortical. This one did not show much increase in density in the surrounding cortical bone which is uncommon.

DR. BARR: What did the synovia show?

DR. MALLORY: Acute and chronic inflammation — there was nothing specific about its appearance at all.

DR. GRANTLEY W. TAYLOR: What were these cases called before they were identified as osteoid osteoma? The patients must have been seen and operated on from time to time.

DR. MALLORY: It seems most probable that they were reported as healing, sclerosing osteomyelitis.

DR. BARR: The evidence for neoplasm is still very uncertain in my mind in these lesions because one rather striking thing is that no matter how long they last they apparently never grow beyond 0.5 to 1.5 cm in diameter. Did you do special stains for nerve fibrils?

DR. MALLORY: No.

DR. ROPES: We wondered what caused the synovitis. It must have been reaction to the material that penetrated from the cortex of the bone into the joint.

## CASE 34502

### PRESENTATION OF CASE

*First admission.* A sixty-one-year-old woman, a schoolteacher, was admitted to the hospital because of nausea and vomiting.

urine was normal. The blood calcium was 9.3 mg, the phosphorus 4.9 mg and the alkaline phosphatase 3.9 units per 100 cc.

X-ray studies of the left hip showed a smoothly rounded area of slightly decreased density, measuring 1 cm in diameter, in the neck of the femur. There was questionable slight bone reaction about the area of decreased density (Fig. 1). Examination of the pelvis, tibiae, fibulae and skull was essentially negative. A tuberculin test was negative when given in 1:100,000 and 1:10,000 dilutions but positive at 1:1000.

The lesion was drilled through a lateral incision with a 0.79-cm drill and some material was curetted. Although it was believed that the drill had entered the lesion, microscopical examination showed only bone spicules. Subsequently the pain was less severe for several weeks but then recurred as before in the left hip and popliteal space. The patient had no other symptoms and was otherwise healthy.

*Second admission.* Five months after discharge she was again admitted for further study. Physical examination showed essentially the same findings as previously.

Examination of the blood showed a hemoglobin of 13.4 gm and a white-cell count of 7200, with 64 per cent neutrophils, 23 per cent lymphocytes and 13 per cent monocytes. X-ray films revealed an oval defect 3 cm in diameter in the neck of the left femur in the area previously described. On the second hospital day an operation was performed.

#### DIFFERENTIAL DIAGNOSIS

DR JOSEPH S. BARR: I assume that the nonweight-bearing cast was actually a brace.

I might point out in passing that "although it was believed that the drill had entered the lesion, microscopical examination showed only bone spicules." Missing a small lesion that they are attempting to explore or to biopsy is an error that all orthopedic surgeons make. Almost all of us want to make certain and take x-ray films in two planes at the time of biopsy, with an instrument or metallic body at the area to assure correct localization.

DR TRACY B. MALLORY: That was done in this case.

DR BARR: Apparently the lesion was missed in spite of that.

May we see the x-ray films?

DR JAMES J. McCORT: This examination was made preoperatively. A small, osteolytic lesion is present in the neck of the femur, measuring 1 cm in diameter. The margins of this lesion show slight irregularity, but there is no sclerosis of the surrounding bone. The lateral view shows it to lie just beneath the anterior cortex of the femoral neck. There is no swelling of the soft tissue over it and no periostitis. Are you interested in seeing the postoperative films?

DR BARR: Yes.

DR McCORT: This is the track made by the instrument at the time of the first biopsy. It appears to lead into the lesion. I cannot definitely identify it in the lateral view.

DR BARR: One can be directly over the lesion in one view and miss it by any distance in the opposite.

DR McCORT: The long bones and skull are normal.

DR BARR: This thirteen-year-old girl had pain in the back of the left knee and in the hip. The onset of symptoms was at the age of eleven and a half years, and the pain was relieved by rest, although finally it became continuous but was somewhat relieved by aspirin. Other points are that the patient apparently ran a very slight fever throughout the course. The legs were equal in length, indicating that the lesion apparently was not near an actively growing epiphysis. If it had been at the epiphysis the length might have been decreased owing to interference with growth. Restriction of motion is interesting in that the leg on flexion went into external rotation and abduction. This finding is most common in slipped upper femoral epiphysis. However, in the slipped upper femoral epiphysis there is usually no permanent flexion but actual increase in hyperextension, and there was permanent flexion deformity in this case. Legg-Calvé-Perthes disease can cause restriction of motion similar to this. There is a rare condition called coxa magna in which the head of the femur is larger than normal and motion is restricted. If restriction of motion is due to muscle spasm, it does not assume this form. The leg may be adducted instead of abducted, and flexion is restricted without external rotation deformity. In addition to the slight elevation of temperature there may possibly have been slight elevation in the white-cell count. The lymphocyte-monocyte ratio was slightly elevated. The tuberculin test was positive, if it had been negative, it might exclude tuberculosis but since it was positive we cannot exclude tuberculosis.

In differential diagnosis I think we can exclude without much further consideration the generalized bone diseases, such as Hand-Schüller-Christian disease, polyostotic fibrous dysplasia and hyperparathyroidism, the skull showed no apparent lesions. The single lesions that we must consider are bone cyst, monostotic fibrous dysplasia, giant-cell tumor, enchondroma, Ewing's sarcoma and Hodgkin's disease, but I think none of them fit the picture very well. If this was a Ewing's sarcoma or Hodgkin's disease, with this duration, the patient should be either not alive or acutely ill, and we would have signs of progression of the process or involvement of the lungs or, in Hodgkin's disease, of the lymph nodes or elsewhere in the body. A bone cyst would not cause such acute symptoms as this patient had unless it had produced a frac-

The temperature was 99°F, and the respirations 20. The blood pressure was 170 systolic, 110 diastolic.

Laboratory data included a hemoglobin of 14.8 gm. The urine gave a ++ test for albumin and the sediment contained occasional granular casts, 10 white cells and a rare red cell per high-power field. A blood sugar determination was 41 mg per 100 cc.

Intravenous glucose was followed by rapid recovery of consciousness. The following day the temperature was elevated to 102°F. She vomited frequently and despite intravenous therapy, died on the second hospital day.

#### DIFFERENTIAL DIAGNOSIS

DR. JOSEPH C. AUB: This seems to be such an obvious case that I am certain that the pathologists have it in for me. Obviously, it is a case in which they want a diagnosis of Addison's disease, and I cannot make any other diagnosis.

One can ascribe the trouble in the knee to tuberculosis. If the pathologists diagnosed tuberculous salpingitis, we have to assume that this woman had tuberculosis.

The blood chloride level is recorded as 82 milliequiv, and yet she had a normal blood pressure at that time. I do not understand that.

The intravenous pyelogram in the second admission was negative, that is important, considering the high blood pressure at death.

It should not be forgotten that cases of Addison's disease are often diagnosed as psychoneurosis. If these people do have Addison's disease, psychotherapy does not help much.

The weight loss is important because all patients with Addison's disease lose weight. They do not look thin, but all have a history of loss of weight. This patient had vomiting, of course, which complicates this fact but goes with Addison's disease.

A biopsy of the buccal mucosa would have been helpful, but I am assuming that the patient had a generalized pigmentation.

The excretion rate of 17-ketosteroids is negligible, and this is important as evidence for Addison's disease. The urine sodium of 2.3 gm. does not mean anything. Every well person eats from 2 to 15 gm of sodium chloride a day, and much of this comes out in the urine. Excretion of 2.3 gm in twenty-four hours is not high for a normal person, but it varies with the diet and medication.

It is not unusual in Addison's disease to find an associated low blood sugar, such as this patient had on her final admission, and this is considered an ominous prognostic sign.

The temperature was high for a woman in an Addisonian crisis.

A weak heart goes with Addison's disease, and she may have had too much intravenous salt, dying of cardiac complications.

There are a great many things that I would like to know about this case. I am not going to ask for anything, however. (Your host gives you a certain number of data, and you accept them, I do not ask for more.)

May we see the x-ray films?

DR. STANLEY M. WYMAN: The film of the chest is not of ideal quality. It shows calcification in the right-upper-lung field and, I think, a questionable area of fibrosis in the right apex. The heart shadow is not small, in fact, it appears somewhat prominent toward the left, possibly in the left ventricle. The aorta is quite tortuous.

DR. OLIVER COPE: When was this film taken in relation to death?

DR. WALTER BAUER: About six months before death.

DR. WYMAN: The right knee shows an old fusion as described in the physical examination.

DR. AUB: Can you ascribe a cause to that appearance?

DR. WYMAN: I cannot say. It is just a fused knee.

The gastrointestinal examination shows a small hiatal hernia, the stomach and colon are normal without evidence of defects. I do not see calcification in the region of the adrenal glands.

DR. AUB: Is there anything in the spine?

DR. WYMAN: There is no evidence of active disease.

The kidneys are normal in size and shape. A film twenty minutes after injection of dye shows fairly good excretion. There is no calcification above the kidneys. The skull examination, not mentioned in the protocol, shows rather prominent vascular lakes in the base, I can see no definite evidence of localized disease or chronic increased pressure. The pituitary body is of good size and not abnormal.

DR. AUB: I do not believe there is good evidence for tuberculosis in the lung, is there?

DR. WYMAN: There is no definite active disease.

DR. AUB: I cannot make any diagnosis except Addison's disease. I should like to know what happened to the size of the heart as the disease went on and as the patient got worse. I should like to know what the basal metabolic rate was, and what the diuresis following ingestion of water was. She had orthopnea, nausea and vomiting, hypoglycemia, probable loss of weight, syncopal attacks, pigmentation, a diagnosis of neurasthenia, low blood chloride and a low blood sugar — all these are consistent with Addison's disease. I believe she died in an acute Addisonian crisis, with hypoglycemia. She had been given a good deal of fluid, and she responded very poorly.

The blood pressure was 170 systolic, 110 diastolic, when she came in in an Addisonian crisis. This is most unusual and puzzling. It is possible that the patient's physician gave large doses of desoxycorticosterone acetate and much intravenous therapy.

Ten days previous to admission the patient suddenly developed nausea and vomiting unrelated to food and with no associated pain. In the preceding eight or nine weeks she had been taking two aspirin tablets every three hours because of pain in the left knee. There was no tinnitus or vertigo.

The past history revealed recurrent episodes of arthritis involving the right knee that began at the age of twelve and continued until the age of thirty, when pulmonary tuberculosis was diagnosed. On bed rest she recovered rapidly, and a fusion of the right knee was performed; tubercle bacilli were not isolated from the joint. She had no further pulmonary symptoms and no difficulty with the right knee except that due to its immobility. Ten years before admission, because of severe menorrhagia, a hysterectomy was performed, and a diagnosis of tuberculous salpingitis was made. Her maternal grandmother and two siblings had died of tuberculosis, but the patient was never exposed to the disease.

Physical examination revealed an obese, dehydrated woman with a slightly acidotic breath. The lungs were clear to percussion, with bronchovesicular breathing over the left apex and below the left clavicle. The right knee was fused in slight flexion. The left knee was slightly warm, and there was slight crepitation on motion.

The temperature, pulse and respirations were normal. The blood pressure was 126 systolic, 80 diastolic.

Examination of the blood revealed a hemoglobin of 12.4 gm and a white-cell count of 10,300, with 62 per cent neutrophils. The urine specific gravity was 1.008, and the sediment contained occasional red cells and 4 pus cells per high-power field. The blood chloride was 82 milliequiv per liter, and the nonprotein nitrogen 27 mg per 100 cc. The fasting blood sugar was 87 mg per 100 cc. The sedimentation rate was 40 mm per hour.

An x-ray film of the chest showed fine, linear areas of increased density extending into the apex of the right upper lobe and one small calcified shadow. The film of the left knee showed considerable sharpening of the tibial spines but no joint narrowing or calcification. The right knee was fused. An upper gastrointestinal series was negative.

The patient was given sedatives and infusions were necessary initially, but she was later able to retain oral feedings. She was discharged improved after five days in the hospital.

*Second admission* (seven days later). Anorexia, nausea and occasional vomiting persisted after discharge. She became progressively weaker and was readmitted.

The physical findings were essentially as before.

The temperature was 98.2°F, the pulse 72, and the respirations 20. The blood pressure was 110 systolic, 70 diastolic.

Examination of the blood showed a hemoglobin of 14 gm and a white-cell count of 8200, with 54 per cent neutrophils, 31 per cent lymphocytes, 13 per cent monocytes and 2 per cent eosinophils. A urine specific gravity of 1.012 was demonstrated; the sediment contained rare hyaline casts and rare pus cells. The stools were guaiac negative. The serum amylase was 35 units, the nonprotein nitrogen 35 mg, and the serum protein 5.3 gm per 100 cc; the chloride was 94 milliequiv per liter. A barium enema, cholecystogram and intravenous pyelogram were negative.

Sedatives and later psychotherapy did not control the vomiting. After three weeks in the hospital the blood chemical findings were as follows: sodium 131 milliequiv, chloride 82 milliequiv and potassium 6.1 milliequiv per liter, sugar 97 mg and total protein 5.1 gm per 100 cc.

The patient lost 7 pounds in weight. Pigmentation of the buccal mucosa and of the creases in the palms as well as a generalized "tan" seemed evident to several observers. Six grams of salt daily, 5 mg of desoxycorticosterone acetate daily, and later 2 cc of lipoadrenal extract every six hours caused slight subjective improvement, but the blood chemical values were altered very little. Blood-pressure readings, which averaged 80 systolic, 65 diastolic, were elevated slightly. The vomiting continued but was less frequent, and intravenous fluids were still necessary. Testosterone, 10 mg daily, was added to the therapy. Lipoadrenal extract was omitted. Desoxycorticosterone acetate 10 mg daily for several days, caused little alteration of the serum sodium content. After two months in the hospital the blood chemical values were as follows: sodium 124 milliequiv, chloride 102 milliequiv, and potassium 4.7 milliequiv per liter, and serum protein 4.5 gm per 100 cc. The twenty-four-hour urinary excretion of 17-ketosteroids was 0.7 mg and of sodium chloride 2.3 gm. Omission of desoxycorticosterone acetate caused anorexia, vomiting, diarrhea and loss of weight but little change in blood pressure. An adrenocorticotrophic hormone test showed no significant change in the blood eosinophil count or urinary creatinine and uric acid. She was discharged with implanted pellets of desoxycorticosterone acetate after four months in the hospital.

*Final admission* (ten weeks later). While at home the patient was ambulatory but vomited almost daily. She had a spell of confusion three weeks and two weeks before admission. These were of one and four hours' duration, respectively. Eight hours before admission this recurred, and she became unresponsive and later comatose.

Physical examination revealed a comatose woman. There were bilateral basal moist rales. Neurologic examination was negative.

involved with tuberculosis. There remains the possibility of making adrenalin in the sympathetic nerve ganglions. It is possible that she had enough ability to secrete epinephrine from the ganglions scattered throughout the body to give a high blood pressure. But I think it very unlikely.

#### CLINICAL DIAGNOSIS

Addison's disease

#### DR AUB'S DIAGNOSES

Addison's disease

Tuberculosis of adrenal glands

Tuberculosis and amyloidosis of kidney

#### ANATOMICAL DIAGNOSES

*Addison's disease*

*Bilateral cortical infarction of kidneys*

*Tuberculosis of adrenal glands, lungs and lymph nodes*

*Pulmonary edema*

#### PATHOLOGICAL DISCUSSION

DR MALLORY: This patient had the anatomic substrate for Addison's disease—complete tuberculous destruction of both adrenal glands. There was tuberculosis elsewhere—it was very extensive in the lungs, though of a low degree of activity. There were also numerous tuberculous lymph nodes scattered throughout the body. The right knee was explored and showed an anatomic fusion of the joint but no evidence of tuberculosis. We unfortunately did not know about the symptoms in the other knee, which was not looked at.

The kidneys were a considerable surprise. They weighed 260 gm. The cortex was 4 or 5 mm in thickness and very slightly scarred, but on microscopical examination it is evident that there was almost complete infarction of the renal cortex. Only a very narrow rim of cortex at the periphery just beneath the capsule and the pyramids was still

visible. This symmetrical cortical infarction, of course, is well known as a complication of pregnancy but does occur in other conditions, and occurs occasionally in members of the male sex. I have never heard of it before in relation to Addison's disease. Whether it can be linked directly to the Addison's disease or should be considered a peculiar complication of the therapeutic measures utilized I cannot answer. It can readily be explained by the mechanism that Trueta\* has recently described of reflex shunting of the renal blood flow into the vasa vitae of the pyramids, with consequent cortical ischemia.

DR AUB: Was there any amyloidosis?

DR MALLORY: No, there was a moderate amount of still recognizable focal lymphocytic infiltration in the kidneys. I think a moderate grade of pyelonephritis existed before this final episode, which was very acute—of only two or three days' duration, I would guess.

DR BENJAMIN CASTLEMAN: Do you think that the kidney lesion was the cause of death?

DR MALLORY: I think that the renal lesion undoubtedly had a great deal to do with death and probably was the immediate cause. There was a moderate grade of pulmonary edema.

DR COPE: Was the renal lesion the probable cause of hypertension?

DR MALLORY: Hypertension is characteristic of the syndrome of symmetrical cortical necrosis.

DR AUB: This case demonstrates an important potential in the Addisonian patient. In the past I have seen a patient menstruate normally in the midst of an Addisonian crisis in spite of a lack of the adrenal hormones. Here we see an example of a Goldblatt hypertension during a crisis, which demonstrates that the mechanism of this hypertension is distinct from the adrenal gland.

\*Trueta, J. et al. *Studies of the Renal Circulation*. 187 pp. Springfield, Ill.: Charles C. Thomas, 1947.

When one is presented with a problem like this, one can always bring in a great many diagnoses just for the sake of naming the diagnosis, but I do not like to do that. I think this woman died of Addison's disease with tuberculosis of both adrenal glands. There is evidence for tuberculosis in what I take to have been a tuberculous knee joint, tuberculous salpingitis and also scrofula in the bone. I would expect that she had tuberculous lymph nodes scattered through the abdomen and that she had a tuberculous peritonitis.

What about the kidney? The urine had a low specific gravity and red cells and a good deal of albumin at the end. She may have had amyloidosis or, what is much more likely, tuberculous involvement of the kidneys, which did not show up in the poor pyelogram that was done. She obviously had something seriously wrong with the kidneys. Let us make two diagnoses: tuberculosis and amyloidosis of the kidneys. Of course, she may have had a malignant tumor involving both adrenal glands, which had destroyed them, with widespread metastases. I do not think we have enough evidence to make such a diagnosis. Recalling the high blood pressure, I think it possible that she was over-treated with intravenous salt on the last entrance to the hospital and that, as a result, she had edema of the lungs with cardiac decompensation. This may be wrong, because with high blood pressure and low blood sugar, the tendency would have been to give glucose and water and not glucose and salt, yet I suggest that she had edema of the lungs. I think she had Addison's disease, which did not respond to desoxycorticosterone acetate because the carbohydrate metabolism was abnormal. It is obvious that with such an abnormality the prognosis is grave, and the response to adrenocortical extract is not always good, particularly if there is an active tuberculosis or other infection.

DR TRACY B MALLORY: Dr Bauer, did you see this patient?

DR BAUER: Yes, indeed, I did. I saw her during the second hospital admission because of her joint disease. One of the members of our group had seen her some months before and thought she had mild rheumatoid arthritis. I must say that when I saw her there was very little in the way of objective findings in the left knee that one could be certain of. The diagnosis rested between tuberculosis and rheumatoid arthritis, however, there was no way of proving either diagnosis. I saw this woman quite a few times and must admit that I felt very strongly that her symptoms were largely psychogenic in nature despite some pigmentation and findings that were in keeping with Addison's disease. Dr Lindeman saw her and agreed to the possibility of a psychogenic illness, however, he did not think it was the sole cause of her chief complaints. What psychotherapy she received from him was the result of my insistence. I think she

received very adequate therapy for the adrenal insufficiency.

DR DANIEL S ELLIS: It is hard now to believe that there was as much difficulty in arriving at a decision in this case as there actually was. But as Dr Bauer has intimated, the diagnoses considered ran from psychoneurosis to cancer. One observer felt very strongly that she should be operated on. What puzzled us on the long second admission was that she did not respond to adequate therapy for adrenal insufficiency. There were doctors of the house staff and some others who felt strongly that it was, without question, a serious consideration and an important one.

Dr Aub asked for certain things that I might supply as far as I can. The basal metabolic rate was +1 and -8 per cent, and the water-excretion test was not done because of the opinion that it was not so accurate as the eosinophilic and uric acid test with adrenocorticotrophic hormones. The results of these, as given in the protocol, were definitely consistent with Addison's disease. There was no change in the uric acid excretion, and the eosinophilic count remained the same, which is true in Addison's disease. Normally, the eosinophilic count falls, and there is increase in uric acid excretion. During the time between the second and third admissions she was at home. For the first month at home the blood pressure was around 105 systolic, 60 diastolic. Because she began to vomit more and eat less and continued to lose weight, in addition to fluids, we decided to give her 5 mg of adrenocortical hormone a day intramuscularly. This was done for another four weeks without any apparent effect. Then she had the onset of these episodes of loss of consciousness, and it was found that at each of the three episodes the blood pressure was higher than it had been on admission: 130 systolic, 70 diastolic, at the first episode, 155 systolic, 90 diastolic, at the second, and 170 systolic, 100 diastolic, at the last. As far as the last admission is concerned, it was believed that she was in a hypoglycemic crisis when she came in. No additional adrenal hormones were given at first, she was given intravenous glucose, and twelve hours later the blood pressure fell to 70 systolic, 40 diastolic. At that time she was given lipoadrenal extract for obvious reasons, which I cannot go into now. It was felt that diuretic therapy should not be given this patient and as far as specific therapy for Addison's crisis was concerned, over a course of thirty-six hours she received 3 cc of lipoadrenal extract and 5 cc of desoxycorticosterone acetate and that is all.

DR AUB: I am fascinated by the elevation of blood pressure with the hypoglycemic reaction. With hypoglycemia one gets increased flow of epinephrine. That might raise the blood pressure, but in Addison's disease, one would not expect it, for the adrenal medulla should not be available if

suggested by the Professional Advisory Committee of the study, with the public-school system, in any event, the profession of nursing the medical profession and the public must be interested and sympathetic in creating a desirable position for the attendant nurse

Certain other observations and recommendations have been made in Dr Brown's report. Of the group of 1125 schools of nursing that participated in the program of the Cadet Nurse Corps, only 13 per cent received a rating by the United States Public Health Service of good or better. This group is made up of the schools that are producing the graduate nurses of today. The current graduate bedside nurse may, indeed, disappear from the scene when nursing of the future is organized on the two levels proposed.

One of these levels will consist of the professional nurses whose training will be limited to the schools that can provide instruction of a grade recognized by educators as professional. These schools will belong in institutions of higher learning and will furnish both cultural education and first-class technical training. They will be on a par with the other university schools and their graduates, as bachelors of science, will serve in technical fields in community health services, in supervisory activities, in executive positions, and in research and teaching.

The nonprofessional nurses with their more limited training, will supply the bedside nursing in the hospitals of the future and, presumably, of the nation's homes. The great need for adequate household service seems to have been largely lost sight of in the preoccupation of the report with the demands of institutions and their hospitalized patients. There are, however, those who still remember that many of the vigils that the nurse must hold in discharging her highest functions are by the sickbeds in the home. Perhaps this need will be met to an increasing degree inside the family itself by those who have profited from the Red Cross Home Nursing courses. God helps those, it is still widely believed, who help themselves.

Nursing, like all the other activities in which humankind engages, is passing through one of its crises. There is, it is said, a shortage of nurses, but

as with the shortage of physicians it is the result of an increased demand for a type of service rather than of any relative decrease in the personnel capable of providing it.

The Commonwealth of Massachusetts is meeting the problem perhaps as intelligently as any state. There is here already the licensed attendant nurse who is filling a need and has achieved a dignity of her own. She is moreover gaining in prestige and in recognition by her more highly trained nursing colleagues.

The profession of nursing needs more help and less criticism, more in the way of respect and less in the way of condescension from others. Perhaps it is not too much to expect that it may some day have its own board of registration with a nurse as secretary and that the Massachusetts Medical Society, as an indication of its own desire to cooperate, may create a special committee to meet with the Massachusetts State Nursing Association.

---

## INFLUENZA AND PNEUMONIA

EACH year after the leaves have fallen the winds and the chill in the air herald in a new "respiratory season." People begin to get colds, many of them have coughs that seem to hang on, and doctors encounter cases of pneumonia and wonder whether there will be any severe outbreak of influenza. Thirty years ago, late in the summer of 1918, a worldwide epidemic struck the Atlantic seaboard and soon swept across the country, attacking about 20,000,000 people in the United States, of whom an estimated 550,000 died of the disease or its complications. Previously, such major outbreaks had recurred at intervals of about twenty or thirty years. Though there has been no cyclic regularity to the occurrence of such pandemics, there is an understandable apprehension that one may strike again. The dread of pandemic influenza is heightened, of course by the lack of precise knowledge concerning the true cause of the previous great pandemics, and for that reason only slight solace can be taken from the vast amount of recently accumulated knowledge concerning the comparatively mild epidemics due to the influenza A and B

# The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established 1828

Official Organ of

THE MASSACHUSETTS MEDICAL SOCIETY

and

THE NEW HAMPSHIRE MEDICAL SOCIETY

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND

PUBLISHED WEEKLY UNDER THE JURISDICTION OF THE

COMMITTEE ON PUBLICATIONS

Richard M. Smith, M.D., Chairman

James P. O'Hare, M.D.

Conrad Wesselhoef, M.D.

Oliver Cope, M.D.

John Fallon, M.D.

Joseph Garland, M.D., Editor

ASSOCIATE EDITORS

Thomas H. Lanman, M.D.

Donald Munro, M.D.

Henry Jackson, Jr., M.D.

Clara D. Davies, EXECUTIVE EDITOR

Robert O. Leary, ASSISTANT EDITOR

EDITORIAL BOARD

C. Guy Lane, M.D.

Maxwell Finland, M.D.

Henry R. Viets, M.D.

James M. Faulkner, M.D.

Robert M. Green, M.D.

Carroll B. Larson, M.D.

Dwight O'Hara, M.D.

Francis D. Moore, M.D.

Fletcher H. Colby, M.D.

C. Stuart Welch, M.D.

Robert L. Goodale, M.D.

Vernon P. Williams, M.D.

Chester M. Jones, M.D.

Benjamin Castleman, M.D.

Harvey R. Morrison, M.D.

Hugh R. Leavell, M.D.

SUBSCRIPTION TERMS: \$7.00 per year in advance, postage paid for the United States (medical students \$4.00 per year); Canada \$8.00 per year (Boston funds); \$9.50 per year for all foreign countries belonging to the Postal Union.

MATERIAL should be received not later than noon on Thursday three weeks before date of publication.

THE JOURNAL does not hold itself responsible for statements made by any contributor.

COMMUNICATIONS, including those concerning classified advertising but not those regarding other advertising, should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts. Telephone KE 6-2094.

NEW ENGLAND ADVERTISING REPRESENTATIVE (except for classified advertising): Edwin B. Tyler, 89 State Street, Boston, Massachusetts. Telephone LA 3-3516.

## PRO RE NATA

THE world is always in revolution. Sometimes its shifts and changes, and re-alignments are so quiet that they signify only the placid progress of a world at peace, at times, like the present, they consist of such general turbulence that every race, every social and economic group, every industrial and professional alliance seems to be pressing for room in which to function, for prestige, sometimes for existence itself.

Less than a hundred years ago nursing rose from a menial service, often degrading in character, and attained the distinction of a profession. Today this profession finds that it must again adapt itself to violently changing conditions of supply and demand and of social unrest and must find the position that

will secure for it the broadest possible field of future usefulness.

In this contingency the National Nursing Council turned to the Russell Sage Foundation for assistance. A study has been made by Esther Lucile Brown, Ph.D., director for the Foundation of the Department of Studies in the Professions, and her report, *Nursing for the Future*, a review of which is published elsewhere in this issue of the *Journal*, is the tangible result.

Maintenance of health rather than the treatment of disease is the future goal of medicine as horizons expand in medical care, in hospitals and in private practice, in public health and in preventive medicine. Nursing must keep pace with these expansions of health services. Hospitals and all the other agencies of health will need an enormous supply of nursing care, and, as "private duty has become proportionately less important," according to Dr. Brown's thesis, "salaried institutional, public health and industrial nursing has come to be largely considered a social necessity."

Nursing service must be still further differentiated according to function. Not only must the place of the registered graduate nurse be considered, but also the necessity for other grades of nurses. Someone must carry on the simpler functions of nursing at a cost to the consumer that will not put decent care in sickness beyond the reach of the ordinary patient.

The status of the practical nurse must be fixed by legislation, but the attractiveness of her position will depend on the interpersonal relations that will exist in the schools of her training and the situations in which she will work. So far there has been an inevitable tendency on the part of the graduate nurse to disparage the use and the quality of less highly trained personnel that introduces the element of lower-priced competition. This attitude must change if the officers of the nursing corps of the future are to find any devotion and loyalty in the ranks.

The position of the practical or the attendant or the bedside nurse must be made secure, and her training must be carried on partly inside the hospital, where her school may coexist with that of the professional nurse. This may also be linked, as

## DEATHS

**DAHLEN**—Carl A. Dahlen, M.D. of Brookline, died on October 23. He was in his fifty-seventh year.

Dr. Dahlen received his degree from Tufts College Medical School in 1918. He was a member of the dermatologic staff at Massachusetts Memorial Hospitals and was a fellow of the American Medical Association.

His widow, a son, a daughter and two sisters survive.

**HOLT**—Earl K. Holt, M.D., of Medfield, died on November 10. He was in his sixtieth year.

Dr. Holt received his degree from Indiana University School of Medicine in 1914. He was superintendent of the Medfield State Hospital and a member of the American Psychiatric Association and the New England Society of Psychiatry.

His widow and a son survive.

**RAYMOND**—Loring H. Raymond, M.D. of Somerville died on November 6. He was in his seventieth year.

Dr. Raymond received his degree from Harvard Medical School in 1903. He was a fellow of the American College of Surgeons and the American Medical Association.

His widow survives.

## MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

### COMMUNICABLE DISEASES IN MASSACHUSETTS FOR OCTOBER, 1948

DISEASE	RESUME		
	OCTOBER 1948	OCTOBER 1947	SEVEN YEAR MEDIAN
Chancroid	2	4	2*
Chicken pox	622	709	370
Diphtheria	39	21	17
Dog bite	751	885	842
Dysentery bacillary	2	60	19
German measles	47	2	52
Gonorrhea	244	314	41*
Granuloma inguinale	1	1	0*
Lymphogranuloma venereum	1	0	1*
Measles	660	120	401
Meningitis meningococcal	7	6	11
Meningitis Pfeiffer bacillus	2	2	2†
Meningitis pneumococcal	1	0	0†
Meningitis staphylococcal	0	0	0†
Meningitis streptococcal	0	0	0†
Meningitis other forms	0	0	0†
Meningitis undetermined	8	2	2†
Mumps	485	574	22
Pneumonia, lobar	60	68	129
Polio myelitis	51	65	65
Salmonellosis	8	14	15
Scarlet fever	245	275	426
Syphilis	141	222	40*
Tuberculosis pulmonary	181	228	216
Tuberculosis other forms	11	19	19
Typhoid fever	2	6	4
Undulant fever	2	5	5
Whooping cough	180	460	224

\*Four year median

†Six year median

#### COMMENT

The diseases with an incidence above the seven-year median were chicken pox, diphtheria, measles and mumps.

The diseases with a prevalence below the seven-year median were bacillary dysentery, meningococcal meningitis, lobar pneumonia, poliomyelitis, pulmonary tuberculosis and whooping cough.

Chicken pox was at the highest level ever reported for October, which may indicate that it will continue at the high level of recent months.

Diphtheria was at the second highest level since 1955. The communities primarily affected continued to be Boston and those immediately to the north.

Measles was at the highest level for October since 1928. It seems likely that the high prevalence of recent months is to continue.

Mumps was at the highest level ever reported for October. A continued high prevalence can be expected during the coming season.

Only three times in the past has scarlet fever been lower in October than prevalence recorded for the month. The high prevalence of recent months after repeated record low levels last year, makes it likely that the disease will be on the increase during the coming season.

Whooping cough was at the lowest prevalence recorded since 1916. It is unlikely, however, that this low figure can be maintained, and the coming season will probably show a considerable increase.

#### GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Diphtheria was reported from Arlington, 2; Berkley, 1; Boston, 14; Cambridge, 1; Chelsea, 1; Danvers, 1; Easton, 1; Everett, 1; Hanover, 1; Malden, 3; New Bedford, 1; Somerville, 1; Watertown, 1; total, 29.

Dysentery, amebic, was reported from Stoneham, 1; total, 1.

Dysentery, bacillary, was reported from Stoneham, 1; Newburyport, 1; Worcester, 3; total, 5.

Encephalitis, infectious, was reported from Clinton, 1; total, 1.

Lymphocytic choriomeningitis was reported from Cambridge, 1; Worcester, 1; total, 2.

Malaria was reported from Barnstable, 1; total, 1.

Meningitis meningococcal was reported from Boston, 2; Haverhill, 1; Lynn, 1; Randolph, 1; Worcester, 2; total, 7.

Meningitis Pfeiffer bacillus, was reported from Hatfield, 1; Lawrence, 1; total, 2.

Meningitis pneumococcal, was reported from Barnstable, 1; total, 1.

Meningitis undetermined was reported from Andover, 1; Beverly, 1; Brockton, 1; Dudley, 1; Northampton, 1; Spencer, 1; Weymouth, 1; Worcester, 1; total, 8.

Poliomyelitis was reported from Amherst, 1; Attleboro, 1; Belmont, 1; Boston, 2; Brookline, 1; Cambridge, 1; Danvers, 1; Littleton, 2; Lynnfield, 1; Marblehead, 1; Medford, 1; Middleboro, 1; Palmer, 1; Plymouth, 1; Salem, 2; Shrewsbury, 1; Springfield, 2; Warren, 1; Wellesley, 1; West Springfield, 1; Worcester, 5; total, 31.

Salmonellosis was reported from Beverly, 2; Stoneham, 1; Wakefield, 1; Worcester, 4; total, 8.

Septic sore throat was reported from Boston, 9; Lynn, 1; Stoneham, 1; West Newbury, 1; total, 12.

Tetanus was reported from Cambridge, 1; Pittsfield, 1; total, 2.

Trachoma was reported from Lynn, 1; total, 1.

Trichinosis was reported from Boston, 1; Fall River, 1; total, 2.

Typhoid fever was reported from Brockton, 1; Springfield, 1; total, 2.

Undulant fever was reported from Hallowell, 1; Norwood, 1; total, 2.

## BOOK REVIEWS

*Nursing for the Future*. By Esther Lucile Brown, Ph.D. 198 pp. New York: Russell Sage Foundation, 1948. \$2.00.

The avowed objective of Dr. Brown's "Nursing for the Future" is refreshing. She states: "First, and most important, was the decision to view nursing service and nursing education in terms of what is best for society—not what is best for the profession of nursing as a possibly vested interest." Quite rightly she says of the nurses that "Many have kept their attention so focused upon professional rights and prerogatives that society has sometimes come to question their interest in serving the needs of our national life."

How closely the author adheres to her objective might be questioned, but her report based on painstaking investigation contains many facts and observations that should be helpful. "So long as attention is centered on the graduate nurse, no other avenue is open except that of the present frantic and probably futile effort to recruit more prospective R.N.'s. Even appreciably better educational preparation is likely to be denied them, so insistent will the demand for nursing service continue to be. Once emphasis is shifted to nursing, however, several roads seem to point to potentially larger supplies of service and to possibly increased efficiency, both on the nonprofessional and the professional levels." It is cheering to learn this.

viruses that have been recurring every two or three years

Some comfort may, nevertheless, be derived from a recent review by the statisticians of the Metropolitan Life Insurance Company\* of the figures on mortality from influenza and pneumonia during the past few years. A most significant downward trend in the figures began in the early 1930's, when specific serum treatment for many types of pneumonia was introduced. Among the Company's industrial policyholders the death rate dropped from 80 per 100,000 in 1930-31 to about 70 per 100,000 in 1936-37, the period during which this type of therapy came increasingly into use. In 1938, when both serum and the sulfonamides were used, the death rate from pneumonia and influenza dropped sharply to 47 per 100,000—a decrease of almost 35 per cent from the year before. Improvements in sulfonamide treatment and the introduction of penicillin brought still further success so that by 1947 the death rate reached an all-time low of 17.4 per 100,000, and it is expected that this will fall still further during the current year. The efficacy of newer methods of treatment is clearly evident from the fact that improvement in mortality has been relatively three times as great in the past decade as in the previous one. Between 1935-37 and 1947 the decrease was more than 60 per cent in every age group among white persons of both sexes, and in most age groups the reduction in the death rate was greater than 75 per cent.

Some forms of pneumonia are still not amenable to treatment. Some of the virus pneumonias are in this category, and there is always a possibility that some virulent form of these pneumonias will occur. Moreover, there is no assurance that a devastating epidemic of influenza similar to that of 1918 will not strike again. So far this year, however, there are no signs pointing to the likelihood of a severe influenza epidemic in the United States or elsewhere. This is unlike the situation in 1918 when months before there were serious outbreaks in various military installations in this country and also in various parts of Europe. Even if such an epidemic should occur, the medical and public-

health professions are much better prepared to cope with the situation now than they were thirty years ago. It is well recognized that the uncomplicated cases of influenza cause relatively few deaths even during pandemics. Most of the deaths occur among cases complicated with severe forms of pneumonia. With the help of the sulfonamides, penicillin and other antibiotics that are now available, physicians should be able to control the complications and thus rob the next pandemic of most of its terrors.

### EMINENT CARDIOLOGIST

DR. PAUL DUDLEY WHITE, of Boston, has been appointed chief adviser for the National Heart Institute and executive director of the National Advisory Heart Council, established by Congress last June as an activity of the United States Public Health Service. Dr. White, who has been physician in charge of the Cardiac Clinic and Laboratory of the Massachusetts General Hospital, has resigned from that position to assume his new duties, which will require a division of time between Boston and the headquarters of the National Heart Institute at the National Institutes of Health, Bethesda, Maryland.

A graduate of Harvard College in the class of 1907 and of the Harvard Medical School in 1911, Dr. White in April, 1948, received the Order of the White Lion from the Czechoslovakian Government, on the occasion of the six hundredth anniversary of the founding of Charles University, in Prague. This award was made as the result of his participation in the medical mission of the Unitarian Service Committee to Czechoslovakia in 1946.

### MASSACHUSETTS MEDICAL SOCIETY HAMPDEN DISTRICT

The Hampden District Medical Society is to be congratulated on the excellent manner in which it has responded to the request of the Council, made in May, that the districts form their own plans for full-time coverage of calls for physicians.

Lists have been issued classifying the members of the district society according to types of practice, and from these a house-call classification sheet has been constructed containing the names of those physicians in the various communities of the district who are willing to respond to emergency calls, and the times at which they are available.

\*Influenza and pneumonia—thirty years after the pandemic. *Statist Bull Metrop Life Insur Co* 29 (No. 9) 8-10 1948

DEATHS

**DAHLEN** — Carl A Dahlen, M D , of Brookline, died on October 23 He was in his fifty-seventh year  
Dr Dahlen received his degree from Tufts College Medical School in 1918 He was a member of the dermatologic staff at Massachusetts Memorial Hospitals and was a fellow of the American Medical Association  
His widow, a son, a daughter and two sisters survive

**HOLT** — Earl K Holt, M D , of Medfield, died on November 10 He was in his sixtieth year  
Dr Holt received his degree from Indiana University School of Medicine in 1914 He was superintendent of the Medfield State Hospital and a member of the American Psychiatric Association and the New England Society of Psychiatry  
His widow and a son survive

**RAYMOND** — Loring H Raymond, M D , of Somerville died on September 6 He was in his seventieth year  
Dr Raymond received his degree from Harvard Medical School in 1903 He was a fellow of the American College of Surgeons and the American Medical Association  
His widow survives

MASSACHUSETTS DEPARTMENT  
OF PUBLIC HEALTH

COMMUNICABLE DISEASES IN  
MASSACHUSETTS FOR OCTOBER, 1948

DISEASE	RESUMÉ		
	OCTOBER 1948	OCTOBER 1947	SEVEN YEAR MEDIAN
Chancroid	2	4	2*
Chicken pox	622	509	570
Diphtheria	29	21	17
Dog bite	751	888	842
Dysentery bacillary	5	60	39
German measles	47	52	52
Gonorrhea	284	354	415
Granuloma inguinale	1	1	0*
Lymphogranuloma venereum	1	0	1*
Measles	660	120	401
Meningitis meningococcal	7	2	11
Meningitis Pfeiffer bacillus	2	2	2†
Meningitis pneumococcal	1	0	0†
Meningitis staphylococcal	0	0	0†
Meningitis streptococcal	0	0	0†
Meningitis other forms	0	0	0†
Meningitis undetermined	8	2	2†
Mumps	48	374	335
Pneumonia lobar	60	68	159
Polio myelitis	31	65	65
Salmonellosis	8	14	13
Scarlet fever	243	273	456
Syphilis	141	222	408
Tuberculosis pulmonary	181	228	236
Tuberculosis other forms	11	19	19
Typhoid fever	2	6	4
Undulant fever	2	3	5
Whooping cough	180	460	554

\*Four year median  
†Six year median

COMMENT

The diseases with an incidence above the seven-year median were chicken pox, diphtheria, measles and mumps  
The diseases with a prevalence below the seven-year median were bacillary dysentery, meningococcal meningitis lobar pneumonia, poliomyelitis, pulmonary tuberculosis and whooping cough  
Chicken pox was at the highest level ever reported for October, which may indicate that it will continue at the high level of recent months  
Diphtheria was at the second highest level since 1935 The communities primarily affected continued to be Boston and those immediately to the north  
Measles was at the highest level for October since 1928 It seems likely that the high prevalence of recent months is to continue  
Mumps was at the highest level ever reported for October A continued high prevalence can be expected during the coming season

Only three times in the past has scarlet fever been lower in October than prevalence recorded for the month The high prevalence of recent months, after repeated record low levels last year, makes it likely that the disease will be on the increase during the coming season  
Whooping cough was at the lowest prevalence recorded since 1916 It is unlikely, however, that this low figure can be maintained, and the coming season will probably show a considerable increase

GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Diphtheria was reported from Arlington, 2 Berkley, 1 Boston, 14 Cambridge, 1 Chelsea, 1 Danvers, 1 Easton, 1, Everett, 1 Hanover, 1 Malden, 3, New Bedford, 1, Somerville, 1 Watertown 1, total, 29  
Dysentery, amebic, was reported from Stoneham, 1, total 1  
Dysentery, bacillary, was reported from Stoneham, 1, Newburyport, 1, Worcester, 3 total, 5  
Encephalitis, infectious, was reported from Clinton, 1, total, 1  
Lymphocytic choriomeningitis was reported from Cambridge 1, Worcester, 1, total 2  
Malaria was reported from Barnstable, 1, total, 1  
Meningitis, meningococcal, was reported from Boston, 2, Haverhill 1 Lynn 1 Randolph, 1 Worcester 2, total, 7  
Meningitis Pfeiffer bacillus, was reported from Hatfield, 1 Lawrence, 1, total, 2  
Meningitis, pneumococcal, was reported from Barnstable, 1 total, 1  
Meningitis, undetermined, was reported from Andover, 1, Beverly, 1 Brockton, 1 Dudley 1, Northampton, 1, Spencer, 1 Weymouth 1, Worcester, 1, total, 8  
Poliomyelitis was reported from Amherst, 1, Attleboro, 1, Belmont, 1, Boston, 2, Brookline, 1, Cambridge, 1 Danvers, 3 Littleton, 2 Lynnfield, 1 Marblehead, 1, Medford, 1, Middleboro 1 Palmer, 1, Plymouth, 1 Salem 2, Shrewsbury, 1, Springfield, 2 Warren, 1, Wellesley, 1, West Springfield, 1 Worcester, 5, total, 31  
Salmonellosis was reported from Beverly, 2 Stoneham, 1, Wakefield, 1 Worcester, 4 total, 8  
Septic sore throat was reported from Boston, 9 Lynn, 1, Stoneham, 1 West Newbury, 1 total 12  
Tetanus was reported from Cambridge, 1, Pittsfield, 1, total, 2  
Trachoma was reported from Lynn, 1 total 1  
Trichinosis was reported from Boston, 1, Fall River, 1, total 2  
Typhoid fever was reported from Brockton, 1, Springfield, 1 total 2  
Undulant fever was reported from Holyoke, 1, Norwood, 1, total, 2

BOOK REVIEWS

*Nursing for the Future* By Esther Lucile Brown Ph.D  
198 pp New York Russell Sage Foundation 1948 \$2.00  
The avowed objective of Dr Brown's "Nursing for the Future" is refreshing She states, "First, and most important, was the decision to view nursing service and nursing education in terms of what is best for society — not what is best for the profession of nursing as a possibly 'vested interest'" Quite rightly she says of the nurses that "Many have kept their attention so focused upon professional rights and prerogatives that society has sometimes come to question their interest in serving the needs of our national life"  
How closely the author adheres to her objective might be questioned, but her report based on painstaking investigation, contains many facts and observations that should be helpful "So long as attention is centered on the graduate nurse, no other avenue is open except that of the present frantic and probably futile effort to recruit more prospective R.N.'s Even appreciably better educational preparation is likely to be denied them so insistent will the demand for nursing service continue to be Once emphasis is shifted to nursing however several roads seem to point to potentially larger supplies of service and to possibly increased efficiency both on the nonprofessional and the professional levels"  
It is cheering to learn this

Observing that everyone desires the best in nursing service but that competent graduate nurses must be used for supervision, administration and teaching, Dr Brown wisely concludes, "We are still far from discovering a financial method whereby the finest in nursing could be furnished to everyone in need. At least it is assumed that neither the patient nor the institution should pay for graduate nursing, if any part of that nursing could be done as efficiently by persons with shorter preparation." Only too true is her statement that the profession has difficulty in visualizing concomitant assistant and professional nursing services, but without them, she says, "we shall almost inevitably have to continue to depend on the graduate bedside nurse as we do today, regardless of the fact that her training has been too long and expensive for performing the simpler functions."

Dr Brown then proceeds to outline three grades of nursing service: professional, nonprofessional and an intermediate group. "In the case of the graduate general nurse, however, emphasis needs to be placed only on preparation for bedside care and some understanding of what constitutes a complete health service." She calls attention to the fact that the Committee of Interests in Accreditation "visualized three classes of members: schools offering the basic curriculum, schools offering advanced curricula, and schools preparing practical nurses." If we add to this the proviso that those demonstrating the ability may progress from grade to grade, we have in effect the recommendation recently adopted by the American Medical Association. When such groups of nurses and physicians are in agreement that three grades of nurses should be trained, and the former comes to the realization that with this plan "nurses will be given a better opportunity to devote themselves to those aspects of clinical practice that require true professional skill," progress should be swift.

Many hospitals, says Dr Brown, are discussing the opening of such schools for practical nurses in addition to their "regular" schools, but "At present provisions for the preparation of practical nurses are negligible when compared with what are needed." "What is advocated is conviction, not lip-service alone, on the part of the nursing profession, hospital administrators, and the laity concerned with social change, that new patterns of nursing service must be evolved both in behalf of adequacy of supply and of quality." And further, "No system of training for practical nurses is likely to succeed unless the public educators, hospitals, nursing associations and state boards of control are prepared to manifest an active interest in practical nursing far beyond any interest yet shown." "Not only the availability of nursing care for large portions of the population, but also the future status of professional nursing itself will be determined by the degree to which rapid and effective action can be achieved in this long neglected field."

In the last two thirds of the book, Dr Brown seems to forget the original objective of what is best for society and to fall under the influence of her advisory committees, composed almost entirely of the leaders of advanced nursing education and from the academic sphere. Since the poor patient is inarticulate, the counsel of a committee of hospital administrators charged with his bedside care, and of doctors responsible for the therapy administered by the nurse might have been helpful. In spite of the fact that there is a dearth of top-grade nurses for administration, teaching, and the aspects of clinical practice requiring true professional skill, Dr Brown points out that even where university affiliation exists, "Relatively few of these students have exhibited an interest in obtaining a degree." Under these circumstances, the emphasis on the need for greatly expanding the opportunities for truly higher education may be questioned, and those primarily interested in the care of the patient may resent the repeated reference to the hospital as the "laboratory" for such institutions of learning. It perhaps recalls too sharply the point of view of the student who wrote, "The patient is the medium through which the nurse expresses her personality."

Aside from this overemphasis on higher education, Dr Brown's book contains much valuable information and common sense. It will be a pity if hospital administration does not integrate the points presented into a plan of action to extricate itself from the present dilemma of nursing service.

*The Pathology of Nutritional Disease*. By Richard H. Follis, Jr., M.D. 8°, cloth, 291 pp., with 71 illustrations. Springfield, Illinois: Charles C. Thomas, 1947. \$6.75.

To those who have not had the opportunity of following the literature on nutrition as it has developed, the problem of orientation in such a complicated, widely applied and somewhat confused field is likely to require so much time as to be prohibitive. Consequently, the appearance of a book that aims at a stocktaking and a clarification of confused issues is warmly welcomed by students and clinicians, if not by those in the research field.

Dr Follis has undertaken the rather ambitious task of discussing the pathophysiology and histopathology resulting from a deficiency of forty-two nutrients essential to mammalian metabolism. He has wisely eliminated many of the early investigations in which the findings were complicated by a multiplicity of deficiencies; he has attempted to restrict himself to those in which, so far as present knowledge is concerned, a single deficiency acts as a limiting factor. The result is a clear demonstration of the wide gaps in knowledge of the specific roles of many of the so-called dietary essentials. Regarding human metabolism these gaps are exceedingly large, and somewhat startling, when compared with the abandon with which the nutrients are used in clinical medicine.

Not only does the author discuss the specific effects of single deficiencies, but also, whenever possible, he indicates the interrelation of various factors. Thus, the interrelations of choline, methionine and cystine, of tryptophan and niacin, of ascorbic acid and phenylalanine and tyrosine and so forth are briefly but concisely considered.

Since the factors discussed are likely to be essential for a variety of tissue cells, it is not surprising that a deficiency of any one may be manifested by morphologic and physiologic lesions in a number of different tissues. Conversely, distortions of structure and function may develop in a given tissue as a result of a deficiency of several factors occurring independently. The author has attempted to emphasize this by approaching his subject initially from the point of view of the individual factors and finally from the point of view of specific tissues.

In this era of unbridled enthusiasm over various concoctions of essential nutrients, it is a healthy sign that a book such as this has been written. If it succeeds in but one thing — a serious re-evaluation of the use of vitamins in clinical medicine — it will have served a useful purpose.

*Brief Psychotherapy: A handbook for physicians on the clinical aspects of neuroses*. By Bertrand S. Frohman, M.D. With the collaboration of Evelyn P. Frohman, and with a foreword by Walter C. Alvarez, M.D. 12°, cloth, 265 pp. Philadelphia: Lea and Febiger, 1948. \$4.00.

This handbook, written particularly for the general practitioner, has many features that will make it attractive to the beginner in psychiatry. Its simple, direct presentation and good glossary make it useful also for the educated patient.

Although it stresses practical clinical approach, theory has been cleverly introduced into the discussions, and advanced in an appealing manner. Case reports, brief and to the point, are interspersed throughout the text. Failures and difficulties are admitted — a rare finding in psychotherapeutic literature.

The psychoneuroses are carefully differentiated, and pitfalls in diagnosis are shown. Etiologic factors are reviewed in an excellent section, being separated according to age groups. There are special chapters on neuroses encountered in the specialties.

The main methods of treatment are given with their indications, and brief psychotherapy is described in more detail. There is a good bibliography.

The orthodox psychoanalysts will disagree with much that is presented in the section on therapy, and there are a few other points in the text that one might criticize. Despite these minor considerations, the book is a most welcome addition to the small group, now available, that present psychotherapy in a concise and practical form for the general practitioner.

*Diabetes Mellitus in General Practice* By Arthur R. Colwell, M.D. 8°, cloth, 350 pp., with 24 illustrations. Chicago: The Year Book Publishers, Incorporated, 1947. \$5.25.

Dr Colwell is such an outstanding investigator and physician that his book on diabetes mellitus is sure of a welcome. Although not conventional, it is certainly provocative that he omits the word pancreas in the first paragraph, captioned "Definition," of the first chapter. All doubt, however, of the writer's belief in the unity of diabetes is dispelled in the pages that follow. Interestingly, he brings out the connection between the anterior pituitary body, the suprarenal glands and the thyroid gland and shows that in the presence of hyperfunction of these ductless glands hyperglycemia and glycosuria are apt to occur. For practical purposes he concedes that diabetes mellitus is a relative insulin deficiency except when specific pituitary, adrenal, thyroid or sympathetic overactivity can be demonstrated and removed.

The reviewer is sure that Dr Colwell did not fully consider the implications of another sentence in that first paragraph which reads as follows: "The anomaly of glucose metabolism with ketosis is subject to control by diet and insulin but the course of the disorder and its arteriosclerotic complications are not influenced to any major degree." But the reader can be assured that the author does enthusiastically believe in the active treatment of the disease and that he points out these results in the retardation of its progress. He emphasizes the desirability of prophylaxis and treatment in the prediabetic stage. This is brought out in his discussion of heredity, in which he cites the anticipation of diabetes in succeeding generations, quoting the work of Woodruff and Spetz and notes the possibility that diabetes will eventually work itself out. He enlarges on this point by describing the rate of progress, rapid in youth and slow in advancing years of diabetes, and then suggests that if these slants are extended backward they converge at the approximate time of birth, indicating that the diabetes of a predetermined type is inherited. He goes so far as to suggest that its course is approximately half run by the time it is recognized clinically. Whether diabetes will work itself out in the fourth or fifth generation will soon be known. There are so many diabetic children now who have grown up and married that it will not be long before it can be determined whether the incidence of diabetes in their offspring, the presumable fourth and fifth generations is actually greater than that in the second and third. Before drawing conclusions, however, one must remember that only one in 25,000 persons under fifteen years of age was found to be diabetic by the National Health Survey.

All interested in diabetes will regard as important the following statements:

Diabetes at the stage, before glycosuria is persistent and harm has occurred, is easily treated and its progress prevented or delayed. It is important to recognize it early and treat it meticulously. Temporary improvement could become permanent, as indicated by animal experimentation, if mild diabetes were taken as seriously as severe diabetes and if the idea of protection from permanent islet damage were entertained. Much diabetes which could be kept innocuous by consistently good control is permitted to become severe because of complacency in regarding the lack of associated symptoms and ease of desugarizing.

The blame for this complacency the author puts largely on the medical profession. By control of diabetes he means control of the hyperglycemia. He is convinced that one should first get the patient sugar free and then increase the carbohydrate slowly as advocated generally by the best European clinicians of a former generation.

The description of the various insulins is excellent, and physicians are indebted to Dr Colwell for details of their manipulations, especially for the description of his own method of mixing two parts of quick insulin with one part of protamine zinc insulin in one syringe. The reviewer agrees with his preference for a syringe of 1-cc capacity divided in tenths. The details of the technique of administering insulin are excellent.

The section on acidosis (forty-three pages) is seriously written but prolix. One wishes the author had seen fit to insert in two or three pages a summary of H. F. Root's version of treatment of diabetic coma, which has been approvingly recognized by R. H. Nicks in a study entitled "Diabetic Coma" (*Bull. M. J.* 2:200-203, 1948). There is always a reason for a writer's adherence to certain methods. This is disclosed by hints here and there that he has so often waited

long for laboratory reports that he has tried to build up a safe method of treatment without them. The reviewer is positive that if Dr Colwell had been afforded reports of blood sugar and carbon dioxide tests within thirty or forty minutes after request, his treatment of diabetic coma would have been entirely different. It is regrettable that his results of treatment are not presented. Potassium is not mentioned although the fish-mouth syndrome might well have occurred in some of his cases since deficiency of potassium is almost exclusively confined to patients treated with injections of glucose or enormous quantities of liquids.

Issue at once must be taken with the following statement upon arteriosclerosis:

It is generally true that the most severe diabetes is not uniformly associated with vascular disease. There is no constancy in the relationship between the severity of the disorder of sugar metabolism and vascular disease, indeed if anything, the reverse seems to be true.

All grades of arteriosclerosis occur in the young as well as in the old, varying with the duration and control of the diabetes. It is not strange that the smaller blood vessels are as notably affected in the young as in the old although for the early manifestations of the arteriosclerotic process in youth one looks most commonly for calcification demonstrable by x-ray examination in the vessels about the ankles, the lower legs and the pelvic arteries. Indeed, the calcification of the pelvic arteries in young female patients with diabetes is one of the best prognostic indications of whether the patient will have a living child. The relative clinical absence of gangrene, cerebral and myocardial lesions of vascular origin in the young is largely due to the malignancy of the vascular disease in the kidneys prematurely shortening life, as is shown at autopsy.

It is regrettable that transmetatarsal amputations, described by McKittrick several years ago and carried out on a large scale, are not even mentioned, because this operation often results in the prevention of an amputation of the thigh. Similarly, it is surprising that after amputation it is advised that the stump should be left open. Nearly a generation ago this practice, at least in this vicinity, was ended by Dr Daniel Fiske Jones. Under no circumstances can one subscribe to the efficacy of penicillin ointment, which in the war proved to be less effective even than Dakin's solution. One would also deny the following statement: "The procedure of greatest value is the use of continuous warm moist compresses of generous thickness which is kept warm with an automatic heat cradle and not permitted to dry out." Warmth in the treatment of active infection we thought belonged to a former era and was even as outmoded as soaking a foot. As a matter of fact, no local surgeons have been heard to recommend soaking of an extremity in any kind of liquid during the last twenty years. In the discussion of carbuncles Dr Colwell suggests that the best available method of treatment is radical incision. Years ago that was true, but since the advent of the sulfonamides and penicillin the carbuncles disappear like dew before the sun, and operation upon a carbuncle is a rarity.

Again, the reviewer cannot subscribe to the idea that "the treatment of diabetic polyneuritis is just about as ineffective as anything in the entire field of medicine." It is granted that treatment is not spectacular in days or weeks, but it is spectacular in months and so remarkable that patients who have been cured are always available, even though they live at a distance, to come to the hospital to cheer a sufferer in the active stage. Moreover, one should combat the idea that the symptoms of neuritis flare up with the beginning of treatment. Careful questioning practically always elicits the presence of these symptoms long before, although they may have been in the background, because of the more intense symptoms associated with the nonutilization of glucose, the "polys," pruritus and loss of weight and strength.

Fat atrophy is very common. The reviewer cannot agree that it "usually is permanent and harmless," because in his experience, especially in children, fat atrophy is temporary.

This book is strongly recommended despite the few criticisms mentioned. It is truly provocative and stimulating. The reviewer knows that he has profited greatly by the hours spent in its perusal and that his own patients will benefit thereby, particularly because of the author's insistence upon very early and aggressive treatment of the disease and the hope thus awakened for its control and the prevention of disturbing complications.

## BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

*Medical Research in War.* Report of the Medical Research Council for the years 1939-45. Committee of Privy Council for Medical Research. Presented by the Lord President of the Council to Parliament by Command of His Majesty, December, 1947. 8°, paper, 455 pp. London: His Majesty's Stationery Office, 1948. 7s. 6d.

This important document summarizes the research work done by the various divisions of the Medical Research Council. Of particular interest are the reports on wounds and injuries, war diseases, penicillin and nutrition. A list of selected references is appended to each subject. The text is well printed on good paper. The monograph should be in all medical libraries.

*Diseases of the Chest Described for students and practitioners.* By Robert Coope, M.D., B.Sc., F.R.C.P., consulting physician, King Edward VII Sanatorium, Midhurst, physician, Liverpool and North-Western Chest Surgical (E.M.S.) Unit, visiting physician, Maghull Epileptic Homes, lecturer in clinical medicine, lecturer in applied physiology and lecturer in clinical chemistry, University of Liverpool, and examiner in medicine in the university of Liverpool, London and Aberdeen. With a foreword by Lord Horder. Second edition. 8°, cloth, 541 pp., with 134 illustrations and 34 color plates. Baltimore: The Williams and Wilkins Company, 1948. \$7.50.

This second edition of a book first published in 1944 has been revised to the extent of correcting certain errors in the description of the anatomy of the bronchial tree. The book was printed in Great Britain and bound in the United States. The type and paper are good, and the color plates are excellent. The volume should prove useful to those interested in the subject.

*Human Neuroanatomy.* By Oliver S. Strong and Adolph Elwyn, associate professor of neuroanatomy, College of Physicians and Surgeons, Columbia University. Second edition. 4°, cloth, 442 pp., 336 illustrations. Baltimore: The Williams and Wilkins Company, 1948. \$6.00.

The text of this new edition of a work, first published in 1943, and reprinted three times, has been revised, but not materially changed. A chapter has been added on segmental peripheral innervations, including a clinicoanatomic survey of the cervical, brachial and lumbosacral plexuses and of the main peripheral nerves. The chapter on the blood supply of the brain has been expanded to give a more complete and fully illustrated account of the arterial supply and venous drainage of the brain. The text is well printed, with a good type in two columns. A selected bibliography is appended. A good index concludes the volume. The book is recommended for all medical libraries and to all surgeons interested in the subject.

*The Hospital Care of Neurosurgical Patients.* By Wallace B. Hamby, M.D., professor of neurology and neurologic surgery, University of Buffalo School of Medicine. Second edition. 8°, cloth, 156 pp., with 30 illustrations. Springfield, Illinois: Charles C. Thomas, 1948. \$3.00.

The second edition of this manual written for nurses and for young physicians has been revised and simplified at the suggestion of its readers. The volume is not intended as a treatise on therapy, which varies greatly in different clinics. A chapter on the relations of house officers has been added to the text.

*Estudios sobre la Coca y la Cocaína en el Perú.* By Carlos Gutierrez-Noriega, M.D., and Vicente Zapata Ortiz, M.D. 8°, paper, 144 pp., with 32 illustrations, 8 tables and 2 plates. Lima: Ministerio de Educación Pública, 1947.

The preliminary chapters of this monograph deal with the history and habitation of the cocoa plant in Peru. The following chapters, based on experimental work, treat of the

physiology, the effects on the nervous system, mental activity and metabolism, and the action on muscular work, resistance to fatigue and toxicity of coca and cocaine.

*The Baby's First Two Years.* By Richard M. Smith, M.D., Sc.D. 12°, cloth, 180 pp., with 15 illustrations. Boston: Houghton Mifflin Company, 1948. \$2.75.

This new edition of a popular manual has been rewritten completely in many sections to conform with recent knowledge concerning the care of infants. The necessity for a fifth edition speaks well for the soundness of the manual, which should prove useful to mothers and others having the care of young children.

*Coronary Heart Disease.* By A. Carlton Ernestine, M.D., chief of the section on cardiovascular disease, Cleveland Clinic, Cleveland, Ohio. 8°, cloth, 95 pp. Springfield, Illinois: Charles C. Thomas, 1948. \$2.50.

This short monograph is simply written, and the material is well arranged. It discusses coronary-artery disease in its various aspects, including angina pectoris, acute myocardial infarction, acute coronary failure, paroxysmal cardiac dyspnea, heart block, disturbances of cardiac rhythm and congestive heart failure. A short chapter on the risk of anesthesia and surgical operations in patients with coronary-artery diseases concludes the text. A selected bibliography and a good index conclude the volume. The text is well printed on good paper and should prove valuable to the practicing physician.

*Physiologic Therapy in Respiratory Diseases.* By Alvan L. Barach, M.D., associate professor of clinical medicine, Columbia University College of Physicians and Surgeons, and assistant attending physician, Presbyterian Hospital, New York City. Second edition. 8°, cloth, 408 pp., with 74 illustrations. Philadelphia: J. B. Lippincott Company, 1948. \$9.00.

The first edition of this book was published in 1944 under the title, *Principles and Practices of Inhalation Therapy*. This new edition includes much new material on other measures than the therapeutic use of gases for counteracting the clinical disorders of breathing. The author defines the term physiologic therapy as treatment designed to restore adequate function to organs impaired by disease. Special emphasis is placed on pathologic physiology. The type and printing are excellent, but the few illustrations do not justify the use of a heavy coated paper. The volume is recommended for all medical libraries and to all physicians interested in the subject.

## NOTICES

### ANNOUNCEMENT

Dr. Field C. Leonard announces the opening of his office at 412 Beacon Street, Boston, for the practice of general surgery in association with Dr. Hollis L. Albright.

### BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

A meeting of the Boston Society of Psychiatry and Neurology will be held at the Boston Medical Library, 8 Fenway, on Wednesday, December 15, at 8:15 p.m.

#### PROGRAM

Topectomy in the Treatment of Psychoses. Dr. J. Lawrence Pool (thirty minutes).

Relief of Intractable Pain by Unilateral Frontal Leukotomy. Dr. John E. Scarff (thirty minutes).

### MASSACHUSETTS TRUDEAU SOCIETY

A meeting of the Massachusetts Trudeau Society will be held in the amphitheater of the Peter Bent Brigham Hospital on Wednesday, December 15, at 8:15 p.m. Dr. René J. Dubos, of the Rockefeller Institute for Medical Research, will speak on the subject "Bacteriologic Aspects of Tuberculosis."

Physicians and medical students are invited to attend.

(Notices concluded on page xxi)

## NOTICES (Concluded from page 944)

NEW ENGLAND SOCIETY OF  
PHYSICAL MEDICINE

A regular meeting of the New England Society of Physical Medicine will be held at the Hotel Kenmore, Boston on December 15, 1948

## PROGRAM

- 6:00 p.m. Informal Dinner in the Empire Room  
7:30 p.m. Meeting of the Council  
8:00 p.m. Scientific Session Dr. Dwight E. Harken will present an address entitled "Surgery of the Heart" followed by a demonstration of specific remedial breathing exercises illustrated by lantern slides and a sound film

Physicians, medical students and physical therapists are cordially invited

## SOUTH END MEDICAL CLUB

A regular meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on Tuesday, December 21, at 12 noon. Dr. Earle M. Chapman will speak on the subject "Use of Atomic Energy in Medicine."

## SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING  
THURSDAY, DECEMBER 16

## FRIDAY DECEMBER 17

- \*9:00-10:00 a.m. Albumin in the Treatment of Hypoproteinemia  
Dr. Sam T. Gibson, Joseph H. Pratt Diagnostic Hospital  
\*9:00 a.m.-12:00 p.m. Combined Medical and Surgical Staff Rounds  
Peter Bent Brigham Hospital  
\*12:00 p.m. X-Ray Conference, Margaret Jewett Hall, Mt. Auburn Hospital, Cambridge

## MONDAY DECEMBER 20

- \*12:15-1:15 p.m. Clinicopathological Conference, Main Amphitheater, Peter Bent Brigham Hospital

## TUESDAY DECEMBER 21

- \*9:00-10:00 a.m. Journal review, Joseph H. Pratt Diagnostic Hospital.  
12:00 p.m. South End Medical Club, Boston Tuberculosis Association, 554 Columbus Avenue, Boston  
\*12:15-1:15 p.m. Clinicoradiogenetological Conference, Peter Bent Brigham Hospital  
\*1:30-2:30 p.m. Pediatric Rounds, Burnham Memorial Hospital for Children, Massachusetts General Hospital

## WEDNESDAY DECEMBER 22

- \*11:00 a.m.-12:00 p.m. Medical Rounds, Amphitheater, Children's Hospital  
\*12:00 p.m.-1:00 p.m. Clinicopathological Conference (Children's Hospital), Amphitheater, Peter Bent Brigham Hospital  
\*2:00-3:00 p.m. Combined Clinic by the Medical, Surgical and Orthopedic Services, Amphitheater, Children's Hospital

\*Open to the medical profession

OCTOBER 1-MAY 20 Metropolitan State Hospital, Page 418, issue of September 9

NOVEMBER 17-JANUARY 26 Boston State Hospital Psychiatric Seminar Schedule, Page 762, issue of November 11

DECEMBER 14 Harvard Medical Society and Boston City Hospital House Officers Association, Page 502, issue of December 2

DECEMBER 14 New England Society of Anesthesiologists, Page 844, issue of November 25

DECEMBER 15 Boston Society of Psychiatry and Neurology, Page 944

DECEMBER 15 Massachusetts Trudeau Society, Page 944

DECEMBER 15 New England Society of Physical Medicine, Notice above

DECEMBER 21 South End Medical Club, Notice above

JANUARY 13 1949 The Present Status of the Peptic Ulcer Problem, Dr. S. Allan Wilkinson, Pentucket Association of Physicians, 8:30 p.m. Haverhill

MARCH 7-9 1949 American Academy of General Practice, Page 728, issue of November 4

MARCH 28-APRIL 1 1949 American College of Physicians, Page 158, issue of July 22

MAY 16-19 1949 American Urological Association, Biltmore Hotel, Los Angeles, California

MAY 26-28 1949 American Gynecological Association, Hotel Lorraine, Madison, Wisconsin

MAY 30-JUNE 3 1949 International Congress on Rheumatic Diseases, Page 800, issue of November 18

NOVEMBER 11-17 1949 Third Inter-American Congress of Radiology, Page 158, issue of July 22

## DISTRICT MEDICAL SOCIETIES

## HAMPDEN

JANUARY 25 8:30 p.m. Academy of Medicine, Springfield, A Review of the Sterility Problem, Dr. John Rock.

## MIDDLESEX EAST

JANUARY 19

MARCH 21

MAY 11

## WORCESTER NORTH

DECEMBER 15 Leominster Hospital, Leominster

FEBRUARY 25 Burbank Hospital, Fitchburg

APRIL 27 Annual Meeting

## Washingtonian Hospital

41-43 WALTHAM STREET, BOSTON, MASS

Incorporated 1859

Conditioned Reflex, Psychotherapy, Semi-Hospitalization  
For Rehabilitation of Male Alcoholics

Treatment of Acute Intoxication and Alcoholic Psychoses  
Included

Outpatient Clinic and Social-Service Department for  
Male and Female Patients

JOSEPH THIMANN, M.D., Medical Director

Visiting Psychiatric and Neurologic Staff  
Consultants in Medicine, Surgery and the Other Specialties  
Telephone MA 6-1750

Wanted . . .

RESIDENT  
PHYSICIAN

Resident physician wanted for private sanitarium located in Orangeburg, S. C. Experience in psychiatry preferred. Must be able to furnish good references or do not apply. If interested, write

P O BOX 765  
ORANGEBURG, S C

## BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

*Medical Research in War* Report of the Medical Research Council for the years 1939-45. Committee of Privy Council for Medical Research. Presented by the Lord President of the Council to Parliament by Command of His Majesty, December, 1947. 8°, paper, 455 pp. London: His Majesty's Stationery Office, 1948. 7s 6d.

This important document summarizes the research work done by the various divisions of the Medical Research Council. Of particular interest are the reports on wounds and injuries, war diseases, penicillin and nutrition. A list of selected references is appended to each subject. The text is well printed on good paper. The monograph should be in all medical libraries.

*Diseases of the Chest. Described for students and practitioners* By Robert Coope, M.D., B.Sc., F.R.C.P., consulting physician, King Edward VII Sanatorium, Aldhurst, physician, Liverpool and North-Western Chest Surgical (E.M.S.) Unit, visiting physician, Maghull Epileptic Homes, lecturer in clinical medicine, lecturer in applied physiology and lecturer in clinical chemistry, University of Liverpool, and examiner in medicine in the university of Liverpool, London and Aberdeen. With a foreword by Lord Horder. Second edition. 8°, cloth, 541 pp., with 134 illustrations and 34 color plates. Baltimore: The Williams and Wilkins Company, 1948. \$7.50.

This second edition of a book first published in 1944 has been revised to the extent of correcting certain errors in the description of the anatomy of the bronchial tree. The book was printed in Great Britain and bound in the United States. The type and paper are good, and the color plates are excellent. The volume should prove useful to those interested in the subject.

*Human Neuroanatomy* By Oliver S. Strong and Adolph Elwyn, associate professor of neuroanatomy, College of Physicians and Surgeons, Columbia University. Second edition. 4°, cloth, 442 pp., 336 illustrations. Baltimore: The Williams and Wilkins Company, 1948. \$6.00.

The text of this new edition of a work, first published in 1943, and reprinted three times, has been revised, but not materially changed. A chapter has been added on segmental peripheral innervations, including a clinicoanatomic survey of the cervical, brachial and lumbosacral plexuses and of the main peripheral nerves. The chapter on the blood supply of the brain has been expanded to give a more complete and fully illustrated account of the arterial supply and venous drainage of the brain. The text is well printed, with a good type in two columns. A selected bibliography is appended. A good index concludes the volume. The book is recommended for all medical libraries and to all surgeons interested in the subject.

*The Hospital Care of Neurosurgical Patients* By Wallace B. Hamby, M.D., professor of neurology and neurologic surgery, University of Buffalo School of Medicine. Second edition. 8°, cloth, 156 pp., with 30 illustrations. Springfield, Illinois: Charles C. Thomas, 1948. \$3.00.

The second edition of this manual written for nurses and for young physicians has been revised and simplified at the suggestion of its readers. The volume is not intended as a treatise on therapy, which varies greatly in different clinics. A chapter on the relations of house officers has been added to the text.

*Estudios sobre la Coca y la Cocaína en el Perú* By Carlos Gutierrez-Noriega, M.D., and Vicente Zapata Ortiz, M.D. 8°, paper, 144 pp., with 32 illustrations, 8 tables, and 2 plates. Lima: Ministerio de Educación Pública, 1947.

The preliminary chapters of this monograph deal with the history and habitation of the cocoa plant in Peru. The following chapters, based on experimental work, treat of the

physiology, the effects on the nervous system, mental activity and metabolism, and the action on muscular work, resistance to fatigue and toxicity of coca and cocaine.

*The Baby's First Two Years* By Richard M. Smith, M.D., Sc.D. 12°, cloth, 180 pp., with 15 illustrations. Boston: Houghton Mifflin Company, 1948. \$2.75.

This new edition of a popular manual has been rewritten completely in many sections to conform with recent knowledge concerning the care of infants. The necessity for a fifth edition speaks well for the soundness of the manual, which should prove useful to mothers and others having the care of young children.

*Coronary Heart Disease* By A. Carlton Ernestine, M.D., chief of the section on cardiovascular disease, Cleveland Clinic, Cleveland, Ohio. 8°, cloth, 95 pp. Springfield, Illinois: Charles C. Thomas, 1948. \$2.50.

This short monograph is simply written, and the material is well arranged. It discusses coronary-artery disease in its various aspects, including angina pectoris, acute myocardial infarction, acute coronary failure, paroxysmal cardiac dyspnea, heart block, disturbances of cardiac rhythm and congestive heart failure. A short chapter on the risk of anesthesia and surgical operations in patients with coronary-artery diseases concludes the text. A selected bibliography and a good index conclude the volume. The text is well printed on good paper and should prove valuable to the practicing physician.

*Physiologic Therapy in Respiratory Diseases* By Alvan L. Barach, M.D., associate professor of clinical medicine, Columbia University College of Physicians and Surgeons, and assistant attending physician, Presbyterian Hospital, New York City. Second edition. 8°, cloth, 408 pp., with 74 illustrations. Philadelphia: J. B. Lippincott Company, 1948. \$9.00.

The first edition of this book was published in 1944 under the title, *Principles and Practices of Inhalation Therapy*. This new edition includes much new material on other measures than the therapeutic use of gases for counteracting the clinical disorders of breathing. The author defines the term physiologic therapy as treatment designed to restore adequate function to organs impaired by disease. Special emphasis is placed on pathologic physiology. The type and printing are excellent, but the few illustrations do not justify the use of a heavy coated paper. The volume is recommended for all medical libraries and to all physicians interested in the subject.

## NOTICES

## ANNOUNCEMENT

Dr. Field C. Leonard announces the opening of his office at 412 Beacon Street, Boston, for the practice of general surgery in association with Dr. Hollis L. Albright.

## BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

A meeting of the Boston Society of Psychiatry and Neurology will be held at the Boston Medical Library, 8 Fenway, on Wednesday, December 15, at 8:15 p.m.

## PROGRAM

Topectomy in the Treatment of Psychoses. Dr. J. Lawrence Pool (thirty minutes).

Relief of Intractable Pain by Unilateral Frontal Leukotomy. Dr. John E. Scarff (thirty minutes).

## MASSACHUSETTS TRUDEAU SOCIETY

A meeting of the Massachusetts Trudeau Society will be held in the amphitheater of the Peter Bent Brigham Hospital on Wednesday, December 15, at 8:15 p.m. Dr. René J. Dubos, of the Rockefeller Institute for Medical Research, will speak on the subject "Bacteriologic Aspects of Tuberculosis."

Physicians and medical students are invited to attend.

(Notices concluded on page xiii)

# The New England Journal of Medicine

Copyright 1948 by the Massachusetts Medical Society

Volume 239

DECEMBER 16, 1948

Number 25

## DELAYS AND ERRORS IN THE DIAGNOSIS OF BRAIN TUMOR\*

FREDRICK C. REDLICH, M.D.,† REMBRANDT H. DUNSMORE, M.D.,‡ AND EUGENE B. BRODY, M.D.§

NEW HAVEN, CONNECTICUT

**M**OST general practitioners, internists and neuropsychiatrists with a sufficiently large and varied practice sooner or later have the distressing experience of mistaking a brain tumor for a psychoneurosis or of unnecessarily delaying the correct diagnosis. As in other disorders involving behavior, the opinions of family and friends as well as of other lay people in the community, often contribute to confuse the opinions of the physician, particularly of the general practitioner. Such considerations stimulated the present investigation of diagnostic errors made in 100 proved cases of brain tumor.

It is impossible to extract a bibliography on diagnostic errors from the vast literature on brain tumors because such a diagnostic consideration is inextricably involved with other viewpoints in books and papers dealing with the general subject of brain tumors. However, it might be stated that the literature on diagnostic errors may be grouped under three headings. The first comprises general statements by neurologists, neurosurgeons and psychiatrists based on prolonged experience in which the authors reflect on their knowledge and offer their advice and warnings. Some of these reflections are contained in the great classics on the subject by Cushing, Bailey and so forth, and others in papers of the editorial type. A second group consists of case reports; there is a wide discrepancy between the classic monographs and the repetitive and often single and not always spectacular case reports. Characteristic of this group is emphasis on differential diagnosis between various tumors and other conditions or fine differentiations between the tumors themselves. The third group consists of reports on techniques (cerebrospinal-fluid examinations, electroencephalography, radiologic diagnosis and so forth) that help to establish or facilitate the diagnosis of brain tumors. A few papers dealing

explicitly with the diagnostic errors in brain tumors are listed.

Horrax<sup>1</sup> differentiated symptomatologically typical tumors easily diagnosed on the basis of adequate history, physical examination and laboratory study, and atypical ones that should be studied with the particular lesion in mind. He believed that a tumor or something simulating a tumor can almost always be diagnosed provided the patient consents to thorough diagnostic study. McIntyre and McIntyre<sup>2</sup> stated that most errors in the diagnosis of brain tumor were due to lack of "brain tumor consciousness" in the mind of the examiner, failure to realize the importance of an adequate history and repeated neurologic examinations, and failure to realize that headache, vomiting and choked disk are *not* early signs of brain tumor.

Purves-Stewart,<sup>3</sup> who reviewed 115 cases of verified brain tumors, concluded that carelessness or insufficient observation, as well as a tendency to cling to the first conception of the case, was the most important factor in what he called available errors. The main problems in what he termed unavailable errors were too short a period of observation and scanty clinical symptoms. A large majority of the diagnostic errors in the series of Hastings<sup>4</sup> were made in the differential diagnosis of cerebral vascular disease and tumor. Bing<sup>5</sup> discussed intracranial tumors with minimal focal signs presenting difficulties in diagnosis. Many authors have stressed the importance of tumor consideration in patients exhibiting convulsive seizures after the age of thirty. The great value of such technical diagnostic aids as electroencephalographic and air studies is generally recognized, and yet, as Poppen and Peacher<sup>6</sup> point out, these are not invariably reliable and cannot replace diagnostic weapons available to all: an adequate history and neurologic examination.

The present study approaches the problem from the viewpoint of public health. It has seemed that the differential diagnosis that concerns the neurologist so greatly actually contributes little to knowledge of why the diagnosis of brain tumors is unduly delayed or missed. The problem is not one of mak-

\*From the Department of Psychiatry and the Department of Surgery, Yale University School of Medicine.

†Associate professor of psychiatry, Yale University School of Medicine; psychiatrist in-chief, Grace-New Haven Community Hospital.

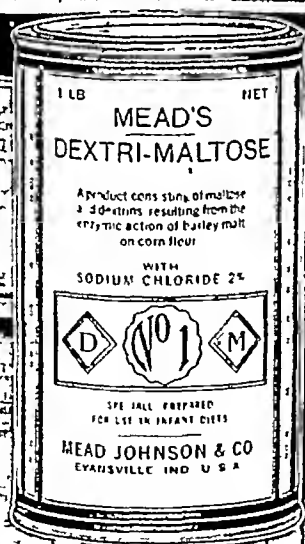
‡Instructor, Yale University School of Medicine; James Hudson Brown Memorial Fellow.

§Instructor, Department of Psychiatry, Yale University School of Medicine; resident, Psychiatric Clinic, Grace-New Haven Community Hospital.

# BACKGROUND

The use of cow's milk, water and carbohydrate mixtures represents the one system of

infant feeding that consistently, for over three decades, has received universal pediatric



recognition. No carbohydrate employed in this system of infant feeding enjoys so rich and enduring a background of authoritative clinical experience as Dextri Maltose.

# The New England Journal of Medicine

Copyright 1948 by the Massachusetts Medical Society

Volume 239

DECEMBER 16, 1948

Number 25

## DELAYS AND ERRORS IN THE DIAGNOSIS OF BRAIN TUMOR\*

FREDRICK C REDLICH, M.D.,† REMBRANDT H DUNSMORE, M.D.,‡ AND EUGENE B BRODY, M.D.§

NEW HAVEN, CONNECTICUT

**M**OST general practitioners, internists and neuropsychiatrists with a sufficiently large and varied practice sooner or later have the distressing experience of mistaking a brain tumor for a psychoneurosis or of unnecessarily delaying the correct diagnosis. As in other disorders involving behavior, the opinions of family and friends as well as of other lay people in the community, often contribute to confuse the opinions of the physician, particularly of the general practitioner. Such considerations stimulated the present investigation of diagnostic errors made in 100 proved cases of brain tumor.

It is impossible to extract a bibliography on diagnostic errors from the vast literature on brain tumors because such a diagnostic consideration is inextricably involved with other viewpoints in books and papers dealing with the general subject of brain tumors. However, it might be stated that the literature on diagnostic errors may be grouped under three headings. The first comprises general statements by neurologists, neurosurgeons and psychiatrists based on prolonged experience in which the authors reflect on their knowledge and offer their advice and warnings. Some of these reflections are contained in the great classics on the subject by Cushing, Bailey and so forth, and others in papers of the editorial type. A second group consists of case reports; there is a wide discrepancy between the classic monographs and the repetitive and often single and not always spectacular case reports. Characteristic of this group is emphasis on differential diagnosis between various tumors and other conditions or fine differentiations between the tumors themselves. The third group consists of reports on technics (cerebrospinal-fluid examinations, electroencephalography, radiologic diagnosis and so forth) that help to establish or facilitate the diagnosis of brain tumors. A few papers dealing

explicitly with the diagnostic errors in brain tumors are listed.

Horrax<sup>1</sup> differentiated symptomatologically typical tumors easily diagnosed on the basis of adequate history, physical examination and laboratory study, and atypical ones that should be studied with the particular lesion in mind. He believed that a tumor or something simulating a tumor can almost always be diagnosed provided the patient consents to thorough diagnostic study. McIntyre and McIntyre<sup>2</sup> stated that most errors in the diagnosis of brain tumor were due to lack of "brain tumor consciousness" in the mind of the examiner, failure to realize the importance of an adequate history and repeated neurologic examinations, and failure to realize that headache, vomiting and choked disk are *not* early signs of brain tumor.

Purves-Stewart,<sup>3</sup> who reviewed 115 cases of verified brain tumors, concluded that carelessness or insufficient observation, as well as a tendency to cling to the first conception of the case, was the most important factor in what he called available errors. The main problems in what he termed unavailable errors were too short a period of observation and scanty clinical symptoms. A large majority of the diagnostic errors in the series of Hastings<sup>4</sup> were made in the differential diagnosis of cerebral vascular disease and tumor. Bing<sup>5</sup> discussed intracranial tumors with minimal focal signs presenting difficulties in diagnosis. Many authors have stressed the importance of tumor consideration in patients exhibiting convulsive seizures after the age of thirty. The great value of such technical diagnostic aids as electroencephalographic and air studies is generally recognized, and yet, as Poppen and Peacher<sup>6</sup> point out, these are not invariably reliable and cannot replace diagnostic weapons available to all: an adequate history and neurologic examination.

The present study approaches the problem from the viewpoint of public health. It has seemed that the differential diagnosis that concerns the neurologist so greatly actually contributes little to knowledge of why the diagnosis of brain tumors is unduly delayed or missed. The problem is not one of mak-

\*From the Department of Psychiatry and the Department of Surgery, Yale University School of Medicine.

†Associate professor of psychiatry, Yale University School of Medicine, Psychiatrist-in-chief, Grace-New Haven Community Hospital.

‡Instructor, Yale University School of Medicine, James Hudson Brown Memorial Fellow.

§Instructor, Department of Psychiatry, Yale University School of Medicine, resident, Psychiatric Clinic, Grace-New Haven Community Hospital.

ing a differential pathological type of diagnosis but of establishing the presence of an intracranial tumor at a stage sufficiently early so that treatment may be effective. The following specific questions must be answered: Does the examination of histories of proved cases of brain tumor suggest unnecessary delays in correct diagnosis? If such delays and errors are found, why do they occur? Who errs and what are the reasons for the errors? What remedies may be suggested?

METHOD

A random sample of 100 brain tumors verified by operation or autopsy or both was chosen and classified according to type and localization. The following aspects of the cases were tabulated: first complaints, first neurologic signs detected, correct

TABLE 1 First Complaints

COMPLAINT	No. of Cases
Headaches	86
Disturbance of eyesight (amblyopia, amaurosis, blurred vision, scotoma and so forth)	36
Gastrointestinal symptoms	
Vomiting	32
Nausea without vomiting	27
Seizures	30
Locomotor unsteadiness (falling, lack of co-ordination and so forth)	29
Double vision, ptosis and so forth	21
Weakness of limbs	21
Personality changes (neurotic complaints)	21
Speech difficulties	19
Dizziness	18
Memory and intelligence deficit	18
Fainting	17
Character changes	15
General weakness and fatigue	14
Drowsiness	12
Loss of bearing	11
Incontinence	9
Weakness of facial muscles	9
Psychoses	8
Amenorrhea	5
Weakness of half of one side	5
Stiffness of neck	4
Weight loss	3
Tremor of hands	2
Tilting of head	1
Loss of sense of smell	1

and false diagnosis by family physicians, correct and false diagnosis after hospitalization before diagnostic study by specialists, correct and false diagnosis by specialists (neurologists, psychiatrists and neurosurgeons), diagnostic contributions of cerebrospinal-fluid studies, air studies and radiologic and electroencephalographic examinations, and time lost between the first appearance of signs and symptoms (when the diagnosis presumably could have been made) and the time of the correct diagnosis. More than one first complaint was often mentioned, but for purposes of tabulation these were broken down into single symptoms (Table 1). Thus, a certain amount of distortion and condensation was unavoidable.

OBSERVATIONS

Pathological Observations

The cases were chosen at random from the files of the Department of Pathology, the Department of Psychiatry and the Department of Surgery. Eighty per cent of the material came from pa-

TABLE 2 Locations of the Tumors

LOCATION	No. of Cases
Temporoparieto-occipital	37
Frontal	24
Posterior fossa	23
Pituitary and hypothalamus	9
Basal ganglions	7
	100

tients who had died, 74 per cent of the patients had had craniotomies. The case records were collected from 1935-1944. The locations of these tumors are presented in Table 2. Their typing, following the customary outline of Cushing,<sup>7</sup> is presented in Table 3. The preponderance of malignant types reflects the fact that many of the cases were chosen from post-mortem files. Thus, this study is not characteristic of brain tumors as the neurosurgeon sees them but of patients with brain tumors who die. This actually represents patients in whom the process was more severe and in whom

TABLE 3 Types of Tumors

TUMOR	No. of Cases
Glioblastoma	46
Astrocytoma	12
Meningioma	11
Spongioblastoma (polare)	7
Craniopharyngioma	5
Chromophobe adenoma	3
Ependymoma	3
Medulloblastoma	3
Acoustic neuroma	2
Astroblastoma	2
Oligodendroblastoma	2
Sarcoma	2
Eosinophilic	1
Tuberculoma	1
	100

the symptoms were therefore probably more striking.

Diagnoses of the Community

Relatively little information was obtained regarding diagnoses by friends or relatives. It is of interest, however, that of the 16 recorded diagnoses, personality disorders were mentioned in 10 cases and that 2 others were considered alcoholism because of the patients' drunken gait. Eye trouble was diagnosed in 2 cases, and epilepsy in one, and a chiropractor made 1 diagnosis of "misplaced axis."

Such diagnoses undoubtedly reflect to some degree the popular interest in nervous disorders and the opinion of many lay people that they are competent to diagnose and prescribe for such difficulties themselves.

### *Diagnoses by Family Physicians*

About half the patients left their physicians presumably dissatisfied with the unsuccessful treatment and lack of diagnosis. The other half were eventually referred to hospitals because of "serious disease" requiring more careful and specialized study. The survey of these diagnoses is given in Table 4. Only 4 per cent correct diagnoses and 2 per cent doubtful diagnoses of brain tumor were made. It is interesting that patients reached specialists in most cases only after having been investigated by internists, surgeons, ophthalmologists and so forth, and in no case were they referred directly by general practitioners in the community.

TABLE 4 *Diagnoses by Medical Practitioners in the Community*

DIAGNOSIS	No of Cases
'Nothing wrong'	20
Emotional disorder (neurosis)	12
Epilepsy	5
Eye disease	5
Brain tumor	2
Suspicion of brain tumor	2
Cerebral accident	1
Appendicitis	1
Sinusitis	1
Facial palsy	1
Anemia	1
Psychosis	1
Rheumatic fever	1
Encephalitis	1
Neuralgia	1
Optic atrophy	1
Head injury	1

The low percentage of correct diagnoses may also have been influenced by the social group. The lay group tends to evaluate any deviation from the normal in terms of nonconformity with accepted patterns of behavior rather than in medical or physical terms.

### *Diagnoses Made in Hospitals by Nonspecialists*

These diagnoses are given in Table 5. The percentage of correct diagnoses has increased considerably, being correct in 29 and at least considered in 8 additional cases. The diagnosis of personality disorder is still high, however (pschoneurosis, 13 cases, and psychosis, 2 cases), and 11 cases were listed as "no diagnosis." It is probable that in the last group there were many patients who were believed by the examining physicians to be psychoneurotic but on whom they were unwilling to make a definite statement. The diagnosis of epilepsy is still considered in an impressive number of patients.

### *Diagnoses Made by Neurologists, Psychiatrists and Neurosurgeons in Hospitals*

Of the 100 patients 94 were seen by specialists, and in all but 7 cases the correct diagnosis of brain tumor was made. The signs observed on neuro-

TABLE 5 *Diagnoses Made in Hospitals by Nonspecialists*

DIAGNOSIS	No of Cases
Brain tumor	29
Personality disorder	13
Epilepsy	13
No diagnosis	11
Cerebral arteriosclerosis	5
Eye disease (unspecified)	5
Hypertension	4
Cerebral accident	3
Optic atrophy	2
Encephalitis	2
Head injury	2
Psychosis	2
Diabetes insipidus	2
Multiple sclerosis	1
Meningitis	1
Hyperthyroidism	1
Central-nervous system syphilis	1
Syngomyelia	1
Carcinoma of stomach	1
Degenerative brain disease	1

logic and psychiatric examination are presented in Table 6. In 5 patients — notably, those with personality disorders — the initial diagnosis made by a specialist was wrong, and observation and the help of another consultant facilitated the correct

TABLE 6 *Signs Found on Neurologic and Psychiatric Examination*

Sign	No of Cases
Papilledema	67
Reflex changes	59
Weakness of muscles innervated by cranial nerves with exception of eye muscles	42
Symptoms pertaining to lesion of oculomotor nerves	41
Weakness of extremities and trunk	32
Disturbances of co-ordination	29
Speech disturbances (dysphasia, dysarthria and so forth)	19
Visual-field disturbances	18
Psychotic syndromes	15
Intellectual deficit	12
Personality changes (neurotic reactions and character changes)	10
Lesions of cranial sensory nerves	8
Symptom of cutaneous nerves including deep pain	8
Loss of olfaction	7
Disturbance of consciousness	5
Meningeal signs	5
Forced grasping	3
General debility	1
Bony prominence of skull	1
Dullness left forehead	1
Seizure observed	1

diagnosis. In 49 patients a correct localization was made, and in 28 patients a correct clinical diagnosis of the histologic type of tumor was made. Three cases in which diagnoses were missed by specialists are briefly reported below.

CASE 1 (A75793) A 72-year-old laborer entered the emergency room with a history of having "fainted" while descending the stairs and of having consequently struck his head and left arm. He also stated he had been treated by his family physician for years for a heart condition.

Physical examination was reported negative except for swelling of the left wrist, abrasion of the left side of the

face and head and auricular fibrillation and cardiac enlargement. X-ray study revealed a Colles fracture of the left wrist and a fracture of the left parietal bone. The patient was treated and discharged 12 days later.

After 3 weeks he was readmitted to the hospital because he had an episode of vomiting at midnight followed by a stool containing bright-red blood. Physical examination was essentially negative except for his cardiac status and the fact that he was noted to be "senile", the fundi were "not well visualized." A positive Romberg test was noted. The diagnostic considerations were mainly concerned with the rectum.

Thirty-three days after admission the patient was observed one night to have a sudden drop in blood pressure. He perspired profusely, and yet the pulse remained full and strong, no temperature changes were noted. It was assumed that he had had a large hemorrhage into his bowel. The next morning he was observed to have a right-sided hemiparesis, a bilateral positive Hoffmann sign, right positive Babinski sign, absent superficial reflexes and drooping of the right corner of the mouth. The diagnostic assumption was that he had a cerebral hemorrhage. No lumbar puncture, electroencephalogram or air study was done. The patient's course was rapidly downhill, and he died 3 days later.

The post-mortem findings were meningioma, compressing the right motor strip, generalized arteriosclerosis with multiple hemorrhages in the small bowel and cardiac hypertrophy.

**CASE 2 (A53451)** A 58-year-old housewife was first seen in the psychiatric inpatient service on March 7, 1935. The past history revealed that approximately 3 years previously she had noted a progressive failing of vision. Two years before admission tinnitus developed, and her appetite was no longer as good as it had been. Approximately 6 months later a left frontal headache developed, which was intermittent, and she began to fear being alone. This was followed by an attack of severe headache accompanied by nausea and vomiting and by several days of depression. She gradually became forgetful and depressed, and had some difficulty in speaking. At about this time her friends noticed personality changes, and two physicians believed that her difficulty was not organic. Six months later her vision became much worse and she was again seen by two physicians, one of whom made no diagnosis, and the other of whom treated her tinnitus with "electricity." Her speech became worse, and on consulting another physician she was referred to the psychiatric inpatient service.

On admission the provisional diagnosis was cerebral arteriosclerosis with encephalopathy. The positive neurologic signs were weakness of the right facial nerve, hyperactive deep tendon reflexes on the right, apraxia and a questionable right homonymous field defect. This was confirmed by neurologic consultation. Lumbar puncture disclosed a spinal-fluid pressure equivalent to 195 mm of water, varying up to 235 mm. No other laboratory studies were done except for routine blood and urine examinations.

The patient died 2 days after admission.

Post-mortem examination revealed a glioblastoma multiforme involving the left temporoparietal lobe.

**CASE 3 (A70941)** A 19-year-old boy was first admitted to New Haven Hospital (neurosurgical service) on August 13, 1942, because of severe frontal and occipital headaches on June 28. These were severe in the early morning, disappearing about 10 a.m. They became progressively worse, and nausea and vomiting appeared after 2 weeks. He complained of transient dizziness but no true vertigo. He had received his draft classification on June 30. The past history was otherwise irrelevant.

Physical examination was entirely negative, including neurologic examination, with the exception that he "staggered in all directions on walking." The diagnostic impression was "hysteria." The patient was noted to be of "low intelligence."

Lumbar puncture on the day after admission showed an initial spinal-fluid pressure equivalent to 110 mm of water, with a protein of 82 mg per 100 cc. On August 17 no pressure was noted, the protein was 42.5 mg per 100 cc.

The patient was to have a skull x-ray film but this procedure was not done. He was discharged on August 17 with a diagnosis of hysteria. He was seen 1 month later in

the clinic and at this time his symptoms were still present, and the diagnosis was the same, he was referred to the psychiatric outpatient clinic.

The patient was followed in the psychiatric outpatient clinic until November 10, when his symptoms became exacerbated and he was admitted to the psychiatric service. At this time he was described as being stuporous, dehydrated and acutely ill. He had cervical rigidity, suboccipital tenderness and a positive Kernig sign on the right. The pupils were dilated, the left one being sluggish to light. Bilateral papilledema (4 diopters), with hemorrhages, was noted. Dysarthria, left-facial-nerve weakness and bilateral ankle clonus were present.

Lumbar puncture on admission showed an initial spinal fluid pressure equivalent to 350 mm of water, with a total protein of 30 mg per 100 cc. The diagnosis of an expansive lesion of the brain was made. The patient died on the night of admission.

Post-mortem examination on November 11 disclosed sarcoma of the left cerebellar hemisphere, with extension into the dura and fourth ventricle, atrophy of the sella and inner table of calvarium and a cerebellar pressure cone.

## DIAGNOSTIC CONTRIBUTIONS OF LABORATORY TECHNIQUES

### *Cerebrospinal Fluid*

Lumbar punctures were recorded on only 41 of the 100 patients. In 38 cases the cerebrospinal fluid was abnormal, and the test confirmatory. In 36, the pressure was over 180 mm of water. The total protein was above 50 mg per 100 cc in 24 patients. In 5 cases no attention was paid to the abnormal spinal-fluid findings, and thus a very important clue to the diagnosis of brain tumor was missed.

### *Radiologic Examination of the Skull*

In 91 patients x-ray films of the skull were taken. This probably reflects the ease of ordering skull films and the prominence of radiologic diagnosis in general medical thinking. In contrast to the high percentage of positive spinal-fluid findings, however, pathologic findings were noted in only 48 cases. In only 2 cases did the x-ray examination lead to erroneous localization.

### *Electroencephalogram*

Since many patients were examined before the electroencephalic laboratory was organized, electroencephalic reports were available in only 21 patients, 19 of these were abnormal, indicating a significant contribution to diagnosis. In 10 of these patients the lesion was localized by the electroencephalogram.

### *Ventriculogram*

Ventriculograms were performed in 33 patients. Localization was correct in 27 cases — a significant proportion. In 2 patients the localization was false.

## DELAYS IN DIAGNOSIS

The number of months elapsing between the first time when a diagnosis seemed possible and the moment of correct diagnosis was estimated. The mean of such delay was fifteen months, the median twenty-four, and the longest interval eighteen years.

In a third of all patients, the time loss was less than three months, however, and in half the cases the time loss was less than one year. Because the delay in the more malignant groups is necessarily low, the time loss in the less malignant tumors seems even more striking.

Diagnostic errors made during the period of hospitalization are presented in Table 7. In some of these cases the correct diagnosis was missed owing to a combination of errors. For example, under the heading of inadequate neurologic examination, both lack of a reasonably thorough examination and a gross lack of interpretation of positive neurologic signs are included.

### DISCUSSION

In about half the patients the diagnosis of brain tumor was seriously delayed (over one year). In almost a fourth of these patients the delay was more than two years. Much of this was due to ignorance and inertia on the part of the patients' families, who did not consult a physician. On the other hand, of course, it is a common experience of many psychiatrists to see patients suffering from fatigue, giddiness and mild headaches who hypothetically assume the diagnosis of brain tumor. On the basis of knowledge of initial signs and symptoms it should be possible to stress the need for medical examination in the presence of headaches, visual impairment and giddiness accompanied by nausea. Education along this line need not remark on the possibility of brain tumor, but only on the necessity for seeking medical advice.

The low percentage of correct diagnoses of brain tumors by general practitioners in the community is striking. This is offset by the fact that about half the patients in whom no appreciable time loss in diagnosis occurred (a sixth of all patients) went through the hands of physicians in the community. An even higher percentage of the total number of patients was referred to hospitals or to other specialists with the diagnostic assumption by the general practitioner of a severe illness requiring more thorough diagnostic study.

In the face of these referrals the question arises why the diagnosis of brain tumor is missed at this early stage. Is this due to unawareness of the signs and symptoms of brain tumor, or to failure to carry out necessary examinations? It is our impression that the most important considerations are pressure of time and certain characteristics of a general medical practice that lead to errors or to omissions. One factor determining this may be the reluctance of physicians practicing in certain social groups to diagnose such illnesses as tumors because of the tendency of patients to blame the physician for the consequences of the disease. This also holds for such diagnoses as "tuberculosis" and "mental illness." More important, however, is the probability that many more correct diagnoses

could have been made if a cursory neurologic examination aimed at the detection of muscular weakness, reflex changes and visual symptoms and signs had been performed. The most important of these is an ophthalmoscopic examination. The question then is, Why do general practitioners not carry out such neurologic examinations including ophthalmoscopy? The following possible factors suggest themselves: insufficient emphasis in medical training on important practical steps in diagnosis and treatment, such as the carrying out of a brief "emergency neurologic examination"; insufficient reward in the way of positive findings seems to result in the abandonment of such special examinations as

TABLE 7 Survey of Diagnostic Errors in Hospitals

Error	No of Cases
Inadequate neurologic history and examination	27
False evaluation of personality disorder	15
Seizures not explored	14
Headaches not evaluated	8
Failure to evaluate visual symptoms	6
Failure to evaluate cerebrospinal-fluid findings	5
Insufficient laboratory work	5
History of head injury overevaluated	4
Overevaluation of hypertension	4
Assumption of degenerative brain disease based on insufficient evidence	4
Examiner sidetracked by medical symptoms (elevated temperature, glycosuria, hyperthyroidism)	3
Overevaluation of alcoholic history	2
Coma not investigated	1
Deafness not investigated	1
Too great dependence on negative laboratory findings	1

ophthalmoscopy by general practitioners — this may explain to some degree why general practices are often considered dull in terms of detection and treatment of rare diseases, the tendency to attribute symptoms to minor neurotic difficulties is strikingly dramatized by the diagnosis of "nothing wrong" in 20 of the 49 diagnoses made by local practitioners and of a personality difficulty in 12 cases. The proportion so diagnosed (51 per cent) was markedly reduced by the nonspecialists' diagnoses made in hospitals (24 per cent). Since a review of early complaints reveals psychiatric and neurologic symptoms or intellectual deficit in 41 patients, the error obviously consists not in assuming personality disorders when they are absent but in neglecting to find the proper cause for such disorders. The simple device of looking for behavioral disorder and organic signs and then correlating both should help to avoid this frequent error.

Hospital physicians have the advantage of observing changes in the patient over a period and in addition, early technics for refined diagnoses are more available. Still, inadequate neurologic examinations and false interpretations of data were very important causes of errors. The lack of investigation of seizures was noteworthy. Symptoms such as these, as well as headaches and visual impairment, were often easily assumed to be due to hypertensive encephalopathy, cerebral arterio-

sclerosis and various progressive degenerative brain diseases

Compared with other groups, the percentage of correct diagnoses made by specialists (neurologists, neuropsychiatrists and particularly neurosurgeons) was high. This demonstrates that available technics and knowledge permit a high degree of diagnostic acumen. On the other hand, it must not be overlooked that previous spade work helps greatly to eliminate errors, and, in addition, it is always easier to diagnose tumors in later stages than at the onset.

Laboratory procedures appeared to have mostly confirmatory value rather than to be useful as independent diagnostic technics. Clinical findings seem to be of primary importance. The early use of radiologic and electroencephalographic technics, however, is highly recommended, and it is our impression that the electroencephalogram is by no means as frequently used as it should be. Lumbar puncture in persons suspected of having tumors seems best reserved for hospital practice. The possible development of a pressure cone, particularly in posterior-fossa tumors, should be seriously considered. Air studies in most cases are late studies to establish localization and should be done only by neurosurgeons equipped to follow through with operation if necessary.

On the basis of the above material, a recommendation for better mass health education regarding early symptoms of dangerous disease—in this case, of tumors and particularly of brain tumors—seems justified. This is an exceedingly delicate problem, however, and a great deal of thought is necessary to spread knowledge on a mature, realistic level without increasing general hypochondriacal concern. Possible agencies of communication are biology classes in school, health drives, appropriate literature and radio talks.

At the level of the physician, teaching of abbreviated neurologic examinations in medical schools and hospitals might decrease the incidence of error and delay in the diagnosis of brain tumor. The principle of appropriate referral to specialists when the practitioner is unable to carry out the necessary examinations needs a more liberal and intelligent interpretation. Attention should be drawn to statistical tables demonstrating early signs and symptoms. Certain general diagnostic procedures—

for example, ophthalmoscopy—seem so basic that they should not be abandoned even under the pressure of a busy practice, or if negative findings are obtained in an overwhelming number of cases. Such frequent diagnostic errors as failure to explore seizures, headaches and visual impairment, failure to examine for changes in the fundi, slight muscular weaknesses and reflex changes can be avoided. Personality changes should be explored from both an organic and a behavioral point of view and should not be used in themselves as an excuse for cessation of further organic or behavioral investigation. Results of laboratory procedures should be used and interpreted within the context of the total clinical situation. Thus, achievements so far the prerogative of the specialist will find a wider and more useful application in the field of general medical practice.

### SUMMARY

A study of 100 proved cases of brain tumor revealed that in approximately half the cases the diagnosis was delayed for a year or longer. Although social and psychologic factors often delayed referral by the family to a physician, the low percentage of correct diagnoses by practitioners in the community was striking. The failure of the practitioner to carry out routine brief neurologic examination and a tendency to attribute symptoms to personality difficulties with subsequent lack of further investigation seem important. A standard survey of early signs and symptoms and errors due to overlooking or ignoring of such findings is made. The value of specific clinical and laboratory studies is assessed. Public-health education designed to avoid such delays in diagnosis is indicated at both lay and professional levels.

### REFERENCES

- 1 Horrax G. Diagnosis and prognosis of brain tumors. *Bull New York Acad Med* 19 125-131 1943
- 2 McIntyre H D and McIntyre A P. Problem of brain tumor in psychiatric diagnosis. *Am J Psychiat* 98 720 726 1942
- 3 Purves-Stewart J. Clinical study of intracranial tumours and especially of errors in their diagnosis. *Proc Roy Soc Med (Sect. Neurol)* 20 1 8 1926
- 4 Hastings D W. Difficulties in differential diagnosis of brain tumor in older age groups. *J Nerv & Ment Dis* 89 44 51 1939
- 5 Bing R. Tumeur cerebrale a symptomatologie fruste. *Schizophr Arch f Neurol u Psychiat* 33 219 227 1934
- 6 Poppen J L and Peacher W G. Brain tumors in presence of normal air studies. *S Clin North America* 23 803 813 1943
- 7 Cushing H. *Intracranial Tumours. Notes upon a series of two thousand verified cases with surgical mortality percentages pertaining thereto*. 150 pp. Springfield Ill. Charles C Thomas 1932. Pp 8 and 11

## THE EFFECT OF SUBACUTE BACTERIAL ENDOCARDITIS ON THE COURSE OF THE UNDERLYING HEART DISEASE\*

BERNARD RAPOFORT, M D,<sup>†</sup> AND LAURENCE B ELLIS, M D<sup>‡</sup>

BOSTON

THE development of a successful treatment for subacute bacterial endocarditis by penicillin has greatly changed the significance of this condition as an event in the life history of a person with chronic heart disease. Formerly, the disease was almost universally fatal, with the infection itself dominating the clinical picture, and therefore it was of relatively little moment whether heart failure developed or not. Now, since the infection can usually be controlled, if increased cardiac damage occurs it may materially increase the disability or lead to early death of the patient from heart failure. Many of the investigators<sup>1-12</sup> who have reported the results of the penicillin treatment of patients with subacute bacterial endocarditis have emphasized both the importance of heart failure or acute cardiac accidents as a factor in a fatal outcome during treatment, and the development of increased cardiac disability following successful arrest of the infection. It is not apparent in most of the reports to what extent decreased cardiac reserve was present in patients before the infection developed or treatment was begun. Fiese,<sup>11</sup> however, made a careful study of the factors responsible for cardiac failure developing after treatment and concluded that this condition is the result of a number of factors, no one of which is exclusively responsible. The most important are the previous reserve and size of the heart, the patient's age, the type of lesion of the heart, the height of the temperature, the general clinical appearance, and the length of time before adequate treatment. Jones et al.<sup>12</sup> have reported a detailed follow-up study. These authors found that although the patients who recovered claimed no subjective increase in disability they often presented objective evidence of increased cardiac damage as evidenced by progressive cardiac enlargement. When the data are given in the case reports of these and other authors it is evident that heart failure developed a few weeks after the conclusion of treatment.

The purpose of the present study was to assess the late results of subacute bacterial endocarditis on the cardiac status of patients. Hence we selected

a group of patients who were treated a minimum of two years before the follow-up studies.

### MATERIAL

The material for this report consists of 15 patients with subacute bacterial endocarditis caused by alpha-hemolytic streptococcus who were treated at the Boston City Hospital during 1944 and 1945, and comprises the total number of such cases seen at the institution during this period satisfying the following criteria. Cases were accepted that had at least two positive blood cultures for *Streptococcus viridans* and had clinical evidence of valvular heart disease. All but one of the patients gave evidence of peripheral emboli. Four of the 15 patients have died, and the diagnosis of subacute bacterial endocarditis was confirmed in each case by post-mortem examination. All the living patients were re-examined two years or later after their original infection by one of us (B R.) in June, 1947. Complete blood counts, urinalyses and blood cultures were done, and teleroentgenograms of the heart and electrocardiograms were taken. The relevant findings are shown in Tables 1 and 2.

### Age and Sex

There were 5 male and 10 female patients. The ages ranged from nineteen to sixty years. Of the 4 patients who died, 2 were men aged forty-nine and fifty-three, and 2 were women aged twenty and twenty-one.

### Etiology of Heart Disease

In all cases the clinical diagnosis was chronic rheumatic heart disease. This was confirmed at autopsy in the 4 fatal cases. In 8 of the 15 patients no preceding history of rheumatic fever could be obtained, in the remainder there were definite histories of rheumatic fever.

### Valvular Involvement

In the 11 living patients evidence of involvement was limited to the mitral valve in 7 cases, and in the other 4 there was evidence of disease of both mitral and aortic valves at the time of treatment for subacute bacterial endocarditis. When follow-up examinations were done, signs of valvular deformities had remained unchanged in all cases. In the fatal cases clinical examination indicated mitral and aortic involvement in 2, and mitral involvement alone in 2. At post-mortem examinations the clinical diagnosis was confirmed in 3, and

\*From the Thorndike Memorial Laboratory, the Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School.

<sup>†</sup>Formerly resident fellow in medicine, Harvard Medical School, formerly assistant in medicine, Boston City Hospital, formerly resident fellow, Thorndike Memorial Laboratory, Boston City Hospital.

<sup>‡</sup>Assistant clinical professor of medicine, Harvard Medical School, assistant visiting physician, Boston City Hospital, associate physician, Thorndike Memorial Laboratory, Boston City Hospital.

in a case suspected clinically of mitral valvular disease alone there was evidence of healed aortic valvulitis of rheumatic etiology as well. The bacterial vegetations involved only the mitral valve in this case.

### Heart Size

The heart size was obtained from 6-foot tele-roentgenograms. Slight changes in serial measurements, which could have been due to altered position of the heart in the chest, were disregarded. The degree of cardiac enlargement was classified

during the infection showed some straightening of the left border of the heart, which was unchanged two years later.

### Rhythm

All the patients in this series had sinus rhythm when admitted for treatment. One (Case 11) developed auricular fibrillation during the active infection and reverted to sinus rhythm on quinidine therapy. Another (Case 3) has developed persistent auricular fibrillation since being cured of his

TABLE 1 Cardiac Status during Infection and at Follow-up Examination

Case No	Sex	Age	Valves Involved	Status of Cardiac Function		
				Before Infection	During Infection	At Follow-up Examination
1	F	37 45	Mitral Aortic	II	II	II*
2	F	22	Mitral Aortic	II	II	II
3	M	43	Mitral	II*	II*	II*
4	F	22	Mitral	II	II	II
5	F	28	Mitral Aortic	II	II	II
6	F	42	Mitral	I	I	I
7	M	28	Mitral Aortic	II	II	II
8	M	60	Mitral	I	I	I
9	F	19	Mitral	I	II	I
10	F	31	Mitral	I	IV	I
11	F	42	Mitral	II	III	II
12	M	53	Mitral Aortic	I	I	Patient died on 15th day of treatment
13	F	21	Mitral Aortic	I	II	Patient died on 6th day of treatment
14	M	49	Mitral Aortic	II	III	Patient died 3 months after treatment
15	F	20	Mitral	I	IV	Patient died 8 months after treatment

\*Patient given digitalis

as "none," "moderate" or "marked." There was evidence of marked cardiac enlargement in 3 of the fatal cases when the patients were admitted for treatment of bacterial endocarditis. In the other fatal case no enlargement was noted. In 4 of the 11 living patients there was marked enlargement at the time of treatment, and on follow-up examination the same degree of enlargement was found. Six showed moderate enlargement during their infection, and in 4 of these on the follow-up examination the hearts were normal in size clinically and by x-ray examination, and 2 remained unchanged. One patient showed no definite cardiac enlargement at any time, but x-ray examination

endocarditis, and his rate has been well controlled on digitalis therapy.

### Electrocardiographic Findings

The results of comparison of electrocardiograms recorded at the start of treatment for bacterial endocarditis and those taken on follow-up study are presented in Table 1. Records were available for comparison on all patients who survived except 1 (Case 5). In 8 cases there was no significant change. One patient developed auricular fibrillation, and in one the T waves in Leads 1 and 2 became inverted.

*Cardiac Reserve*

In Table 1 the functional capacity in each case is shown before, during and two to three years after the infection, rated in accordance with the classification of the American Heart Association<sup>13</sup> In 3 living patients (Cases 9, 10 and 11) there was clinical evidence of decrease in cardiac reserve occurring during the febrile illness, and in 1 of these the transient auricular fibrillation occurred In another patient (Case 10), in whom signs of cardiac decompensation were most marked and required

physical signs of congestive heart failure She was improved by digitalis and has continued on it, leading a fairly active life and working twenty hours a week as a saleswoman in a department store

All 11 patients, when examined in June, 1947, reported themselves to be at least as well as they had been before their illness They were all as active as they had been in the years immediately prior to their subacute bacterial endocarditis, and in some cases stated that they could do more than they had been able to do before their illness In

TABLE 1 (Continued)

Case No	RHYTHM		CARDIAC ENLARGEMENT		ELECTROCARDIOGRAPHIC CHANGES
	DURING INFECTION	AT FOLLOW-UP EXAMINATION	DURING INFECTION	AT FOLLOW-UP EXAMINATION	
1	Normal sinus rhythm	Normal sinus rhythm	Moderate	Moderate	No change
2	Normal sinus rhythm	Normal sinus rhythm	Marked	Marked	No change
3	Normal sinus rhythm	Auricular fibrillation	Marked	Marked	None except auricular fibrillation
4	Normal sinus rhythm	Normal sinus rhythm	Moderate	None	No change
5	Normal sinus rhythm	Normal sinus rhythm	Moderate	Moderate	No record during infection
6	Normal sinus rhythm	Normal sinus rhythm	None	None	No change
7	Normal sinus rhythm	Normal sinus rhythm	Marked	Marked	Inversion of T waves
8	Normal sinus rhythm	Normal sinus rhythm	Moderate	None	No change
9	Normal sinus rhythm	Normal sinus rhythm	Moderate	None	No change
10	Normal sinus rhythm	Normal sinus rhythm	Moderate	None	No change
11	Normal sinus rhythm with transient auricular fibrillation	Normal sinus rhythm	Marked	Marked	No change
12	Normal sinus rhythm	—	None	—	—
13	Normal sinus rhythm	—	Marked	—	—
14	Normal sinus rhythm	—	Marked	—	—
15	Normal sinus rhythm	—	Marked	—	—

vigorous therapy with oxygen and digitalis, the heart failure was precipitated by the combination of the infection and the pregnant state, since her infection and her heart failure became manifest in the early puerperium All 3 of these patients improved after treatment to a point where their cardiac reserve was as good as that before the infection developed

One patient who did not develop any signs or symptoms of heart failure during treatment for endocarditis was started on digitalis therapy about ten months later because of the complaint of dyspnea although the degree of shortness of breath had not increased At this time there were no

none of these patients were there any clinical or urinary findings suggesting chronic renal disease

It will be noted that there was a diminution in cardiac reserve in 3 of the fatal cases associated with the infection and that in the fourth case no change was noted In 3 of these cases there was evidence of persistent active bacterial infection at autopsy, and thus they represent failures in the treatment of the infection One patient (Case 15) who developed the most marked cardiac failure during her infection, was cured of the infection and died of a coronary embolus eight months after the eradication of the infection During this period she remained in severe heart failure, requiring digi-

tal and frequent mercurial diuretics. The case history of this patient is as follows:

A 20-year-old woman was first admitted to the hospital on June 16, 1945, with a history of chills, fever and headache of 11 days' duration and a history of a known heart murmur for 4 years. There was no history of rheumatic fever or cardiac disability. She was found on this admission to have a meningococcal (Group I) infection of the blood and spinal fluid. She was successfully treated with sulfadiazine and penicillin, with rapid improvement and was discharged as cured after 8 hospital days. Cardiac examination during this admission showed a heart that was enlarged, the border of cardiac dullness extending to the left anterior axillary line, and there was a loud, harsh apical systolic murmur. There was no evidence of cardiac decompensation.

She was readmitted to the hospital 5 months later, with a 2-month history of night sweats, anorexia and malaise and a 3-week history of cough and some dyspnea on exertion. On entry she was febrile, no petechiae were noted on the skin, and the lungs were clear. The heart was enlarged, with a

present, and there was a moderately loud apical presystolic murmur. A moderately loud systolic murmur was heard in the aortic area. The liver edge was palpable six fingerbreadths below the costal margin. There was minimal clubbing of the fingers, no pitting edema was noted. The patient failed to respond to therapy and died a few hours after admission.

At autopsy on the following day the heart appeared grossly enlarged, weighing 450 gm., and the left auricle was moderately dilated. The epicardium was not remarkable, and the endocardium was not remarkable except for the left auricle and the mitral valve. On the wall of the auricle there were many somewhat orange-tinged plaques of elevation, which were glairy in appearance and seemed to be part and parcel of the auricular wall. On the margin of the aortic cusp of the mitral valve, which was somewhat thickened, there were many yellowish irregular glistening masses, and three or four of the chordae tendineae enmeshed in these masses seemed to have been ruptured and healed on the surface. Lodged in the orifice of the right coronary artery there was a mass of material resembling the vegetations on the mitral valve. This completely occluded the orifice, and distally the artery was filled with a recent thrombus. The

TABLE 2 *Penicillin Treatment of 15 Patients with Subacute Bacterial Endocarditis*

CASE NO.	TIME FROM FIRST SYMPTOM TO END OF PENICILLIN TREATMENT	TOTAL DOSE OF PENICILLIN	DURATION OF TREATMENT	METHOD OF ADMINISTRATION	OUTCOME
		<i>units</i>	<i>days</i>		
1	8 wk.	4 200 000	16	Intermittent intramuscular	Patient living
2	4 wk.	5 670 000	20	Intermittent intramuscular (heparin given intravenously for 12 days)	Patient living
3	10 wk.	5 895 000	19	Intermittent intramuscular and continuous intravenous	Patient living
4	9 wk.	3 555 000	13	Intermittent intramuscular	Patient living
5	4 mo.	5 725 000	21	Intermittent intramuscular	Patient living
6	4 wk.	5 460 000	22	Continuous intramuscular	Patient living
7	24 mo. (3 recurrences)	3 700 000 6 265 000 10 980 000 33 000 000	14 22 38 50	Intermittent intramuscular Intermittent intramuscular and continuous intravenous Intermittent intramuscular and continuous intravenous Continuous intravenous	Patient living Patient living Patient living Patient living
8	14 mo. (2 recurrences)	4 225 000 5 100 000 9 600 000	12 15 33	Intermittent intramuscular Intermittent intramuscular Intermittent intramuscular	Patient living Patient living Patient living
9	8 wk.	5 600 000	21	Continuous intramuscular	Patient living
10	12 wk.	3 010 000	14	Intermittent intramuscular	Patient living
11	4 mo.	6 120 000	25	Continuous intramuscular and intravenous intramuscular	Patient living
12	9 wk.	4 525 000	15	Intermittent intramuscular	Patient dead
13	4 wk.	1 865 000	6	Intermittent intramuscular	Patient dead
14	8 mo.	4 200 000	16	Intermittent intramuscular (heparin intravenously for 5 days)	Patient dead
15	12 wk.	6 080 000	25	Intermittent intramuscular	Patient dead

rapid regular rhythm, the sounds were of good quality, and there was a loud apical systolic murmur with a palpable thrill. The spleen was palpable. There was minimal pitting edema of both ankles, and questionable clubbing of the fingers. Roentgenographic examination of the chest showed cardiac enlargement and congestive changes in both lung fields. Three positive blood cultures for *S. viridans* were obtained, and 2 days after admission petechiae were noted in the left conjunctiva and a diastolic murmur was heard at the apex. Treatment with penicillin (30,000 units intramuscularly every 3 hours) was begun on December 3, and continued until December 28. No positive blood cultures were obtained after December 3, and the temperature remained normal after discontinuation of therapy. However, tachycardia persisted and because of persistent signs of cardiac decompensation, digitalis and diuretic therapy was begun. The patient remained in the hospital until February 13, 1946, when she was discharged home still showing signs of cardiac failure. She remained home under the care of a private physician in chronic heart failure until 6 months after discharge, when she was readmitted to the hospital complaining of chilly sensations and an acute severe knifelike substernal pain radiating through to the back and aggravated by respiration.

Physical examination revealed her to be cyanotic, and the extremities were mottled, blue and cold, no pulses could be obtained in the feet, and the radial pulses were rapid and thready. The lungs were clear, the heart was enlarged, the border of cardiac dullness extending to the anterior axillary line in the fifth left interspace, the rate was 100, and the rhythm was irregular, a loud apical systolic murmur was

remainder of the valves and the left coronary artery were not remarkable. There was an area in the center of the base of the interventricular septum that appeared to be slightly yellowish red and mottled. Microscopically, the endocardium of the left auricle showed regions of subendocardial fibrous thickening. The myocardium disclosed focal fibrosis, most marked in perivascular locations. A section from the center of the interventricular septum demonstrated more marked fibrosis than in the ventricular wall, and a section from near the septum at the junction of the left auricle and left ventricle showed areas of polymorphonuclear-leukocyte infiltration between the muscle fibers. Culture from the mitral valve was negative for streptococcus with alpha hemolysis. The final pathological diagnoses were rheumatic heart disease, old, with mitral insufficiency, cardiomegaly, myocardial fibrosis, healed bacterial endocarditis, with rupture of chordae tendineae of the mitral valve, vegetations on mitral valve, embolus in orifice of right coronary, with myocardial infarction, healed infarcts in spleen and kidney, focal embolic glomerulonephritis, healed, chronic passive congestion of liver, spleen, kidneys and gastrointestinal tract, ascites, and bilateral hydrothorax.

#### Cardiac Status

In 5 cases data were available to permit some comparison of the cardiac status before the development of the bacterial endocarditis with later findings. One patient (Case 15) had developed

progressive cardiac failure after cure of the infection and died of a coronary embolus eight months later. In this case the marked enlargement of the heart and harsh apical systolic murmur, which was present when treatment was started, had also been noted five months earlier. In the 4 other cases (Cases 3, 4, 7 and 9) the cardiac findings noted at the time of admission with the bacterial infection had been present in the same degree on previous examinations made two, six, ten, and five years earlier respectively.

### Treatment

Table 2 contains a summary of the treatment with penicillin in all cases. Several of these cases have previously been reported.<sup>14</sup> These patients were treated when penicillin supplies were scarce, and the dosages were somewhat lower than those used in the treatment of this disease at present. In most cases the daily dose was between 200,000 and 300,000 units of penicillin.

### Discussion

Subacute bacterial endocarditis can increase cardiac damage in spite of cure of the infection either by causing rupture of a valve cusp or of chordae tendineae, or by the later scarring and distortion of the valves resulting from the healing and absorption of vegetations producing increased mechanical inefficiency of the heart. The effects may be severe, with rapidly developing heart failure, especially when there is great destruction of a valve.<sup>1, 2, 12</sup> Such failure develops during or soon after the active infection. Several observers have commented on the development of failure of this type particularly when the aortic valve is involved.<sup>6, 14</sup> The late development of a diminished cardiac reserve is in many cases related to the scarring process.

Heart damage accompanying subacute bacterial endocarditis may also be produced by acute myocardial lesions. It has been observed that the hearts of patients dying of subacute bacterial endocarditis very commonly show histologic evidence of myocarditis, especially small infarcts<sup>15</sup> due to minute coronary emboli.<sup>16</sup> Such lesions may well be an important factor in heart failure developing during or shortly after the active infection, and the myocardial fibrosis that may follow could be a contributory element in a later decrease in cardiac reserve.

In our series there was no correlation between the development of cardiac failure and the age of the patient or the length of time the infection had persisted prior to the successful treatment. This is shown most obviously in the 2 patients with relapses, who had recurrent and probably persistent active endocarditis for more than twenty-four and fourteen months. One of the patients (Case 8) was sixty years old, and his heart was actually smaller two years after his cure. The other (Case 7)

had cardiac enlargement with free aortic regurgitation when he first came under observation, which had not demonstrably changed nearly three years later.

### SUMMARY

Fifteen cases of subacute bacterial endocarditis caused by streptococcus with alpha hemolysis, which were treated in 1944 and 1945 and re-examined in June, 1947, at least 2 years after the original infection, are reported.

Eleven patients were living and well. Subjectively they all felt as well as they had prior to their infection. In 4 patients the cardiac size decreased after cure of the infection, in the other 7 there was no change. One had developed auricular fibrillation, and another has been taking digitalis for dyspnea although it is not clear that her condition has changed materially. In another patient the electrocardiogram showed evidence suggesting an increase in myocardial damage. These changes could as well have been due to the inevitable course of rheumatic heart disease in general as to any specific effect of the bacterial endocarditis.

Four patients in the group had died and were autopsied. In 3 there was post-mortem evidence of persistent active infection. One patient died in spite of eradication of the infection. Death in this case was due to a coronary embolus, but the patient had been in chronic congestive failure since cure of the infection.

### REFERENCES

1. Rosenblatt P. and Loewe L. Healed subacute bacterial endocarditis. *Arch. Int. Med.* 76: 1-10 1945.
2. Bloomfield A. L. and Halpern R. M. Penicillin treatment of subacute bacterial endocarditis: some problems. *J. A. M. A.* 129: 1135-1141 1945.
3. White, P. D., Matthews M. W. and Evans E. Notes on treatment of subacute bacterial endocarditis encountered in 88 cases at Massachusetts General Hospital during six-year period 1939 to 1944 (inclusive). *Ann. Int. Med.* 22: 61-74 1945.
4. Dawson M. H. and Hunter T. H. Treatment of subacute bacterial endocarditis with penicillin: results in 20 cases. *J. A. M. A.* 127: 129-137 1945.
5. Flippin H. F., Maycock R. L., Murphy F. D. and Wolferth C. C. Penicillin in treatment of subacute bacterial endocarditis: preliminary report on twenty cases treated over one year ago. *J. A. M. A.* 129: 841-845 1945.
6. Mokotoff R., Brame W., Katz, L. N. and Howell, E. M. Treatment of bacterial endocarditis with penicillin: results of 17 unselected cases. *Am. J. M. Sc.* 211: 395-416 1946.
7. Glaser R., J. Smith R. O., Harford C. G. and Wood W. B., Jr. Treatment of bacterial endocarditis with penicillin. *J. Lab. & Clin. Med.* 31: 291-312 1946.
8. Favours C. B., Janeway C. A., Gibson J. G. II and Levine S. A. Progress in treatment of subacute bacterial endocarditis. *Am. Eng. J. Med.* 234: 71-77 1946.
9. Dawson M. H. and Hunter T. H. Treatment of subacute bacterial endocarditis with penicillin: second report. *Ann. Int. Med.* 24: 170-185 1946.
10. Honigsmann A. H. and Karns J. R. Healed subacute bacterial endocarditis: report of two cases with death due to congestive heart failure. *Ann. Int. Med.* 26: 704-712 1947.
11. Fiese M. J. Cardiac failure in penicillin treated subacute bacterial endocarditis. *Arch. Int. Med.* 79: 436-448 1947.
12. Jones A. M., Herrington R., Langley F. A. and Oleesky S. Penicillin treatment of subacute bacterial endocarditis. *Brit. Heart J.* 9: 38-64 1947.
13. DeGraff A. C. et al. *Nomenclature and Criteria for Diagnosis of Diseases of the Heart*. Fourth edition 282 pp. New York: New York Heart Association 1939.
14. Meads M., Harris H. W. and Finland M. Treatment of bacterial endocarditis with penicillin: experiences at Boston City Hospital during 1944. *Am. Eng. J. Med.* 232: 463-474 1945.
15. Saphir O. Myocardial lesions in subacute bacterial endocarditis. *Am. J. Path.* 11: 143-156 1935.
16. deNavasquez, S. Incidence and pathogenesis of myocardial lesions in subacute bacterial endocarditis. *J. Path. & Bact.* 49: 33-35 1952.

## GENERALIZED BULLOUS ERUPTION FOLLOWING TESTING FOR SULFONAMIDE HYPERSENSITIVITY\*

DAVID A. STRAUS, M.D.†

CHAMBLEE, GEORGIA

**E**RYTHEMA multiforme exudativum is a well recognized clinical entity, but despite extensive investigation its etiology is obscure.<sup>1-4</sup> Eruptions due to drug idiosyncrasy, which are compatible with the clinical picture of erythema multiforme exudativum, are not uncommon and have frequently been described.<sup>5-12</sup> The sulfonamides are among the drugs that have been incriminated<sup>5-9</sup>

observed phenomena reproduced the picture of erythema multiforme exudativum, it is thought desirable to call attention to the reaction.

### CASE REPORT

J. W., a 31-year-old Negro sawmill laborer, had a history of having received in 1943 a course of antisyphilitic therapy consisting of 19 intravenous injections of an arsenical and 20 intramuscular injections of a bismuth com-

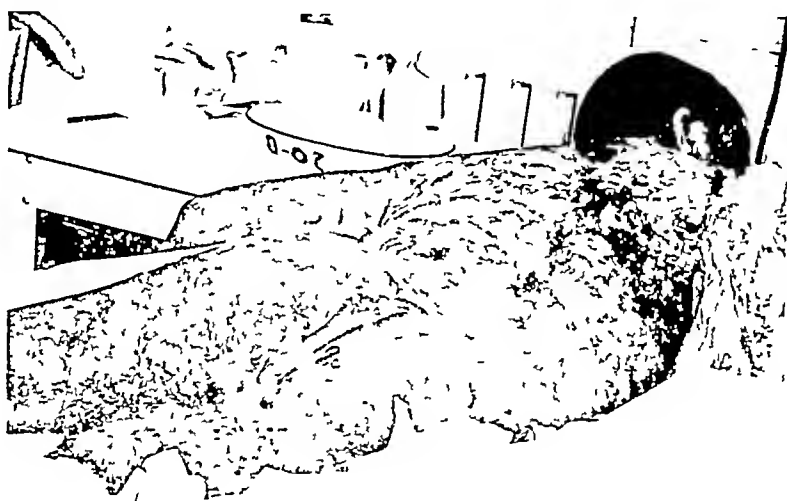


FIGURE 1 Site of the Bullous Eruption Where Most of the Bullae Had Ruptured, Leaving a Raw Granulating Surface

There is no real agreement, however, regarding whether such an eruption, although morphologically and clinically indistinguishable from the idiopathic erythema multiforme exudativum, should be classified as truly part of the syndrome.<sup>2-4</sup> Regardless of how this drug reaction is classified, the importance of establishing or excluding the sulfonamides as etiologic agents when the possibility of their future therapeutic use is considered can easily be appreciated.

Recently, a patient whose clinical course fulfilled the criteria of erythema multiforme exudativum was observed. In an attempt to establish the etiology of the syndrome the passive transfer test, as described by Leftwich,<sup>13</sup> was used. Because an atypical and severe reaction ensued after what is usually regarded as a benign test and because the

pound. In 1945 there was a history of his being seen in a public-health center, where diagnoses of "early latent syphilis" and "erythema multiforme" were made and he was given 1,200,000 units of penicillin, 300 mg of arsenoxide and 60 mg of bismuth subsalicylate during a 10-day period. Nothing further could be learned about his condition at that time. On December 2, 1947, he was admitted to a state venereal-disease-treatment center with a penile ulcer of 1 year's duration and a pruritic rash between his toes. Negative serologic tests for syphilis were obtained from the blood and spinal fluid, and diagnoses of "chancroid" and "scabies" were made. He was given sulfathiazole orally and treated with an "antiscabetic routine"—the medication used in the latter was not ascertained. Two days later, after having received 2 gm of sulfathiazole, he had an epileptiform convulsion, and the temperature rose to 103.8°F. (It was learned subsequently that he had had similar convulsive seizures about twice yearly since a head injury incurred at the age of 14.) The temperature remained elevated, and on the next day, ulcerated lesions appeared on the mucous membranes of the mouth. The sulfathiazole was discontinued. On the following day, flaccid bullae appeared on the extremities, and on the next day, on the eyelids, buttocks, penis and scrotum. He was given 300,000 units of penicillin in oil and beeswax daily, as well as intravenous fluids. He was transferred to Lawson Veterans Administration Hospital on December 28, 1947, with the diagnosis of "pemphigus."

Physical examination showed an acutely and severely ill patient. Swallowing was painful, and was possible only with liquids. The mucous membranes of the mouth and lips were

\*From the Medical Service, Lawson Veterans Administration Hospital, Chamblee, Georgia, and the Department of Medicine, Emory University School of Medicine, Atlanta, Georgia.

Published with permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the author.

†Resident in medicine, Lawson Veterans Administration Hospital.

raw and bleeding, and there were numerous, small bullae on the tongue. There were marked scleral injection and chemosis and a moderate amount of milk conjunctival suppuration. A few coarse inspiratory and expiratory rhonchi were heard scattered throughout the lung fields which were otherwise normal. The skin of the entire body exhibited numerous bullae. These were varied in size, but most were of the size and shape of Brazil nuts. They were located superficially in the skin and most of them had been ruptured and part of the clear serous fluid evacuated, leaving a thin, loose membrane over their surface and giving the bullae a flaccid appearance. The surface skin of many of the bullae was absent, leaving a red, granulating, moist area (Fig 1). There was no inflammatory reaction surrounding the bullae. The face was clear except for a bullous eruption on the upper eyelids and ears and the lip lesions described above. The entire surface of the palms and soles was covered by a large bullous formation (Fig 2). The patient exhibited a balanitis, and there were small, denuded areas on the penis and scrotum (Fig 3). There was a moderate, generalized lymphadenopathy. The spleen was not palpable.

The temperature was 101.2°F, the pulse 96, the blood pressure 100/50, and the respirations rapid, shallow and grunting.

Examination of the blood disclosed a hemoglobin of 15 gm (Alett method) and a white-cell count of 7450, with 58 per cent neutrophils, 36 per cent lymphocytes, 1 per cent monocytes and 5 per cent eosinophils. Serologic tests for syphilis yielded three "doubtful" Kahn reactions and a negative Wassermann reaction. Urinalysis showed a +++ test for albumin and innumerable erythrocytes in the sediment. The erythrocyte

later, the passive transfer test, after the method described by Leftwich,<sup>12</sup> was performed by the intradermal injection of 0.05 cc. of serum from another patient, who had a sulfadiazine blood level of 7.0 mg per 100 cc. and whose serologic test was negative. There was no reaction, either local or systemic, and the next day the patient was discharged from the hospital. On the day of discharge his face and scalp began to itch, and 3 days later bullae began to appear on his thighs and forearms and then on his eyelids and in his mouth and finally on the rest of his body. He stated that he had taken no medication of any kind.



FIGURE 3 Balanitis and Denuded Areas on the Penis and Scrotum



FIGURE 2 Large Bullous Formation on the Feet, Which Was Even More Extensive over the Soles

sedimentation rate was 31 mm per hour (Wintrobe method). The blood nonprotein nitrogen was 34 mg, and the total serum protein 7.0 gm per 100 cc, with 3.8 gm of albumin and 3.2 gm of globulin. The icteric index was 6, and the thymol turbidity 8.4 units. A culture of the bullous fluid was sterile.

The patient was treated with intramuscular aqueous penicillin and boric acid soaks and ointment locally, saline mouth washes, 10 per cent zinc sulfate solution was instilled in the eyes three times daily. He made a gradual and uneventful recovery, the skin lesions healing without scarring in about 5 weeks and the urine returning to normal.

After he had recovered clinically, he was tested for sulfonamide sensitivity. First, a patch test, consisting of a pulverized sulfathiazole tablet made into a paste by mixture with a small amount of distilled water, was administered to the unbroken skin. The results were negative, and 2 days

since discharge and knew of no contact that could have caused the eruption. On readmission, 1 week after his discharge, his appearance, physical findings and laboratory data were almost identical to those of the previous admission. The same course of treatment was pursued, and again, in approximately 3 weeks, the lesions had healed. Since the relation between the passive transfer intradermal test for sulfadiazine and the eruption, which started 2 days later, was not recognized, he was given a test dose of 0.5 gm of sulfadiazine orally. Within 2 hours he began to have a generalized pruritus, and 3 hours later the temperature rose to 101°F, and he had a shaking chill. Subsequently, he became comfortable and slept for 3 hours, after which he awoke nauseated and vomited intermittently, for 2 hours and, while walking to the lavatory, became giddy and fell to the floor. At this time the respiration became fast and labored, at a rate of 30 per minutes, the pulse was 110 and weak, and the blood pressure was 100/60. He was given 100 mg of pyribenzamine orally four times daily. About 12 hours later he complained of a "skim" over his eyes, and conjunctival injection was noted. At this time, one of the darkly pigmented areas that marked the sites of the bullae of the previous eruption had formed a new bulla. A purulent urethral discharge was also noted, which yielded *Staphylococcus albus* on culture. The temperature rose to 104°F. By the next morning, his skin, mucous membranes and conjunctivas were involved as before, and identical treatment was instituted. Because of the large amount of serum that continued to ooze from the denuded areas, the patient was given transfusions of 500 and 1000 cc. of whole blood on the 3rd and 4th days of the eruption respectively and a pressure dressing over petrolatum-impregnated gauze was applied to the extremities, furacin ointment was applied to the trunk and buttocks because of the development of suppuration. Two weeks after the administration of the oral sulfadiazine, the temperature gradually subsided to normal. The mucous membranes had healed, and conjunctivitis disappeared in 3 more days, the remaining skin lesions had again healed without scarring.

## GENERALIZED BULLOUS ERUPTION FOLLOWING TESTING FOR SULFONAMIDE HYPERSENSITIVITY\*

DAVID A. STRAUS, M.D.†

CHAMBLEE, GEORGIA

**E**RYTHEMA multiforme exudativum is a well recognized clinical entity, but despite extensive investigation its etiology is obscure.<sup>1-4</sup> Eruptions due to drug idiosyncrasy, which are compatible with the clinical picture of erythema multiforme exudativum, are not uncommon and have frequently been described.<sup>5-12</sup> The sulfonamides are among the drugs that have been incriminated.<sup>5-9</sup>

observed phenomena reproduced the picture of erythema multiforme exudativum, it is thought desirable to call attention to the reaction.

### CASE REPORT

J. W., a 31-year-old Negro sawmill laborer, had a history of having received in 1943 a course of antisyphilitic therapy consisting of 19 intravenous injections of an arsenical and 20 intramuscular injections of a bismuth com-



FIGURE 1 Site of the Bullous Eruption Where Most of the Bullae Had Ruptured, Leaving a Raw Granulating Surface

There is no real agreement, however, regarding whether such an eruption, although morphologically and clinically indistinguishable from the idiopathic erythema multiforme exudativum, should be classified as truly part of the syndrome.<sup>2-4</sup> Regardless of how this drug reaction is classified, the importance of establishing or excluding the sulfonamides as etiologic agents when the possibility of their future therapeutic use is considered can easily be appreciated.

Recently, a patient whose clinical course fulfilled the criteria of erythema multiforme exudativum was observed. In an attempt to establish the etiology of the syndrome the passive transfer test, as described by Leftwich,<sup>13</sup> was used. Because an atypical and severe reaction ensued after what is usually regarded as a benign test and because the

pound. In 1945 there was a history of his being seen in a public-health center, where diagnoses of "early latent syphilis" and "erythema multiforme" were made and he was given 1,200,000 units of penicillin, 300 mg of arsenoxide and 60 mg of bismuth subsalicylate during a 10-day period. Nothing further could be learned about his condition at that time. On December 2, 1947, he was admitted to a state venereal-disease-treatment center with a penile ulcer of 1 year's duration and a pruritic rash between his toes. Negative serologic tests for syphilis were obtained from the blood and spinal fluid, and diagnoses of "chancroid" and "scabies" were made. He was given sulfathiazole orally and treated with an "antiscabetic routine"—the medication used in the latter was not ascertained. Two days later, after having received 2 gm of sulfathiazole, he had an epileptiform convulsion, and the temperature rose to 103.8°F. (It was learned subsequently that he had had similar convulsive seizures about twice yearly since a head injury incurred at the age of 14.) The temperature remained elevated, and on the next day, ulcerated lesions appeared on the mucous membranes of the mouth. The sulfathiazole was discontinued. On the following day, flaccid bullae appeared on the extremities, and on the next day, on the eyelids, buttocks, penis and scrotum. He was given 300,000 units of penicillin in oil and beeswax daily, as well as intravenous fluids. He was transferred to Lawson Veterans Administration Hospital on December 28, 1947, with the diagnosis of "pemphigus".

Physical examination showed an acutely and severely ill patient. Swallowing was painful, and was possible only with liquids. The mucous membranes of the mouth and lips were

\*From the Medical Service, Lawson Veterans Administration Hospital, Chamblee, Georgia, and the Department of Medicine, Emory University School of Medicine, Atlanta, Georgia.

Published with permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the author.

†Resident in medicine, Lawson Veterans Administration Hospital.

## FERTILITY STUDIES IN THE HUMAN MALE WITH TRAUMATIC INJURIES OF THE SPINAL CORD AND CAUDA EQUINA\*

HERBERT W. HORNE, M.D.,† CAPTAIN DAVID P. PAULL, MC, AUS,‡ AND DONALD MUNRO, M.D.§  
BOSTON AND FRAMINGHAM, MASSACHUSETTS

**H**UMAN males who have suffered traumatic injuries of the spinal cord and cauda equina have long been considered sterile. This study was performed to determine whether or not this assumption is true. A previous paper<sup>1</sup> discussed the incidence of erection and ejaculation in the human male with traumatic injuries of the spinal cord and cauda equina.

The 18 cases studied in the present series were patients at Cushing Veterans Administration Hospital who had suffered traumatic injuries of the spinal cord and cauda equina. Their ages ranged from twenty-one to thirty-five years, with an average age of twenty-seven years. The length of time that had elapsed since the original spinal-cord or cauda-equina injury ranged from nine to seventy-two months, with an average of forty-seven months. No effort was made to select the cases to be studied, and the only requirements on the part of the patient were that he show consistent interest in the project, that he be voiding without a catheter and that he be in good general physical condition. Many other patients were anxious to be included in the investigation, but time did not permit a larger series.

For the purpose of this paper, the patients are classified as to the level of injury and as to the type of injury. The levels of injury of the spinal cord are reported as dermatome segments. Injuries of the cauda equina are classified separately.

The types of injury are classified in the same manner as that used in the first paper of this series.<sup>1</sup>

Patients diagnosed as suffering from a transection have been divided into two groups, depending upon the accuracy of verification of the diagnosis. In those diagnosed as Anatomic-Visualized Transection (Tr-A) the injury has been actually seen at laminectomy to be one in which there is a complete separation of the cut ends of the cord. In those diagnosed Clinical-Not Visualized Transection (Tr-C) either the cord injury has not been seen or, if seen, the continuity of the cord was found to be either grossly intact or maintained by intervening scar tissue. The character and length of the clinical course taken by the patient, however, have justified the diagnosis of transection. In both instances, only patients with a complete sensory and voluntary motor loss of function below the level of the cord injury are included as cord transections. Patients diagnosed as suffering from a Partial Cord Injury (P) are those in whom it has been

possible to demonstrate some degree of retention of either sensation or voluntary motion, or both, in the body and extremities below the level of maximal cord injury. The same diagnostic criteria have been applied to patients with cauda equina (CE) injuries.

Clinical investigation of these cases included, in addition to routine procedures, evaluation of the external and internal genital organs and the neurologic status. There were no gross changes in the external genitalia except for the cases in which an attack of epididymitis had occurred. In these cases there was invariably a persistent residual induration of the involved epididymis. One patient (Case 7) had a unilateral testicular atrophy secondary to mumps in childhood, and another (Case 1) had a unilateral cryptorchid testis. Virtually all the prostate glands were small, flat, nonnodular and soft.

Semen samples were obtained by electrical stimulation in all cases except 3 (Cases 1, 5 and 18), in which masturbation produced the specimen. A McIntosh No. 5005 portable-wall-plate physiotherapy machine was used to supply the stimulus. This machine delivers predetermined variable amounts of current across a 90-volt potential. The inactive electrode was soaked in tap water and placed under the patient's sacrum with the patient lying on his back. The active electrode was a No. 28 curved urethral sound. This sound was covered with rubber tubing except for the handle and the terminal 5 cm. Electrical stimulation was accomplished by applying sinusoidal and faradic current of 45 and 60 milliamperes, respectively, to the active electrode, which had been introduced into the rectum. The bare tip of the sound was applied successively to the region of each seminal vesicle and the prostate, this sequence being carried out first with sinusoidal, then faradic and, finally, sinusoidal current again. The duration of stimulation in each position was approximately 4 seconds. After withdrawal of the active electrode digital massage successively of the seminal vesicles and the prostate was performed. The semen was then milked from the urethra. No complications, local or otherwise, have followed over 100 treatments of this sort. Massage of the seminal vesicles and prostate without prior electrical stimulation produced fluid devoid of spermatozoa in all but 1 case, when a few spermatozoa were found on one occasion. Electrical stimulation followed by massage produced semen specimens as shown in Table 1. We are frank to state that how or why the electrical stimulation is effective is not clear. Suffice it to say that

\*From the Surgical and Paraplegia Services, Cushing Veterans Administration Hospital, Framingham, Massachusetts.

Presented at the annual meeting of the New England Surgical Society, New Haven, Connecticut, October 2, 1948.

Published with the permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or the conclusions drawn by the authors.

†Assistant resident, Free Hospital for Women, formerly resident in surgery, Cushing Veterans Administration Hospital.

‡Resident in surgery, Cushing Veterans Administration Hospital.

§Assistant professor of neurosurgery, Harvard Medical School, associate professor of neurosurgery, Boston University School of Medicine, chief, Department of Neurosurgery, Boston City Hospital.

## DISCUSSION

Although the patient was able to give no past history of exposure to sulfonamide, the onset of fever followed by the eruption and conjunctivitis, which occurred on the second day (rather than after seven or ten days) of sulfonamide therapy in December, 1947, suggested previous sensitization to the drug. In retrospect, it might be conjectured that the "erythema multiforme" reported from 1945 followed the use of the drug at that time.

There are numerous reports in the literature of cases in which very small doses of a sulfonamide caused severe, generalized skin reactions.<sup>7-14</sup> Cohen, Thomas and Kalisch<sup>14</sup> reported the appearance of a generalized pruritic rash six hours after the local application of 8 mg of sulfathiazole powder, the patient having developed a skin rash two weeks previously, after the use of sulfathiazole ointment locally. Farrington and Wolff<sup>15</sup> described the reproduction of a generalized, oozing, vesicular eruption by simultaneous patch testing with sulfanilamide and sulfathiazole a month after the original eruption, which had been caused by the local use of sulfanilamide. They also described "an intense necrotizing reaction of the buccal mucosa upon application of approximately 8 mg of sulfathiazole to the mouth of a previously sensitized patient" after the method described by Goldman and Goldman.<sup>16</sup> The patient discussed above, on the other hand, showed neither a local nor systemic reaction after application of a patch test of sulfathiazole, although the eruption that appeared in December, 1947, was apparently due to the oral administration of that drug.

Although Leftwich<sup>13</sup> performed 300 intradermal tests for sulfonamide sensitivity, he reported no generalized reactions, and of 30 sensitive patients, 28 had positive tests, the reactions appearing immediately and fading within thirty minutes to an hour and a half. In contrast to these results, the patient in the case reported above showed no immediate or local reaction, but responded to the test by a delayed (twenty-four to forty-eight hours) generalized, severe reaction.

The experience of Farrington and Wolff with the patch test, the reaction with the intradermal passive transfer test and the patch test and the oral test dose discussed above, as well as the reports of others describing severe reactions from small doses of the drug, administered both locally and systemically, have illustrated the potential danger and unreliability of testing for sulfonamide sensitivity. It should be emphasized also that despite reports in the literature describing the treatment of erythema multiforme by sulfonamides, this form of therapy should be used with caution unless one is absolutely certain that the syndrome was not caused itself

by use of the drug.<sup>17-20</sup> This, of course, is true because of the difficulty in clinical differentiation of the bullous eruption sometimes seen in sulfonamide toxicity from idiopathic erythema multiforme.

## SUMMARY

The bullous eruptions that may result from sulfonamide toxicity are often clinically indistinguishable from idiopathic erythema multiforme exudativum. To establish the role of the sulfonamides in an obscure case, several tests for sulfonamide hypersensitivity are available.

A case illustrating the unreliability of the patch test, an untoward and at first unrecognized reaction to the intradermal passive transfer test and a severe reaction following an oral test dose of sulfonamide is reported. It is believed, therefore, that testing for sulfonamide sensitivity should be approached with care, as should the treatment of erythema multiforme exudativum with sulfonamide, as recommended by some, unless it is certain that this drug is not the etiologic agent.

## REFERENCES

- 1 Hebra F. *Diseases of the Skin*. Vol. 1. Translated and edited by C. H. Fagge. London: New Sydenham Society, 1866.
- 2 Keil H. Erythema multiforme exudativum (Hebra), clinical entity associated with systemic features. *Ann Int Med* 14:449-494, 1940.
- 3 Bailey J. H. Lesions of cornea and conjunctiva in erythema exudativum multiforme (Hebra): report of three cases with grave ocular sequelae. *Arch Ophth* 6:362-379, 1931.
- 4 Fletcher M. W. C. and Harris R. C. Erythema exudativum multiforme (Hebra)—bullous type cases seen in contagious disease hospital. *J Pediatr* 27:465-479, 1945.
- 5 Dardinski V. J. Erythema multiforme bullosum following use of sulfadiazine. *Am J Clin Path* 15:28, 1945.
- 6 Greenberg S. I. and Messer A. L. Fatal bullous dermatitis following administration of sulfadiazine. *J A M A* 122:944, 1943.
- 7 Livingston C. S. and Pillsbury D. M. Sulfathiazole in eczematous pyoderma: sensitization reaction to successive local and oral therapy: report of 12 cases. *J A M A* 121:406-408, 1943.
- 8 Robitzek E. H. Fatal pemphigoid reaction to diarsone. *Am. Rev. Tuberc* 51:473-477, 1945.
- 9 Raffetto J. F. and Nichols S. Nearly fatal reaction to sulfadiazine in ten-year-old girl involving skin, eyes and nucharynx. *J Pediatr* 20:753-755, 1942.
- 10 Ellis F. A. Reactions to nitrannal, phenytoin sodium and phenobarbital: report of case of ectodermosis crassa pluririficalis following ingestion of phenytoin sodium. *Souk M J* 36:575-579, 1943.
- 11 Ritchie E. B. and Kalb W. Reaction to sodium diphenyl hydantoinate (dilantin sodium): hemorrhagic erythema multiforme terminating fatally. *Arch Dermat & Syph* 46:856-859, 1942.
- 12 Newman B. A. Phenolphthalein intoxication. *J A M A* 101:761-764, 1933.
- 13 Leftwich W. B. Intradermal test for recognition of hypersensitivity to sulfonamide drugs. *Bull Johns Hopkins Hosp* 74:26-48, 1944.
- 14 Cohen, M. H. Thomas H. B. and Kalisch, A. C. Hypersensitivity produced by topical application of sulfathiazole. *J A M A* 121:408-411, 1943.
- 15 Farrington J. and Wolff B. P. Exfoliative dermatitis caused by sulfonamides and its reproduction by patch testing. *North Carolina M J* 7:555, 1946.
- 16 Goldman L. and Goldman B. Contact testing of buccal mucous membrane for stomatitis venenata. *Arch Dermat & Syph* 50:79-84, 1944.
- 17 Kove S. Stevens-Johnson syndrome (eruptive fever with stomatitis and conjunctivitis). *Am J M Sc* 210:611-623, 1945.
- 18 Bregman, A. Treatment of erythema multiforme exudativum with sulfanilamide. *Arch Dermat & Syph* 38:623, 1938.
- 19 Fitzgerald P. J. Fatal bullous dermatitis with multiple lesions of mucous membranes: therapeutic failure of sulfadiazine and penicillin. *U S Ar M Bull* 47:134-141, 1947.
- 20 Wright, D. O. Gold E. M. and Jennings C. Stevens-Johnson syndrome: report of nine patients treated with sulfonamide drugs or penicillin. *Arch Int Med* 79:510-517, 1947.

total sperm counts. Patients with injuries to the cauda equina and lumbosacral cord have lower counts in this series, but it is believed that there are not a sufficient number of cases for definite conclusions to be drawn. It is interesting that the patient in Case 13, who had a clinical-not visualized transection at the first lumbar segment, had a normal right testicle by biopsy. This particular patient has had repeated attacks of epididymitis bilaterally, which may well explain the absence of spermatozoa in the semen specimen.

Basal metabolic rates fell, for the most part, within the lower limits of normal. Testicular biopsies in 7 cases varied from complete atrophy of spermatogenic cells to normal testicular activity. The correlation of the spermatozoa counts and the testicular biopsies is reasonably close except in Case 13. The reason for this one aberration is discussed above.

## CONCLUSIONS

Traumatic injury of the spinal cord does not in itself preclude fertility.

A technic is described for obtaining semen specimens from patients having spinal-cord injuries who are unable to ejaculate.

A patient with a clinical-not visualized transection at the fifth thoracic dermatome is capable of erection and ejaculation of normal semen and has successfully impregnated his wife.

We are indebted to Dr Fred A Simmons and Dr George P Denny for their assistance respectively in the sterility and medical aspects of this study.

## REFERENCES

1. Meuro D, Horne H W Jr and Paull D P. Effect of injury to spinal cord and cauda equina on sexual potency of men. *Neu Eng J Med* 239:905-911 1948.
2. Williams W W and Simmons F A. Clinical approach to diagnosis of sterility. *Urol & Gynaecol Rev* 47:558-570 1942.

## MEDICAL PROGRESS

### THORACIC SURGERY (Concluded)

J GORDON SCANNELL, M D \*

BOSTON

#### Results of Treatment

•It is difficult to assess the problem of cancer of the lung in relation to the population as a whole on the basis of reported hospital series. However, it is apparent that in the course of the past ten years, the operability and resectability rates of cancer, as seen by the surgeon, have increased. Björk<sup>70</sup> has reported at length the clinical experience with bronchogenic carcinoma at the Brompton and Royal Cancer hospitals. Of 996 cases in which the clinical diagnosis was made (combining the material of both medical and surgical services from 1937-1944), 15.3 per cent were adjudged suitable for thoracotomy, and 7.5 per cent (or 49 per cent of those explored) were resectable. However, annual operability and resectability rates increased from 8.2 per cent and 5.1 per cent of 134 total cases seen in 1937 to 25.6 per cent and 13.5 per cent, respectively, of 133 cases in 1944. Ochsner, DeBakey and Dixon<sup>71</sup> report that of 360 cases seen on a surgical service between 1936 and 1946, 251 (70 per cent) were considered operable, 210 (58 per cent) were actually explored, and 129 (36 per cent) were resectable. In reviewing the Johns Hopkins series of 327 cases of carcinoma of the lung "referred for surgical

treatment" and presumably explored, Rienhoff<sup>72</sup> reports that 34 per cent were resectable. Thus, of 1950 cases in nine surgical reports since 1940, 782 (40 per cent) were operable and 432 (22 per cent) were resected.<sup>62</sup> By and large, however, these reports represented total experience with the disease and therefore do not reflect changing trends over the years. The importance of defining the material studied in terms of microscopical rather than clinical diagnosis has long since been amply demonstrated (Churchill 1940). Furthermore, the tremendous number of variables, not always apparent in the random selection of clinical material, must be kept in mind.

During the period of increasing limits of operability and of technical standardization, statistics of operative mortality have required almost annual revision downward. The figures of a mere ten years ago are currently of historical interest chiefly. Of more significance as a basis for evaluating present-day surgical therapy are such figures as those of Jones<sup>73</sup>—52 consecutive pneumonectomies, 1942-1946 with 2 deaths (based on a resectability rate of approximately 20 per cent of cases seen)—and of Adams<sup>74</sup>—an operative mortality of 5.1 per cent in 39 resections for carcinoma, 1942-1947 (resectability rate of approximately 30 per cent of cases seen).

\*Instructor in surgery, Harvard Medical School; assistant in surgery, Massachusetts General Hospital.

with electrical stimulation, followed by massage, semen specimens containing spermatozoa have been consistently obtained in 11 of the 18 cases in which simple massage had failed. In each case the first few examinations were not productive of spermatozoa, whereas subsequent trials usually were successful.

Semen analysis was carried out by the technic of Williams and Simmons.<sup>2</sup> In all except Case 5,

in Case 1 has a partial cervical injury and is able to have erections, ejaculations and intercourse in an approximately normal manner. The patient in Case 5 is of particular interest because he has a clinically complete transection of the spinal cord at the sixth thoracic segment. This case was reported in detail in the previous paper.<sup>1</sup> On March 6, 1948, this patient was left alone in a room and asked to obtain a semen specimen. He shortly

TABLE 1 *Data in Patients with Injuries to the Spinal Cord and Cauda Equina*

CASE No	LEVEL OF INJURY	TYPE OF INJURY	BLOOD COUNT	BASAL METABOLIC RATE	TESTICULAR DISEASE AND EPIDIDYMITIS	TESTICULAR BIOPSY	TOTAL MOTILE SPERMATOZOA COUNT	ERECTIONS	EJACULATIONS	COITUS	PREGNANCY
1	C5	Partial cord injury	Normal	-10	Cryptorchid unilateral	—	30 000 000	Yes	Yes	Yes	Yes
2	T3	Clinical-not visualized transection	Normal	0	Epididymitis, unilateral	—	48 000 000	Yes	No	Not tried	—
3	T4	Clinical-not visualized transection	Normal	—	—	—	500 000	Yes	No	No	—
4	T6	Anatomic-visualized transection	Normal	-2	—	—	0	No	No	No	—
5	T6	Clinical-not visualized transection	Normal	-10	—	—	110 000 000	Yes	Yes	Yes	Yes
6	T6	Clinical-not visualized transection	Normal	-25	—	—	3 000 000	No	No	No	—
7	T6	Partial cord injury	Normal	+3	Post-mumps atrophy, unilateral	—	3 000 000	Yes	No	No	—
8	T8	Anatomic visualized transection	Normal	-13	—	Spermatogenic arrest	600 000	Yes	No	No	—
9	T11	Clinical-not visualized transection	Normal	-13	—	Practically no spermatogenic cells occasional active tubule	500 000 (non-motile)	No	No	No	—
10	T11	Partial cord injury	Normal	—	—	—	None	Yes	No	No	—
11	T12	Partial cord injury	Slight anemia	—	Unilateral epididymitis	—	None	Yes	No	Yes	—
12	T12	Partial cord injury	Slight anemia	-9	—	Normal	75 000 000 (non-motile)	No	No	No	—
13	L1	Clinical-not visualized transection	Normal	—	Recurrent, bilateral severe epididymitis	Left atrophy right, normal	None	No	No	No	—
14	L1	Clinical-not visualized transection	Normal	+2	—	Normal	30 000 000	Yes	No	Yes	—
15	L1	Partial cord injury	Slight anemia	-4	—	Maturation arrest of germinal epithelium	None	No	No	No	—
16	Cauda equina	Clinical-not visualized transection	Normal	+5	—	Tubular atrophy Leydig hyperplasia without germ cells.	Rare non-motile	No	No	No	—
17	Cauda equina	Partial injury	Normal	+13	Unilateral epididymitis	—	None	Yes	No	No	—
18	Cauda equina	Partial injury	Normal	—	Unilateral epididymitis	—	80 000 000	Yes	Yes	Yes	—

semen analyses were carried out on each patient a minimum of three times. The figures stated in Table 1 represent the highest values obtained in each case. Case 5 had one examination only. The chemical determinations, the blood counts and the determinations of basal metabolic rates were done in the hospital laboratory. Reports on seven testicular biopsies were made by the hospital pathologist, Dr. Robert Fienberg, and reviewed by Dr. Fred Simmons.

The wives of the patients in Case 1 and 5 have become pregnant since these patients have returned home from the hospital. The patient

presented a specimen, the analysis of which was as follows:

AMOUNT	TURBIDITY	SPERMATOZOA COUNT	MOTILITY	DIFFERENTIAL
cc		million/cc	26%	
4	++++	115	+ to +++++	Normal 75 Pyn 17 AA 5 Macro 0 Micro 3 Misc 0

## DISCUSSION

In this study there seems to be no striking correlation between the level or type of injury and the

imals, the cases resembled emphysema. The cases of lobectomy showed a similar but less marked deviation from the predicted levels. Maximum breathing capacity, breathing reserve and rate of oxygen utilization were not reported. Of possibly greater significance than the actual laboratory measurements were the estimates of working capacity and dyspnea after the two procedures. In the 12 cases in which pneumonectomies were performed, 9 patients had full working capacity, 2 were unable to work, and 1 was limited to half capacity. All 14 of the patients with lobectomies were reported to have full working capacity. Rienhoff<sup>72</sup> has reported that all his patients except 1 (a professional boxer) who lived any significant time after pneumonectomy for cancer were restored to normal activity. Quantitative measure of rehabilitation of the patient after pneumonectomy is obviously difficult, but some estimate is essential in the planning of the surgical program for the patient.

When one evaluates the efficacy of surgical treatment, it is only fair to contrast it to alternative forms of therapy or no therapy at all. From the point of view of survival, the evidence appears to be clear. Untreated, survival beyond one year of the onset of symptoms or establishment of the diagnosis is rare. Radiation therapy holds some promise of palliation over and above the rigors of treatment, and appears to prolong survival beyond predicted limits. Widmann<sup>55</sup> has contrasted 167 patients with microscopically proved cases that were treated against 119 not treated. Of the latter, none lived a year. Of the 167 patients treated, 18 lived over one year, 2 for two years, 1 for three years and 1 for 5 years, and 1 was free of clinical evidence of disease six years after treatment. However, on the other side of the ledger, 89 per cent of the patients treated lived less than a year. Leddy and Moersch,<sup>86</sup> in 1940, compared 125 radiation-treated cases to a control series of 125 untreated. Clinical characterization of the two groups was remarkably similar. A salient fact of their study was that no untreated patient survived more than one year, whereas after treatment 25 patients lived one or more years, and 5 for five years or more, with 1 fourteen-year and 2 ten-year survivals in the latter group. All cases were proved histologically. Beyond improving survival time, the procedure was considered worth while on the evidence for palliation of pain and cough. Shorvon<sup>87</sup> has recently reported 111 cases treated by "radical" x-ray therapy. No patients survived beyond three years. Hocker and Guttman,<sup>88</sup> at the Memorial Hospital, discussed as a preliminary report 93 patients receiving million-volt therapy. At the time of publication in 1944, 21 patients were surviving, 4 for more than two years, and but 2 of these had no clinical evidence of disease.

### *Metastatic Tumors of the Lung*

Alexander and Haight<sup>89</sup> have recently collected 24 cases in which pulmonary resection has been carried out for presumably solitary metastatic carcinoma or sarcoma. Six of these cases were from their own clinic and the remainder were collected from the literature or by personal communication. Twelve patients had no recurrence, 8 of them sufficiently long (twelve, seven, six, five, four, three, one and a quarter and one year) after operation to justify optimism. In this series, the patients with sarcoma appeared to do better than those with carcinoma. Six of the cases were done for renal-cell carcinoma, including 1 case in which the patient has survived for thirteen years after pulmonary resection of a metastatic hypernephroma.

Effler and Blades<sup>90</sup> have recently added 3 cases, including 1 patient who, nine months after resection of a pulmonary metastasis from a sigmoid carcinoma, resected two years previously, had a cerebral metastasis removed. A recent case at the Massachusetts General Hospital demonstrates the vagaries of metastatic disease. The patient, a seventy-two-year-old man, underwent a removal of the right upper lobe for malignant melanoma metastatic to the lung. Fifteen years before, he had had an enucleation of the left eye for a similar tumor.

### TUBERCULOSIS

In his progress report for 1944, Strieder<sup>91</sup> pointed out that only recently had accepted technics been generally applied to excisional surgery for pulmonary tuberculosis. Useful as tourniquet lobectomy had been, results in the treatment of tuberculosis had been most disappointing and marred by innumerable difficulties with the bronchial stump and spread of disease during a complicated convalescence from surgery. With the proved value of individual ligation technic, the incidence of these hazards was reduced, and the question of lobectomy reopened with new enthusiasm.

By 1944, a sizable number of cases of lobectomy, with relatively few complications directly chargeable to the operative technic, had been compiled. Strieder has reviewed these at length, and pointed out the need of more time before any proper evaluation of the results can be made.

At present the long-term results of lobectomy for tuberculosis still await definition, and a new technical consideration — namely, the use of streptomycin — has entered the picture. Streptomycin therapy for tuberculosis has had extensive and critical trial in the facilities of the Veterans Administration. A report of its Streptomycin Committee<sup>92</sup> demonstrates that the practice of combining surgical procedures with streptomycin is of proved value. Beginning in March, 1947, a study

A correct appraisal of operative risks is obviously important in a decision for pneumonectomy versus lobectomy in carcinoma of the lung. Majority opinion at present favors total pneumonectomy with as extensive a lymph-node dissection as possible, to include the subcarinal nodes, the azygos node on the right and the nodes in the pulmonary ligament. If one chooses to argue by analogy to carcinoma of the breast, the position is a strong one, and certainly, other things being equal, total extirpation of a cancer-bearing organ with regional-lymph-node dissection en bloc is a major desideratum of cancer surgery. However, if one argues by analogy to gastric carcinoma, in which mortality, morbidity and disability of total versus subtotal gastrectomy are not equal, the question of lobectomy for cancer of the lung must be kept open.

Granted that it may be more informative to consider that Graham's patient, in whom a total pneumonectomy was done in 1933 for squamous-cell carcinoma of the lung, is still alive and well than to consider survival statistics at present on record, a preliminary estimate of efficacy of resection, when it is possible, may be made from the reported experience of Adams<sup>74</sup> (1948), Rienhoff<sup>72</sup> (1947), Ochsner et al.<sup>71</sup> (1947) and Graham<sup>76</sup> (1948). In so doing, one finds a total of 133 cases of pneumonectomy done five or more years prior to publication. Of these, 36 patients, or 27.1 per cent, survived five years. One of the greatest variables in the material has been the extent of the disease at the time of operation, for, as Ochsner and his associates have reported, if the disease extended beyond the lung—that is, encroachment on contiguous structures or metastasis to regional lymph nodes—only 2 of 27 patients survived three years, and none beyond six years. Yet of 15 of Graham's 53 patients who survived pneumonectomies beyond five years, 6 had positive lymph nodes at the time of operation. Coleman<sup>76</sup> has recently made the interesting observation that of 88 histologically proved cancers of the lung in his series, 6 that invaded ribs were all of squamous-cell origin (as opposed to 47 per cent of the entire series). Resection could be carried out in 5 of these patients, of whom 1 was alive and well six years and 1 two years after operation. Resection of portions of the chest wall had been carried out in 6 of Ochsner's series.

By way of contrast it would be desirable to present survival statistics for a comparable series of lobectomies done with a "curative" rather than a "palliative" objective. Unfortunately, such statistics are not presently available. In 1947 Adams<sup>77</sup> reported 5 cases of lobectomy for carcinoma with five-year survivals in 3, and Neuhof and Aufses<sup>78</sup> 24 cases with two-year survivals in 7. The latter authors have urged the importance of reporting results on the basis of the topographic features of the patient's disease, and have advocated pneumonectomy in the carcinomas of main and branch

bronchus—usually infiltrative with diffuse lymph-node involvement—and lobectomy for the circumscribed cancers without lymph-node spread and peripherally invasive carcinomas. They have stated, and this opinion was shared by few, that microscopical features were of relatively little significance after radical excision. Needless to say, survival statistics of two years in carcinoma must be accepted with caution.

Graham<sup>76</sup> has agreed that lobectomy may have a place in the treatment of carcinoma of the lung, but that if the mortality and morbidity of pneumonectomy can be kept low, the latter is the procedure of choice. As noted above, in 15 of his series of 53 pneumonectomies done prior to 1942, the patients were living and well in 1947. Head<sup>79</sup> has argued that in the older age group, pneumonectomy is a "crippling" operation, and that he has preferred lobectomy in this group when feasible. He has also warned against pneumonectomy under a mistaken diagnosis of cancer, believing that lobectomy is often indicated as a relatively safe excision biopsy when the diagnosis is in doubt. Janes<sup>80</sup> has recently reported 2 instructive cases of lipoid pneumonia simulating bronchogenic carcinoma treated surgically. Adams has suggested the following three broad indications for consideration of lobectomy: peripheral lesions of the lower lobes without grossly involved lymph nodes, upper-lobe lesions in which a clean dissection of the lobar bronchus is possible, and "palliation." Consideration of the anatomy of the tracheobronchial lymphatics<sup>81</sup> serves to emphasize the relatively small increment of lymph-bearing tissue removable by pneumonectomy over lobectomy in many lesions, particularly of the upper lobe.

Birath, Crafoord and Rudstrom<sup>82</sup> have recently discussed the quantitative measurement of pulmonary function after lobectomy and pneumonectomy. Their point of departure was the well known and previously studied<sup>83</sup> distention of the remaining lung following pneumonectomy. Total lung volume and its fractions were measured by external spirometry with a closed-circuit system, and respiratory dead space estimated by construction of a washing-out curve of nitrogen from the lungs. The latter principle has been explored extensively by Courmand and others, and has recently been elaborately refined by Bateman<sup>84</sup> at the Mayo Clinic. The material of Birath et al.<sup>82</sup> included 12 cases of pneumonectomy and 14 of lobectomy, all in adults, two to thirteen years after operation. As one might expect, after pneumonectomy the volume of the remaining lung was found to exceed by about 15 per cent the calculated normal values, the functional residual air was approximately 50 per cent higher than the predicted value for a normal lung, and the absolute residual air was even greater than 50 per cent. Thus, within the limits of the method, particularly regarding prediction of nor-

vocated routine postresection thoracoplasty in an effort to control excessive expansion of the remaining lung. In 1944, Chamberlain<sup>91</sup> stressed the factor of overdilatation as a real consideration in the choice of selective thoracoplasty over upper lobectomy. His argument was supported by bronchspirometric studies. Maier,<sup>91</sup> after similar studies challenged this position. Of Overholt's patients, only 16 per cent with upper lobectomies done as alternative to thoracoplasty had ipsilateral exacerbations if post-lobectomy thoracoplasty (second, third and fourth ribs) were done whereas the exacerbations appeared in 50 per cent who had no postoperative collapse therapy. It seems important, therefore, to demonstrate the superiority of lobectomy and thoracoplasty over thoracoplasty alone — a demonstration still forthcoming.

The heterogeneous field of extirpation for pulmonary tuberculosis has been extended to include segmental resection in a certain number of cases. The physiologic considerations of conserving lung tissue, for both its respiratory and its space-filling functions, seems to be secondary to pathologic considerations regarding the segmental nature of the disease in any given case. Reluctance to transect tuberculous tissue has been a well established principle, although streptomycin may alter this established conviction, and increasing familiarity with technics of segmental resection add some degree of safety. The fundamental nature of the disease and the objectives of surgical treatment must, however, remain the most important considerations.

#### COCCIDIOIDOMYCOSIS

Coccidioidomycosis, heretofore considered rare but disabling and often fatal, has achieved rather widespread clinical significance as a result of infection and dissemination of the disease among members of the armed forces. Its pathogenesis and pathology have been authoritatively reviewed by Forbus and Bestebreurtje.<sup>97</sup> Ninety-five cases of the disseminated form of the disease occurring in the armed forces between 1941 and 1946 are reported, 50 of these were studied clinically and at autopsy, the other 45 were confirmed by biopsy. It was apparent that coccidioidomycosis is primarily a pulmonary disease and rarely fatal except in association with endogenous reinfection. Pathologically, it is a "granulomatous" process, with many characteristics of tuberculosis, and also of many of the ordinary pyogenic infections. Primary pulmonary coccidioidomycosis is usually represented by a focal or diffuse nongranulomatous inflammatory response with regional lymphadenitis. In its severe forms, genuine suppurative and granulomatous lesions, which are sometimes destructive enough to go on to cavity formation, develop. The severe forms, which are rare, heal by scar formation and these lesions may become calcified. Secondary or disseminated disease often develops during the

active progress of the primary infection, or may spring from vegetative organisms smouldering in clinically healed but residual lesions. The authors collected 5 cases in which operation was performed when neoplasm was suspected on x-ray examination and could not be excluded. It is believed that, for approximately ten years, disseminated endogenous reinfection will continue to occur among members of the armed forces who were trained in endemic areas of the Southwest, but it does not appear likely that the disease will spread to non-endemic areas.

Greer Forsee and Mahon<sup>98</sup> have reported 15 surgically treated patients from Fitzsimons General Hospital, in whom focal pulmonary coccidioidomycotic lesions were present. These appeared as either solitary or cavitory circumscribed lesions, which closely simulated tuberculosis and from which positive pathological differentiation was possible only by recognition of the organism in tissue sections or by isolation in cultures of the lesion. Nine were treated by lobectomy, and 6 by wedge excision. In the presence of cavitation, the presence of daughter granulomas made lobectomy the preferable procedure. The indications for operation included recurrent hemoptysis, failure of the cavity to close after months of observation, spontaneous pneumothorax and inability to exclude neoplastic disease.

Churchill<sup>99</sup> has described the futility of resection in the presence of disseminated disease. In a case reported the organisms could not be recovered from the sputum in spite of a widespread consolidation of the left upper lobe, with abscess formation. The patient had obviously no biologic defense against fungous infection. A skin test with coccidioidin was negative in this case, as well as in 12 of the 28 cases so tested in the series of Forbus and Bestebreurtje.<sup>97</sup>

Studer and Morgenstern<sup>100</sup> have recently reported a case — the fourth so reported — of coexisting pulmonary coccidioidomycosis and tuberculosis.

#### SUPPURATIVE DISEASE

##### *Lung Abscess*

External drainage has gradually given way to primary lobectomy in the treatment of chronic lung abscess. Though at times life saving and occasionally the only possible surgical attack, external drainage in the past has been a relatively unsatisfactory compromise with a lethal "benign" disease. Sweet<sup>101</sup> has reviewed the experience at the Massachusetts General Hospital with lung abscess over two pre-penicillin five-year periods, 1933-1937 and 1938-1942. Each period included approximately the same number of cases (124 and 120, respectively). Comparing the two groups, he found that the curability rate rose from 49.2 to 59.2 per cent, whereas the mortality fell from 33.9 to 18.3 per cent.

was carried out in 27 hospitals in which the drug was given arbitrarily for seven days preoperatively and fourteen days postoperatively, to alternate thoracoplasty patients. Daily dosage varied between 10 and 20 gm. Streptomycin was also given to the great majority of other patients undergoing extensive surgical procedures for tuberculosis. In all, 1559 operations were performed upon 709 patients, of whom 406 received streptomycin. In the thoracoplasty group, the difference of spreads between treated (20 per cent), and untreated (56 per cent) was statistically significant, but in spite of this, the routine use of streptomycin was not advocated in thoracoplasty patients, not only because the relatively low incidence of spread in untreated cases made the practice somewhat wasteful of a rather expensive agent, but also because of toxic implications and a definite hazard of producing bacteriologic resistance. An incidence of only 4 postoperative spreads following 144 pneumonectomies and lobectomies was regarded as ample demonstration of the value of streptomycin in these procedures, in which its routine use was recommended. A total of 10 gm daily, divided into two doses and administered intramuscularly, appeared to be effective and was relatively innocuous.

The subject was accorded considerable recognition at the 1948 meeting of the American Association for Thoracic Surgery. Noteworthy was the increasing enthusiasm shown for pulmonary resection, and the reporting of rather large series of cases in which major surgical procedures could be carried out under the "benevolent mantle" of streptomycin. O'Brien et al.<sup>94</sup> rejoiced that now the maximum of definitive surgery for pulmonary tuberculosis was possible with a minimum of preliminary procedures. Active cases required a less prolonged cooling-off period than formerly before a surgical program was undertaken. In terms of operative morbidity and mortality, and also of early conversion of sputum to normal, it was apparent that immediate results were improved by use of the agent.

In 1946 Sweet<sup>91</sup> reported the total experience with pulmonary resection for tuberculosis at the Massachusetts General Hospital in the period before streptomycin was employed. The material consisted of 27 lobectomies, including the 6 reported by Churchill and Klopstock<sup>95</sup> in 1943, and 36 pneumonectomies. The surgical problems of the two groups were kept clearly distinct.

Of great interest were the 11 lobectomies that were done as alternative to thoracoplasty. The other 16 were done for the more generally acceptable indications: location of cavity unfavorable for collapse therapy, tuberculoma, atelectasis distal to stenosis, and large, rigid-walled cavity. In many of the cases adjudged suitable for lobectomy, it was striking to discover how much disease not

clearly visualized by x-ray examination existed in other portions of the lung. One, therefore, could speak with propriety of reactivation rather than of spread. Among the 27 lobectomies there were 2 postoperative deaths, 5 patients died later of their disease, 7 were alive with their disease (with positive sputum), and 13 were apparently well one to three years after operation. Among the 13 apparently well patients were 7 of the 11 patients in whom ordinarily a thoracoplasty would have been done in anticipation of a good result. Four of the 11 "alternative to thoracoplasty" patients were alive with disease at the time of the report. Of the 2 lobectomy cases that showed early reactivation of the disease, 1 was fatal, and the other cleared. Of 11 patients who suffered "late" reactivation of the disease, 4 were dead, and the remainder ill at the time of the report.

Of the 36 pneumonectomy cases, 18 were considered "desperate risks" with an excavated and almost functionless lung, and all with obviously bilateral disease on x-ray study. Of the other 18, stenosis of the main bronchus accounted for 6, and persistent cavity under properly performed thoracoplasty for 4 cases. In 5 the choice of pneumonectomy was made at operation when incomplete or absent fissures made transection of tuberculous disease almost inevitable. Seven of the patients with pneumonectomies (19.4 per cent) died in the early postoperative period, 7 died later of their disease, 5 were alive with disease, and 17 were apparently well. Among the latter were 3 of the 18 with "destroyed lungs," 5 of the 6 with "bronchostenosis," 4 of the 5 in whom the operation was done for technical reasons, and 3 of the 4 in whom thoracoplasty was a failure. The salvage of only 3 of 18 patients regarded as desperate risks, with 4 early and 6 late deaths in this group, was disappointing, and emphasized the importance of the patient's response to his disease as predetermining the success of radical surgery. In the other patients who handled their disease well biologically, radical surgery as a mechanical corrective measure appeared to be quite effective.

Overholt<sup>96</sup> has also reported his extensive pre-streptomycin experience with resection for pulmonary tuberculosis—192 cases done between 1934 and 1946—and has advocated certain technical points. Of these the face-down position has been much debated. According to its proponents, its advantages lie in less gravity drainage to the sound lung, less impairment of the chest wall and diaphragm on the sound side, less mediastinal shift, elimination of the necessity of positive pressure and the direct approach to the hilus posteriorly, with less need for hilar traction. In reply, others have advanced cogent reasons for employing the posterolateral and the anterior approach according to individual indications and preferences of both the operator and the anesthetist. Overholt has ad-

saccular disease upon which his report was based. He therefore injects a note of caution into the treatment of cases showing a maximal bronchographic extent of otherwise minimal disease.

## THE ESOPHAGUS

### Cancer

A British surgeon recently reviewed the history of esophageal resection for carcinoma, and remarked how "the bold early experiments in esophageal surgery were followed by decades spent trying to circumvent, rather than face the dangers, and recently by a return to straightforward resection with anastomosis."<sup>112</sup> In the ten years since Adams and Phemister reported the first successful intrathoracic esophagogastrostomy for carcinoma, techniques of esophageal resection in primary anastomosis have been standardized and so widely applied that a preliminary estimate of the efficacy of this, one of the latest fields of cancer, can be made. The June, 1948, issue of *Surgery* has been devoted to this subject, and contains excellent clinical characterizations of the disease, discussions of technique and editorial opinions of many of the leaders in the field. It is apparent that the majority are willing to abandon the Torek operation — credited with the first certain cure (in 1913) of carcinoma of the midesophagus — as inadequate for palliation and inefficient for cure. In support of this opinion, Sweet<sup>113</sup> has reported the total experience with the Torek procedure at the Massachusetts General Hospital. Of 14 patients 12 survived the removal of the tumor, but of these 4 died before construction of an antethoracic esophagus was begun, 4 died before the procedure was completed, 2 died after its completion, and 2 were surviving at the time of the report (four and two years, respectively).

Cancer of the esophagus differs from cancer of the lung in that its symptoms are generally so urgent that by far the great majority come to exploration, the age of the patient and his general condition notwithstanding. The distressing symptoms of slow starvation and the inability to swallow one's own saliva justify considerable operative risk and discomfort. The palliation afforded these patients if, at operation, resection and anastomosis are feasible has been deemed ample justification for the risks and surgical efforts involved, even if the prospect of cure is dim or nonexistent. Unfortunately, the anatomic relations of the esophagus make involvement of adjacent vital structures likely, though collected statistics indicate that the present resectability rate of 60 per cent of cases explored compares favorably with that of carcinomas elsewhere in the gastrointestinal tract. (To choose an example, 40 per cent of all gastric carcinomas seen at the Memorial Hospital are found to be resectable.<sup>114</sup>) Adding together the recorded experience of Sweet,<sup>113</sup> Garlock,<sup>115</sup> Strie-

der,<sup>117</sup> Clagett,<sup>118</sup> and Pack and McNeer,<sup>114</sup> which consist of total operative experience without revision by years, one finds that of 589 cases, 343 were resected, a rate of 58 per cent. Again, a compilation of the immediate operative mortality of low resection by the same group, in addition to the experience of deAmesti and Otaiza,<sup>119</sup> in Chile, and Lewis,<sup>112</sup> in Great Britain, yields 80 operative deaths in 303 cases — a rate of 26 per cent. The returns are, of course, incomplete and show considerable variation between patients, but serve as a preliminary estimate of the surgical risk involved.

Carcinomas of the midesophagus requiring a high resection and usually an anastomosis at the level of the ante-aortic or supra-aortic arch should be distinguished from those demanding a low resection. The midzonal cancers represent patients for whom, until 1944, the Torek operation was the only generally accepted procedure. In that year, Garlock<sup>120</sup> and Sweet<sup>113</sup> independently reported their experience with resection and primary intrathoracic anastomosis for these high and difficult lesions. I have been unable to find a report of Garlock's over-all experience in this regard. However, Sweet<sup>121</sup> has recently recorded his in detail, and, as the number of cases is significant and the results represent the application of a uniform technic, his report may serve to characterize the current status of surgery of the midesophagus. In contrast to a mortality of 12 per cent in 109 cases of low resection, Sweet reports 17 postoperative deaths in 72 cases of mid-thoracic esophageal resection — a rate of 23.6 per cent. Of 50 such patients reported previously, 21 had infra-aortic anastomosis, with a mortality of 19 per cent, and 29 had supra-aortic anastomosis, with 24.1 per cent mortality. The significant portion of this mortality was attributable to cardiac disorders — not surprising in view of the magnitude of the procedures and the clinical characteristics of the patients. It was believed, however, that the cardiologist's advice regarding the use of quinidine, and the limitation of salt and fluid intake, did much to reduce this type of complication.

Quite apart from the immediate results of operation and the dramatic palliation it affords, there is some reason for optimism concerning ultimate results. Sweet has analyzed his cases from the point of view of survival. His figures indicate that the majority of deaths from metastasis or recurrence of the disease occurred during the first two years after operation. Of 30 patients who had resections of the lower esophagus or cardia more than three years before the report, 23 survived operation and 9 were alive and clinically well at the time of writing (1 for seven, 2 for five, 2 for four, and 4 for three years after operation). From the point of view of survival, 82 per cent of patients who withstood the operation survived for six months, 48 per cent for a year, 44 per cent for eight months, and 31.5 per cent for two years. In most cases this

The number cured spontaneously rose slightly, from 19.3 to 23.3 per cent, and the number cured by surgery from 29.9 to 35.8 per cent. The number of lobectomies increased from 6 primary and 11 secondary lobectomies to 15 primary and 11 secondary lobectomies. In the last five years at the same hospital, it is my impression that the proportion of lobectomies, particularly primary procedures, is far higher. In the 1938-1942 group, it is of interest that of 60 drainage cases, only 19 patients could be considered cured, 9 died, 11 had secondary lobectomy, and 21 were alive with disease, which in most cases meant a troublesome fistula and a pulmonary focus of considerable potential hazard.

Glover and Clagett<sup>102</sup> have reported 37 cases of chronic lung abscess treated by pulmonary resection at the Mayo Clinic for the ten-year period, January, 1937, through December, 1946. Among 21 lobectomies there was 1 death—a bilobectomy patient who died of shock with pulmonary edema forty-eight hours postoperatively. The final result in the remaining 20 cases was an asymptomatic cure. Of the 16 pneumonectomies in which the infection had been permitted to ravage an entire lung, the results were far different. Six patients died postoperatively, and an additional 3 died of brain abscess within five months of leaving the hospital. In another 2 cases empyema developed, 1 patient requiring subsequent thoracoplasty. An additional patient had sufficient cough and dyspnea to require thoracoplasty for correction of overexpansion and mediastinal shift. Thus, in 12 of the 16 cases in which the disease had had the upper hand, either death (9 cases) or serious complications (3 cases) followed surgical treatment. These results argue strongly for a surgical attack upon the lesion when lobectomy will suffice. Unfortunately, in an urban community, many of the patients have multilobar disease when first seen by any medical adviser.

Glover and Clagett have agreed with Neuhof and associates regarding early drainage before widespread secondary changes occur, and are not prepared to decide whether in a majority, or even a significant number of these patients, bronchiectatic changes will require extirpation. They have urged resection in cases in which secondary, presumably irreversible, changes have occurred, in those anatomically unsuited to drainage, in those associated with excessive bleeding, in children, in patients in whom cancer cannot be excluded, and in cases secondary to unremovable foreign bodies.

These indications agree essentially with Lindskog's<sup>103</sup> experience. He recommends primary resection without preliminary drainage as the procedure of choice in chronic lung abscess under the following conditions: multiple abscesses or extensive destruction in one or more lobes, secondary bronchiectasis, atelectasis and pneumonitis unrelieved by bronchoscopic treatment, uncontrolled

bleeding, and perforation and localized empyema. He also reports 22 acute lung abscesses treated at the New Haven Hospital. On conservative therapy 5 patients were cured, and 3 much improved. After external drainage, 4 were cured and 4 much improved, and 1 died. Four patients required drainage of an empyema at the time of initial therapy, and 1 refused treatment.

It is probable that the place of early drainage of acute lung abscess needs redefinition if the powerful antibiotics now available can, by preventing invasive infection, reduce the amount of irreversible secondary change that converts an acute abscess into a chronic one. It is conceivable that the problem of lung abscess will resolve itself chiefly into a decision between nonoperative treatment and extirpation.

### BROCHIECTASIS

At a symposium held before the Massachusetts Medical Society in 1947 on the subject of bronchiectasis, Mallory<sup>104</sup> summarized the present theories of its pathogenesis. For each of five factors—direct bronchial infection, congenital malformation of the bronchial tree, bronchial stenosis, pulmonary atelectasis and pneumonitis—there is positive evidence of a causal relation, but none of the factors are constant or all-explanatory. He concluded that primary bronchitis and secondary atelectasis, with or without pneumonitis, could best explain the usual case, and that congenital cystic disease and bronchostenosis were relatively uncommon. The strategic point of attack, therefore, appears to be the prevention or prompt alleviation of atelectasis.

Carter and Welch<sup>105</sup> have recently presented a most interesting account of the development of bronchiectasis in 8 patients after the inhalation of a specific type of foreign body,—namely, a timothy head,—oriented stem downward. The report serves again to emphasize the respiratory hazards of childhood.

Surgical progress in bronchiectasis has been largely that of increasing safety and selectivity of operative procedures.<sup>106, 107</sup> More effective supportive measures, technical advances and extension of anatomic knowledge have contributed to the wider application of segmental resection and bilateral programs. There can be little doubt that penicillin has contributed greatly to the safety and ease of convalescence of these patients, and there is clinical evidence that aerosol penicillin may be of considerable help as a preoperative measure, particularly in patients producing copious amounts of sputum.<sup>108, 109</sup> Flooding of the airway under anesthesia has always been one of the major operative hazards.

King,<sup>110</sup> whose classic review of the subject has often been quoted to show the dismal future of bronchiectasis without surgical therapy, has recently commented<sup>111</sup> on the comparatively few patients seen nowadays that have the extensive

Unfortunately many benign strictures extend high in the esophagus, occasionally well into the cervical region. At the time of the last progress report on this subject (1944) much interest was displayed in the procedure described by Yudin<sup>129</sup> consisting of an anterior esophagus constructed from small intestine. Longmire<sup>130</sup> has recently described a modification of this maneuver by which in patients having mesenteric vessels of inadequate length, blood supply is reconstituted by direct arterial and venous anastomosis to the internal mammary vessels. Longmire<sup>131</sup> has also presented an ingenious method of enclosing a segment of jejunum in a skin tube, which is then advanced onto the chest in multiple stages, in the course of which it is freed from its mesenteric blood supply. Rienhoff<sup>132</sup> has reported a method dividing the base of the mesentery of the small bowel so as to maintain the integrity of the vascular arcades. A sufficiently long segment of jejunum is thereby obtained, and can be brought well into the chest, permitting safe esophagojejunal anastomosis at a high level. Puestow and Chess<sup>133</sup> have described 4 cases of high resection and esophagogastric anastomosis, with 1 death. They employed the technic previously described by Sweet<sup>134</sup> and used by him for high strictures of the esophagus with very satisfactory results. Harrison<sup>135</sup> has reported 2 cases of lye stricture, both in three-year-old children, in whom esophageal continuity was re-established by a three-stage procedure, in which a single loop of jejunum was brought up intrathoracically to bridge the gap between the cervical esophagus and the stomach.

Of great current interest are cases of benign stricture of the lower portion of the esophagus in which the etiology is obscure. In these cases the esophagus is frequently shortened, and there may be associated peptic ulceration. Such cases are not to be confused with idiopathic dilatation of the esophagus (cardiospasm, achalasia), whose pathogenesis reveals the confusion regarding its cause. Both the latter forms of benign lower esophageal obstruction are usually amenable to conservative measures, including instrumental dilatation. However, if these become burdensome to the patient or fail to achieve the desired functional results, a direct surgical attack is necessary.

In the idiopathic dilatation — cardiospasm-achalasia group — usually some form of pyloroplasty will suffice. Whether this is done transthoracically or transabdominally will depend on the preference of the operator.<sup>136-142</sup> The safety and versatility of the transthoracic approach has often been demonstrated, and is to be preferred when resection may be necessary.

Olsen and Harrington<sup>144</sup> have reported a series of 220 cases of esophageal hiatus hernia of the short-esophagus type. Eighty-nine of these had significant ulcerations of the esophagogastric junction,

which could be controlled in the majority of cases by conservative therapy, including instrumental dilatation if obstruction was present. Abdominal operation in this group was unsatisfactory. The authors have discussed the etiology of peptic ulceration of the lower esophagus and drawn freely from the literature on the subject. Several interesting hypotheses are advanced to explain the short esophagus. They agree with Allison's<sup>145</sup> suggestion that peptic ulceration of the lower end of the esophagus may be the cause. The peptic ulceration may result from excessive or prolonged vomiting, or from constant bathing of the lower end of the esophagus in acid secretion, owing to incompetence of the physiologic sphincter of the cardia in association with hiatus hernia. The authors also refer to experimental evidence of Dev et al.,<sup>146</sup> who demonstrated reflex shortening of the esophagus on direct or indirect vagal stimulation. The latter might be translated to their 18 patients who had an associated duodenal ulcer, and 39 others with long histories of "dyspepsia."

Clark and Adams<sup>147</sup> have discussed transthoracic esophagogastronomy in 5 cases of benign obstruction of the lower end of the esophagus after failure of conservative therapy. One of these patients had esophagitis associated with scleroderma, in 3 the etiology was obscure. No ulceration was described. Allison<sup>145</sup> has urged operative attack when conservative measures fail. When the peptic ulceration is accompanied by inefficiency of the diaphragm, which allows the stomach and abdominal esophagus to slide up into the mediastinum — a "landslide" type of hernia — he suggests that the length of the esophagus be restored, the stomach replaced in the abdomen, and the size of the hiatus corrected. When chronic ulceration and fibrosis make reduction of the anatomic deformity impossible, excision of this segment may be necessary.

Sweet<sup>145</sup> has reported 51 cases of repair of hiatus hernia by a transthoracic approach, which he favors because of the greater exposure obtained, the versatility of access and the freedom from complications. In the 51 cases described, intractable pain was the indication for operation in 68 per cent, incarceration in 18 per cent, and acute or chronic blood loss in 14 per cent. Soutter<sup>148</sup> has reviewed all the cases of surgical repair of hiatus hernia done at the Massachusetts General Hospital over the years and has concluded that the incidence of recurrence is lower and symptomatic relief greater after transthoracic rather than subdiaphragmatic repair.

In the course of a comprehensive review of the subject of diaphragmatic hernia, Harrington<sup>150</sup> has discussed the many aspects of the problem and has reviewed his experience with 404 cases treated surgically. Two hundred and eighty-seven of these were esophageal hiatus hernias, for which he preferred an abdominal approach to the defect, usually preceded by a temporary phrenic paralysis.

meant prolongation of life with relative comfort, for recurrence in the anastomotic site was uncommon. With this in mind it is difficult to agree with the following statement of Nielsen<sup>122</sup>

To us there is no doubt that the difficult task of trying to treat esophagus cancer both radically and symptomatologically will, to a very great extent, continue to be the domain of radiotherapy. All imaginable advances of thoracic surgery notwithstanding, only a small percentage of carcinomas in the esophagus will be amenable to surgical treatment, and the number of these in which a complete cure will be obtained will be smaller, still.

Nielsen has described an ingenious method of therapy, which delivers an effective amount of radiation to the tumor by rotating the patient vertically in the radiation field. Since the esophagus is an axial structure, the effective tumor dose is delivered with a minimum amount of radiation to any one area at the periphery. Of a total of 194 cases of carcinoma seen, only 8 were considered unsuitable for x-ray therapy. Of the 174 patients treated by rotation therapy, 140 received satisfactory tumor dosage. Of those treated by rotation therapy, 25 per cent were alive in one year, and 15 per cent in two years. If one corrects Sweet's survival statistics to total number of cases resected and not merely those surviving operation and therefore having the opportunity to survive, 42 per cent were alive at one year, and 34 per cent survived for two years. The point is well taken, however, that in the nonresectable cases x-ray therapy may have palliative value. It is fair to state that the experience of others with x-ray therapy for carcinoma of the esophagus has not been so encouraging as that of Nielsen. Thus, Holmes and Schulz,<sup>123</sup> using supervoltage radiotherapy, found that only 8 per cent of patients survived for one year, and 2 per cent for two years.

Cancer of the cervical esophagus has stubbornly maintained the upper hand over surgical attack, although occasional successes in this region have been reported. Watson and Pool<sup>124</sup> have reviewed the historical aspect of the problem and made note of a twenty-three-year survival following surgical resection of a lesion of the cervical esophagus, reported by Evans in 1934, and a ten-year cure reported by Trotter in 1937. The authors themselves reported 2 cases ten years after combined surgical and x-ray therapy, and 1 case clinically free of disease seven years after surgical excision. Reviewing 77 cases of surgical esophageal cancer admitted to the Memorial Hospital from 1940 to 1947, they found that 22 per cent had clinically positive lymph nodes on admission. Survival after x-ray therapy averaged fifteen months in cases in which treatment failed to arrest the disease, but 3 patients treated more than fifteen months before the time of report were alive and well at that date. Of 7 patients treated by resection, 1 died within three months of operation, and the remainder were alive four, six, nine, twelve, thirty-

six and eighty-four months, respectively. Using a similar operative approach Sweet<sup>115</sup> has reported 7 cases with excellent immediate results, but in each case, within six months to a year after operation, local recurrence or evidence of cervical-lymph-node metastasis became apparent. With 1 exception, all patients were dead at the time of his report.

The technic of cervical esophagectomy has been described in detail by Wookey,<sup>125, 126</sup> of Toronto. The procedure is designed to re-establish esophageal continuity at a second stage, and in many cases the larynx can be preserved. The operation, which is historically related to procedures described by Trotter and Eggers, consists of a block excision of the involved cervical esophagus.

Cancers in this area are almost invariably epidermoid, and the Memorial group,<sup>114</sup> at least, have believed that etiologically they bear a definite relation to chronic irritation in the oral cavity and to leukoplakia. As in other cancers, one of the major difficulties has been delay in diagnosis, occasioned chiefly by the surprising vagueness and lateness of symptoms of cancer in this region,—a scrappy throat, halitosis and ill defined discomfort on swallowing,—many of the ills often being ascribed to excessive smoking, postnasal drip or bad teeth. Pack<sup>127</sup> has decried the ritualistic aura surrounding the esophagoscope that has prevented its early and widespread use.

Perhaps the most difficult of all zones to resect, and fortunately the one least commonly involved in carcinoma, is the upper fourth of the thoracic esophagus. Cancer at the thoracic inlet is difficult of access, for both removal and reconstruction. Sweet<sup>115</sup> has reported a successful case in which, after removal of such a growth, an intracervical esophagogastrostomy was performed, the fundus of the stomach having been brought up through a defect in the upper thorax formed by resection of the inner end of the clavicle and first rib. Bricker and Burford<sup>128</sup> have recently described a pedicle tube flap for reconstruction of the upper esophagus following resection, with radical neck dissection and anterior thoracotomy.

### *Benign Obstructions*

It is not surprising that heroic measures refined to a point of safety in the treatment of malignant lesions of the esophagus should be extended to include certain benign but often distressing conditions. Thus, although bougienage may be adequate for cicatricial obstruction resulting from chemical burn, in a variable number of patients it will be distasteful to the point of intolerability and occasionally impossible or extremely hazardous. Under these circumstances, resection and direct esophago-gastric anastomosis seems logical, especially in the group of younger persons whose cardiopulmonary systems are sufficiently resilient.

the graft had taken well to the diaphragm and pleura

Asthma continues to be a relatively undiscovered country for the thoracic surgeon. In 1948, Carr and Chandler<sup>65</sup> reported 5 patients in whom encouraging clinical results followed post-ganglionic resection of the upper dorsal sympathetic ganglions. In discussion of their report, Abbott pointed out that head his associates approached the problem by an attack on the parasympathetic system. Similar conflicting clinical evidence was added by Adams. The problem awaits definition of the pathologic changes and disturbances of physiology under attack, and the relation of the lung to the autonomic nervous system.

## REFERENCES

- 70 Björk, V. O. Bronchiogenic carcinoma. *Acta chir Scandina* 95 (Supp 123) 1-113 1947
- 71 O'haier A, DeBakey M E and Dixon L. Primary pulmonary malignancy treated by resection: analysis of 129 cases. *Ann Surg* 125:22-540 1947
- 72 Renhoff W F. Present status of surgical treatment of carcinoma of lung. *Ann Surg* 125:541-565 1947
- 73 Jones J C. Surgical aspects of bronchiogenic carcinoma. *J A M A* 134:113-117 1947
- 74 Adams R. Carcinoma of lung: factors affecting survival after resection of cancer of lung. *J Thoracic Surg* 17:306-322 1948
- 75 Graham E. A. Discussion of Adams.<sup>74</sup>
- 76 Coleman F P. Primary carcinoma of lung with invasion of ribs: pneumonectomy and simultaneous block resection of chest wall. *Ann. Surg* 126:156-165 1947
- 77 Adams R. Primary lung tumors. *J A M A* 130:547-553 1946
- 78 Neuhoef H., and Anfers A. H. Cancer of lung: interval and late results of operation in relation to topography and gross pathology. *J Thoracic Surg* 17:297-305 1948
- 79 Head J R. Discussion of Adams.<sup>74</sup>
- 80 Jones R. M. Lapid pneumonia simulating bronchiogenic carcinoma. *J Thoracic Surg* 16:451-457 1947
- 81 Nelson, H P. Tracheo-bronchial lymphatic glands. *J Anat* 66:228-241 1932
- 82 Birath G, Crafoord C., and Rudström P. Pulmonary function after pneumonectomy and lobectomy. *J Thoracic Surg* 16:922-511 1947
- 83 Courmand A and Berry F B. Effect of pneumonectomy upon cardiopulmonary function in adult patients. *Ann Surg* 116:522-532 1942
- 84 Bateman J B. Measurement of intrapulmonary mixing and pulmonary midcapacity (functional residual air). *Proc Staff Meet., Mayo Clin* 21:112-120 1946
- 85 Widmann B P. Roentgen therapy for bronchiogenic cancer. *Am J Roentgenol* 51:61-69 1944
- 86 Leddy E. T. and Moersch H J. Roentgen therapy for bronchiogenic carcinoma. *J A M A* 115:2239-2242 1940
- 87 Shorvon L. M. Carcinoma of bronchus with especial reference to its treatment by radiotherapy. *Brit J Radiol* 20:443-449 1947
- 88 Hocker A F and Guttman R. J. Three and one-half years' experience with 1000 kilovolt roentgen therapy unit at Memorial Hospital. *Am J Roentgenol* 51:85-94 1944
- 89 Alexander J and Haight, C. Pulmonary resection for solitary metastatic sarcomas and carcinomas. *Surg Gynec & Obst* 85:129-146 1947
- 90 Effer D B., and Blades B. Surgical treatment of solitary lung metastasis. *J Thoracic Surg* 17:27-37 1948
- 91 Strieder J W. Thoracic surgery. *New Eng J Med* 231:360-366 and 388-396 1944
- 92 Streptomycin in the Treatment of Tuberculosis. Report to Council on Pharmacy and Chemistry of American Medical Association by Streptomycin Committee on the Veterans Administration 1948
- 93 Chapman P T, O'Brien E. J. and O'Rourke P V. Role of streptomycin in surgical treatment of pulmonary tuberculosis. Paper presented at meeting of American Association for Thoracic Surgery 1948
- 94 Sweet R. H. Lobectomy and pneumonectomy in treatment of pulmonary tuberculosis. *J Thoracic Surg* 15:373-385 1946
- 95 Churchill E. D. and Klopstock R. Lobectomy for pulmonary tuberculosis. *Ann. Surg* 117:641-649 1943
- 96 Overholt, R. H. Langer L., Szyplowski J. T. and Wilson N. J. Pulmonary resection in treatment of tuberculosis: present-day technique and results. *J Thoracic Surg* 15:384-413 1946
- 97 Forbes W. D. and Bestebreurtje A. M. Coccidioidomycosis: study of 95 cases of disseminated type with special reference to pathogenesis of disease. *Mil Surgeon* 99:63-719 1946
- 98 Greer S J, Forsee J H. and Mahon H W. Surgical management of pulmonary coccidioidomycosis in focalized lesions. Paper presented at meeting of American Association for Thoracic Surgery 1948
- 99 Churchill E. D. Malignant lymphoma of lung and pulmonary coccidioidomycosis: clinic on surgical lesions of lung with consolidation. *S Clin North America* 27:1113-1120 1947
- 100 Study R S. and Morgenstern P. Coexisting pulmonary coccidioidomycosis and tuberculosis. *New Eng J Med* 238:857 1948
- 101 Sweet R. H. Analysis of Massachusetts General Hospital cases of lung abscess from 1938 through 1942. *Surg Gynec & Obst* 80:568-574 1945
- 102 Glover R. P. and Clagett O. T. Pulmonary resection for abscess of lung. *Surg Gynec & Obst* 86:385-394 1948
- 103 Lindskog G E. Surgical treatment of chronic pulmonary abscess. *Surgery* 15:783-788 1944
- 104 Mallory T B. Pathogenesis of bronchiectasis. *New Eng J Med* 237:795-798 1947
- 105 Carter M G. and Welch K J. Bronchiectasis following aspiration of timothy grass: report of eight cases. *New Eng J Med* 238:852-856 1948
- 106 Strieder J W. Surgical aspects of bronchiectasis. *New Eng J Med* 238:109-112 1948
- 107 Meade R. H. Jr, Kay E. B. and Hughes F. A. Report of one hundred and ninety six lobectomies performed at Kennedy General Hospital Chest Surgical Center from 1945 to 1946 with one death. *J Thoracic Surg* 16:16-29 1947
- 108 Findlay C. W. Jr., and Sweet R. H. Aerosol penicillin as therapeutic adjunct in preparation of patients with suppuration of lung for pulmonary resection. *J Thoracic Surg* 16:81-90 1947
- 109 Donnelly J. H., Phillips F. J., Bartlett J. P. and Adams W. E. Evaluation of methods of penicillin therapy in thoracic surgery. *Ann Surg* 126:579-591 1947
- 110 Perry K. M. A. and King D. S. Bronchiectasis: study of prognosis based on follow up of 400 patients. *Am Rev Tuberc* 41:531-548 1940
- 111 King D. S. Personal communication
- 112 Lewis I. Surgical treatment of carcinoma of oesophagus with special reference to new operation for growths of middle third. *Brit J Surg* 34:18-31 1946
- 113 Sweet, R. H. Surgical management of carcinoma of midthoracic esophagus: preliminary report. *New Eng J Med* 233:1-7 1945
- 114 Pack G. T., and McVeer G. Surgical treatment of cancers of gastric cardia. *Surgery* 23:976-1019 1948
- 115 Sweet, R. H. Treatment of carcinoma of esophagus and cardiac end of stomach by surgical extirpation. *Surgery* 23:952-975 1948
- 116 Garlock J. H. Causes of mortality following radical resection of esophagus for carcinoma. *J Thoracic Surg* 13:415-423 1944
- 117 Strieder J. W. Surgical management of carcinoma of lower two-thirds of esophagus and cardiac end of stomach. *J Thoracic Surg* 17:143-161 1948
- 118 Payne J. H. and Clagett, O. T. Transthoracic gastric resection for lesions of cardia of stomach and lower part of esophagus. *Surgery* 23:912-920 1948
- 119 deAmesti F. D. and Otaziz E. Cardioesophageal cancers treated via transthoracic and transdiaphragmatic route. *Surgery* 23:921-934 1948
- 120 Garlock, J. H. Re-establishment of esophagogastric continuity following resection of esophagus for carcinoma of middle third. *Surg Gynec & Obst* 78:23-28 1944
- 121 Sweet, R. H. Carcinoma of esophagus and cardiac end of stomach: immediate and late results of treatment by resection and primary esophagogastric anastomosis. *J A M A* 135:485-490 1947
- 122 Nielsen J. Clinical results with rotation therapy in cancer of esophagus: preliminary report based on 174 cases. *Acta radiol* 26:361-389 1945
- 123 Holmes G. W. and Schulz, M. D. Supervoltage radiation: review of cases treated during eight year period (1937-1944 inclusive). *Am J Roentgenol* 55:535-534 1946
- 124 Watson W. L. and Pool J. L. Cancer of cervical esophagus: discussion of treatment. *Surgery* 23:895-905 1948
- 125 Woolley H. Surgical treatment of carcinoma of pharynx and upper esophagus. *Surg Gynec & Obst* 75:499-506 1942
- 126 Idem. Surgical treatment of carcinoma of hypopharynx and oesophagus. *Brit J Surg* 35:249-256 1948.
- 127 Pack G. T. Introduction to symposium on cancer of esophagus and gastric cardia. *Surgery* 23:867-873 1948
- 128 Bricker E. and Brnford T. H. Use of pedicle tube flap in carcinoma of upper esophagus. Paper presented at meeting of American Association for Thoracic Surgery 1948
- 129 Yudin S. S. Surgical construction of 80 cases of artificial esophagus. *Surg Gynec & Obst* 78:561-583 1944
- 130 Longmire W. P. Jr. Modification of Roux technique for antethoracic esophageal reconstruction: anastomosis of mesenteric and internal mammary blood vessels. *Surgery* 22:94-100 1947
- 131 Longmire W. P. Jr. and Ravitch M. M. New method for constructing artificial esophagus. *Ann Surg* 123:819-835 1946
- 132 Riehnhoff W. F. Jr. Intrathoracic esophagojejunostomy for lesions of upper third of esophagus. *Sowk. M J* 39:928-940 1946.
- 133 Puestow C. B. and Chess S. J. Resection of esophagus for persistent stricture. *Arch Surg* 56:34-47 1948
- 134 Sweet, R. H. Subtotal esophagectomy with high intrathoracic esophagogastric anastomosis in treatment of extensive cicatricial obliteration of esophagus. *Surg Gynec & Obst* 83:417-427 1946
- 135 Harrison A. W. Transthoracic esophagojejunogastrostomy for high stricture of esophagus. Paper presented at meeting of American Association for Thoracic Surgery 1948

In conclusion, a final word might be added — namely, the obvious importance of ruling out cancer in cases considered to be benign obstruction. To this end, the combination of careful x-ray study and esophagoscopy examination is necessary, and often must be repeated before cancer can be ruled out beyond reasonable doubt.

### *Congenital Atresia*

At the other end of the time scale from resection of the esophagus for carcinoma is an equally formidable operative procedure for the correction of esophageal atresia and tracheoesophageal fistula. Haight,<sup>161</sup> who is credited with the first successful direct anastomosis of the esophagus in 1941 (there were several near misses just prior to that time, notably Shaw's case in 1939), has recently reported 52 cases in which an effort was made to restore esophageal continuity. In 11 of the 52 patients an esophageal anastomosis was not possible, and in another patient it was not done. In 1 of these cases an esophagogastric anastomosis was done by Dr F X Byron. Of 40 patients for whom an esophageal anastomosis was completed, 22 died, and 18 recovered — a recovery rate of 45 per cent. The over-all recovery rate in the 52 patients explored was 34.6 per cent. Haight and his associates favor a right extrapleural exposure of the anomaly, particularly if the preoperative x-ray film demonstrates air in the stomach — a sign that there should be a sufficient length of the two segments to permit anastomosis. When air is not present in the stomach before operation, agenesis of the lower esophagus is commonly found and direct end-to-end anastomosis of the esophagus is impossible. Haight<sup>16</sup> had previously emphasized the great difficulty in securing a suture line without tension since swallowing and crying, after the effects of the anesthesia have worn off, tend to raise the upper portion of the esophagus, and the descent of the diaphragm on inspiration exerts traction downward.

Ladd and Swenson<sup>153, 154</sup> have reported experience with this disease at the Children's Hospital and suggested a new classification of the anomaly to supersede that of Vogt. Thirty-nine primary anastomoses were carried out, with 20 recoveries. Forty-three multiple-stage procedures produced 16 living patients, of whom 5 subsequently had an antethoracic esophagus completed. Their experience with a transpleural approach was disheartening: 4 deaths out of 5 attempts. Swenson<sup>154</sup> has recommended a two-layer, watertight interrupted-fine-silk anastomosis, and reports only one fistula in 15 patients, and this closed spontaneously.

In the occasional case in which, for anatomic reasons, direct anastomosis is not possible, a multiple-stage procedure may be considered, aiming first at the closure of the tracheoesophageal fistula, cervical esophagostomy, ligation of the lower esophageal segment, some form of gastrostomy, and

finally reconstruction of an anterior esophagus. As Lam<sup>155</sup> has demonstrated, the last may require great persistence in the face of many discouragements. Sweet<sup>156</sup> has attacked the problem successfully in 2 children who had esophagostomy and gastrostomy early in infancy as a life-saving measure. He subsequently performed a successful intracervical esophagogastrostomy after advancing the stomach through the chest, posterior to the hilus and out through a new thoracic inlet formed by resection of the inner end of the clavicle and first rib.

Pulmonary complications have been a limiting factor in the surgical correction of this major developmental anomaly. For this reason, the use of small amounts of lipiodol are much to be preferred over barium at the time of x-ray examination. Furthermore, because of the danger of spilling over into the tracheobronchial tree, operative intervention should not be postponed beyond the minimum time necessary to attend to the physiologic needs of the infant.

### MISCELLANEOUS CONSIDERATIONS

Surgery of the heart and great vessels qualifies for a progress report in its own right and will not be considered here. However, a rather closely related entity, variously called pulmonary arteriovenous aneurysm,<sup>157</sup> pulmonary cavernous hemangioma,<sup>158</sup> hemangioma of the lung<sup>159</sup> and arteriovenous fistula of the lung,<sup>160</sup> has been the subject of many recent reports. As the names imply, this lesion furnishes a vascular shunt across the pulmonary circuit so that deficient oxygenation of the systemic arterial blood results. On the basis of this deficiency, with its clinical manifestations of cyanosis, clubbing and polycythemia, in addition to the finding of a lung tumor that emits a bruit, the diagnosis can be made. Dramatic improvement has followed lobectomy in the cases reported.

Mediastinal tumors continue to be a source of never-ending speculation. Maier<sup>161</sup> has reviewed the problem of bronchogenic cysts of the mediastinum and recorded 8 additional cases. Within the past year, Byron, Alling and Samson<sup>162</sup> have each had a case of intrathoracic meningocele that presented as a smooth outlined and lobulated posterior mediastinal mass. Review of their cases, as well as the 5 previously recorded in the literature, showed that the lesion is frequently associated with widening of the intervertebral foramina, erosion of the rib and vertebra and even diffuse neurofibromatosis. Since excision of the meningocele is usually deemed inadvisable or impossible, they have suggested the use of a contrast medium intraspinally in the x-ray differential diagnosis.

Watson and James<sup>163</sup> and Maier<sup>164</sup> have described the management of large defects of the chest wall. The former have suggested a large fascia-lata graft, and in 1 patient, who died of pulmonary embolism eighteen days after such a repair, they found that

A barium enema, gastrointestinal series and films of the spine were reported normal. X-ray films of the chest showed cardiac enlargement, a possible dilatation of the ascending aorta and wide aortic pulsations. The serum nonprotein nitrogen was 23 mg and the sugar 106 mg per 100 cc. The prothrombin time was 18 seconds (normal, 17 seconds). The amylase was 32 units per 100 cc and the serum albumin 4.6 gm, and the globulin 3.7 gm per 100 cc, giving an albumin-globulin ratio of 1.26. The urine culture was negative. A lumbar puncture was not remarkable, the Wassermann reaction was negative, and the spinal-fluid protein was 38 mg per 100 cc. An electrocardiogram was not diagnostic.

The patient had several severe attacks of left-upper-quadrant pain while on the ward without definite relation to food intake or defecation. During one such typical episode he was found sitting in bed hunched over a bed table. Deep palpation of the abdomen revealed acute tenderness just to the left of the umbilicus, and there was a sense of resistance to palpation without detection of a definite mass in the area. Neither nitroglycerin nor sodium bicarbonate gave any relief. He was discharged to be followed in the Out-Patient Department.

**Final admission** (two weeks later). The patient returned to the hospital by ambulance, having been bed ridden at home. He appeared dehydrated and emaciated and gave a history of continued, severe, nonradiating, left-upper-quadrant pain since discharge. On two or three occasions he had vomited, with temporary relief of pain. In addition he appeared weaker.

Physical examination was the same as on the previous admission, except the liver was felt to descend three fingerbreadths on deep inspiration. An intravenous pyelogram and a left retrograde pyelogram were negative. Sigmoidoscopy to 16 cm was normal. The stool was guaiac positive on four of seven occasions. The urine concentrated to 1.027 and gave a + test for albumin and there were 20 white cells, 5 red cells and occasional casts per high-power field in the sediment. The hemoglobin was 10.5 gm. The white-cell count was 8000, with 20 per cent myelocytes and myeloblasts. A hematologic consultant found myeloid hyperplasia on the smear and sternal biopsy. The serum lipase was 1.2 mg, and the nonprotein nitrogen 38 mg per 100 cc. The van den Bergh reaction was negative, the cephalin flocculation test was negative. The calcium was 9.6 mg, and the phosphorus 4.6 mg per 100 cc and the alkaline phosphatase 6.6 Bodansky units.

The patient was prepared for exploration by 12 gm of sulfasuxidine and 2 gm of sulfadiazine daily (as urinary antiseptic), transfusion and Miller-Abbott intubation. The white-cell count rose to 13,400 on the thirteenth hospital day, when

a urine culture was positive for colon bacilli and *Staphylococcus aureus*. On the seventeenth hospital day he was drowsy, and an emergency non-protein nitrogen was 116 mg per 100 cc. The operation was cancelled, and the Miller-Abbott tube withdrawn. He continued to be lethargic and apathetic, and at 1:30 a.m. of the eighteenth day he went into sudden collapse and died.

#### DIFFERENTIAL DIAGNOSIS

**DR. RICHARD B. CATTELL\*** This man's past history evidently had little to do with the present findings and complaints. There are two things that we can begin with in this case: he was in the cancer age, at sixty-two, and this is supposed to be a conference for the New England Cancer Society. I think Dr. Cabot always said that if one is frequently out on a limb the percentage diagnosis is the one to take. We will assume it is cancer.

In the past history it is stated that he had a diverticulum of the cecum. This is exceedingly rare. Dr. Castleman will tell you how many cases they have in their files.

**DR. BENJAMIN CASTLEMAN** I do not believe I have ever seen one.

**DR. CATTELL** That bears out my impression. This man had syphilis, syphilitic heart disease, aortic regurgitation and hypertensive heart disease and probably, as indicated by the x-ray film, dilatation of the aorta. He did not have a palpable mass at any time. He could localize the symptoms in the left upper quadrant, and there are certainly lesions that occur in this region. The findings in the gastrointestinal tract were all negative except for guaiac-positive stools on the second examination, which should exclude involvement of the stomach or colon, although a positive guaiac reaction can occur without an actual ulcerative lesion. On this admission there was a new blood finding—myeloblasts were found in the sternal marrow. This was a terminal blood condition and was not, in my opinion, myeloblastic leukemia, although that is a definite possibility.

I think from all we have pointed out here in the way of symptoms that we have a lesion in the retroperitoneal area, probably not involving the pancreas or if it did involve the body or tail of the pancreas it extended to involve other organs as it became progressive. With carcinoma of the body of the pancreas "in the silent area" where few symptoms are produced, the commonest symptom in our experience is pain in the back, not in the left upper quadrant but in the back, that usually passes over to involve the other side. The second group of symptoms is entirely missing in this history, and that is the usual presence of bowel symptoms, which are characteristic of any pancreatic lesion that involves and obstructs the duct of Wirsung. We have had 165 carcinomas of the pancreas since

\*Member, Department of Surgery, Lacey Clinic, Boston.

- 136 Ochsner, A and Dehaquey, M Surgical considerations of achalasia review of literature and report of three cases *Arch Surg* 41 1146-1183 1940
- 137 Clagett O T, Moersch H J and Fisher, A Esophagogastrostomy in treatment of cardiospasm *Surg Gynec & Obst* 81 440-445, 1945
- 138 Schiebel H M Treatment of esophageal achalasia or cardiospasm report of four patients treated surgically *Surgery* 20 558-570 1946
- 139 Grimson K S, Reeves R J, Trent J C and Wilson A D Treatment of patients with achalasia by esophagogastrostomy *Surgery* 20 94-103 1946
- 140 Sweet R H Idiopathic dilatation of esophagus *S Clin North America* 27 1128-1135 1947
- 141 Kay E B Surgical treatment of cardiospasm. *Ann Surg* 127 34-39 1948
- 142 Gill D C and Child C G III Esophagogastrostomy in treatment of cardiospasm *Surgery* 23 571-583 1948
- 143 Scott W J M Idiopathic dilation of esophagus differentiation of clinical types and successful operation in intractable cases *Ann Surg* 122 582-605 1945
- 144 Olsen, A M and Harrington S W Esophageal hiatal hernias of short esophagus type etiology and therapeutic considerations *J Thoracic Surg* 17 189-209 1948
- 145 Allison P R Peptic ulcer of esophagus *J Thoracic Surg* 15 308-317, 1946
- 146 Dey, F L, Gilbert, N C, Trump R and Roskelley, R C Reflex shortening of esophagus in experimental animal with production of esophageal hiatus hernia *J Lab & Clin Med* 31 499-506 1946
- 147 Clark D E and Adams W E Transthoracic esophagogastrostomy for benign strictures of lower esophagus *Ann Surg* 122 942-953, 1945
- 148 Sweet, R H Repair of hiatus hernia of diaphragm by supra-diaphragmatic approach technique and results *New Eng J Med* 238 649-653 1948
- 149 Soutter L Analysis of cases of hiatus hernia treated by surgery at Massachusetts General Hospital *S Clin North America* 27 1121-1127 1947
- 150 Harrington, S W Surgical treatment of more common types of diaphragmatic hernia esophageal hiatus traumatic, pleuropulmonary hiatus, congenital absence and foramen of Morgagni report of 404 cases *Ann Surg* 122 546-568 1945
- 151 Haight, C Discussion of Lyon G and Johnson S G Discussion of congenital esophageal atresia and tracheoesophageal fistula. *J Thoracic Surg* 17 162-177 1948
- 152 Idem Congenital atresia of esophagus with tracheoesophageal fistula *Ann Surg* 120 623-655 1944
- 153 Ladd W E and Swenson O Esophageal atresia and tracheoesophageal fistula *Ann Surg* 125 23-40 1947
- 154 Swenson O End-to-end anastomosis of esophagus for esophageal atresia *Surgery* 22 324-334 1947
- 155 Lam C R Further experiences in surgical treatment of congenital atresia of esophagus with tracheo-esophageal fistula *Surgery* 20 174-179, 1946
- 156 Sweet, R H New method of restoring continuity of alimentary canal in cases of congenital atresia of esophagus with tracheoesophageal fistula not treated by immediate primary anastomosis. *Ann Surg* 127 757-768 1948
- 157 Watson W L Pulmonary arteriovenous aneurysm new surgical disease *Surgery* 22 919-929 1947
- 158 Bisgard J D Pulmonary cavernous hemangioma with arteriovenous fistula surgical management. case report. *Ann Surg* 126 965-972 1947
- 159 Wodehouse G E Hemangioma of lung review of four cases including two not previously reported one of which was complicated by brain abscess due to *H influenzae* *J Thoracic Surg* 17 405-415 1948
- 160 Maier H C, Hummelstein A, Riley R L and Bunin J J Arteriovenous fistula of lung *J Thoracic Surg* 17 13-26 1948
- 161 Maier H C Bronchiogenic cysts of mediastinum *Ann Surg* 127 476-502 1948
- 162 Byron F V, Alling E E, and Samson P C Intrathoracic meningocele Paper presented at meeting of American Association for Thoracic Surgery, 1948
- 163 Watson W L and James A G Fascia lata grafts for chest wall defects *J Thoracic Surg* 16 399-406 1947
- 164 Maier H C Surgical management of large defects of thoracic wall. *Surgery* 22 169-178 1947
- 165 Carr D and Chandler H Dorsal sympathetic ganglionectomy for intractable asthma *J Thoracic Surg* 17 1-12 1948

## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

TRACY B MALLORY, M D, *Editor*

BENJAMIN CASTLEMAN, M D, *Associate Editor*

EDITH E PARRIS, *Assistant Editor*

### CASE 34511\*

#### PRESENTATION OF CASE

*First admission* A sixty-two-year-old Negro janitor entered the hospital complaining of left-upper-quadrant pain of three weeks' duration.

Five months previously the patient developed a nonradiating, dull pain in the left upper quadrant, which responded quickly to the bland diet on which he was placed. Recurring three weeks before admission this pain became increasingly severe and was especially bad after the evening meal and during the night. He had no other digestive complaints except mild constipation. There

was a 20-pound weight loss during these three weeks.

Nineteen years before admission he had had an excision of the cecum and appendix, with side-to-side ileocolostomy for diverticulitis of the cecum. Eight years before admission he received a one-year course of intramuscular injections following the detection of a positive serologic test at another hospital. He had been aware of high blood pressure and a heart murmur for two years, without specific cardiovascular symptoms. He had an increase of nocturia from one to four or five times during the month before entry.

Physical examination showed a tall, thin man who had water-hammer pulses, a blood pressure of 210 systolic, 50 diastolic, and a heart enlarged to the sixth interspace in the anterior axillary line. The aortic second sound was increased over the pulmonic second sound. Grade III aortic diastolic and Grade I apical systolic murmurs were heard. The abdominal aorta was prominent. No masses were felt.

Examination of the blood revealed a white-cell count of 7400, with 80 per cent neutrophils. The hemoglobin was 13 gm. A blood Hinton test was negative. The urine concentrated to 1028 and gave a + test for albumin, and there was a rare red blood cell, white blood cell and cellular cast per high-power field. The stool was guaiac negative.

\*Presented at a meeting of the New England Cancer Society held at the Massachusetts General Hospital.

region. There was also a metastasis within the liver and one to the serosa of the stomach. On microscopical section the cells tended to be quite spindle shaped and in some places were composed of dense collagen. The appearance was most consistent with a fibrosarcoma, probably of neurogenic origin, that had involved both sides of the abdomen. The cells in many places were very atypical with numerous mitoses, and it seems to me that he could not have had a tumor as wild as this for a long time. The fact that the tumor occurred on both sides would be in favor of some form of neurogenic tumor perhaps arising from neurofibromas. There were no metastases to the lung. Pressure on the ureters perhaps accounted for some degree of the pyelonephritis and probably was the cause of the elevated nonprotein nitrogen toward the end. An incidental finding was the presence in the second and third lumbar vertebrae of grayish-white tissue, not at all connected with the tumor in the retroperitoneal space, that the prosector thought was another metastasis but, on microscopical examination, proved to be a chordoma. It was just picked up on routine sectioning of the vertebral column. I do not believe it produced any symptoms. I wonder if Dr. Robbins can possibly see it in these x-ray films.

DR. LAURENCE L. ROBBINS: Certainly the density of the lumbar vertebrae is increased, but I do not remember a chordoma doing that.

DR. CASTLEMAN: It was very soft.

DR. ROBBINS: I would not be able to make a definite diagnosis of the lesion.

DR. CATTELL: You cannot see anything in the right or left adrenal gland?

DR. ROBBINS: No.

## CASE 34512

### PRESENTATION OF CASE

*First admission.* A thirteen-year-old girl was admitted to the hospital complaining of a dry, persistent cough.

At the onset of the dry cough three years before admission nasal polyps were found. The cough continued following polypectomy. Several months later her tonsils and adenoids were removed, as were recurrent nasal polyps, without improving the chronic cough. Ten weeks before admission the cough became severe and was accompanied by large amounts of greenish-yellow, foul-smelling sputum. Vomiting followed severe paroxysms of coughing. She complained of headache and abdominal pain. She lost 13 pounds during this period. Five days before admission the temperature was 102°F.

The patient was the fifth of five children. Two older siblings, twenty-six and seventeen years old, were well. One sibling had died at the age

of eight months from pneumonia which had been present for a long time. Another had died at the age of eight weeks of vomiting, which had been present since birth.

The patient had been born at term following an uneventful pregnancy. The birth weight was 9 $\frac{3}{4}$  pounds. Development during the first ten years of life was similar to that of her siblings except that she was slightly obese. Since infancy she had been a voracious eater, and the stools were always large and bulky. She had had measles, chicken pox, mumps and German measles, and in each case apparently recovered without aftereffects. She had annual winter colds with cough from early childhood on, which tended to last all winter and were more severe than the other siblings' colds.

Physical examination showed a poorly developed and undernourished girl, with wasting of the buttocks and extremities. The right anterior chest was prominent, and the fingers and toes were clubbed. The chest was emphysematous and hyperresonant, with diffuse, dry rales throughout. The abdomen was round, protuberant and tympanic with active peristalsis. The liver and spleen were questionably enlarged. A white, glistening mass obstructed the right nares. The weight was 26.7 kg, and the height, 153 cm.

The temperature was 101°F, the pulse 110, and the respirations 20. The blood pressure was 90 systolic, 60 diastolic.

The urine was normal, the stools were light, foul smelling and fatty. The fat percentage of dry weight was 21.4. The stool nitrogen was 5.2 gm in twenty-four hours. The white-cell count was 23,600, with 68 per cent neutrophils, 28 per cent lymphocytes and 4 per cent monocytes. The hemoglobin was 12.2 gm. The reticulocyte count was 0.8 per cent. The fasting blood sugar was 67 mg per 100 cc. The total protein was 6.9 gm per 100 cc. The prothrombin time was normal, the cephalin flocculation test was +++ in twenty-four and forty-eight hours. The bromsulfalein test was normal. The vitamin A tolerance test showed a fasting level of 0.1 units per cubic centimeter (carotenoids) and 0.1 units per cubic centimeter (vitamin A). Five hours after a test dose of oil-soluble vitamin A the levels were 0.1 and 0.6 units per cubic centimeter. The calcium was 8.3 mg per 100 cc, and the phosphorus 3.6 and the alkaline phosphatase 8.6 units.

X-ray study of the chest demonstrated increased lateral and anteroposterior chest diameters and a low diaphragm (Fig 1). Throughout both lungs there was irregular, strand-like, parenchymal density (Fig 2). Clouding of all the nasal sinuses was found. The bones of the lumbar spine, pelvis, hands and wrists showed moderate generalized decalcification. The bone age was not retarded. Throat cultures demonstrated a varied flora on consecutive examination. Friedländer's bacillus,

August, 1942 They usually begin with bowel symptoms caused by decreased pancreatic enzymes available in the bowel No bowel symptoms were present in this patient, but this is possible with carcinoma of the body and tail, particularly if a portion of the pancreas remains available to furnish the external pancreatic enzymes through the duct of Wirsung into the duodenum I do not believe we have an ulcerative lesion that involves or invades the gastrointestinal tract, although one can see this with a lesion in this location, with involvement of the first portion of the jejunum as well as the more common lesions of the pancreas that ulcerate into the second portion of the duodenum There are some things inconsistent with pancreatic primary neoplasm There is no evidence that this was one of the tumors arising in the islands of Langerhans There was no change in metabolism of glucose About 30 per cent of these were carcinoma in our experience at the time the patients were operated on So we would consider this to be a primary lesion arising in the tail or body of the pancreas, with gradual extension The pain of carcinoma of the pancreatic body may be relieved by leaning forward and is characteristically found Whoever saw this patient and took this history was impressed with that one clinical fact

The other diagnosis we have to consider is kidney neoplasm This can reasonably be excluded Would you like to show the x-ray films?

DR CASTLEMAN The only x-ray films available are those taken between the first and second admissions and these are all normal

DR CATTELL A definitely ulcerated lesion in the region of the ampulla of Vater may occasionally be demonstrated by roentgenographic means In carcinoma of the body of the pancreas one may see displacement of the stomach upward, and sometimes can see evidence of displacement of the ligament of Treitz If this is a large retroperitoneal tumor, the commonest ones are neurofibroma, fibrosarcoma, leiomyosarcoma and lipomyosarcoma We ought to be able to feel a mass and see displacement of the kidney, stomach, small bowel or colon I do not believe this is a retroperitoneal tumor because of the rapid progression to death

DR RALPH E MILLER What do you think this blood picture was due to?

DR CATTELL I know very little about hematologic findings I would think it was a terminal state in a failing patient due to marked stimulation of the marrow I do not believe he had a myelogenous leukemia

DR MILLER Do you think it consistent with extreme metastases to the liver from a carcinoma?

DR CATTELL I do not believe so from the findings, although it might well be

DR GRANTLEY W TAYLOR Did you consider an aortic aneurysm in the differential diagnosis? He had a background of syphilis

DR CATTELL As I read the report I considered it seriously but threw it out on the basis of my first remarks

A PHYSICIAN How about the barium enema? Was that negative?

DR CASTLEMAN It was reported as negative.

A PHYSICIAN On the first admission?

DR CASTLEMAN Yes

DR KNOWLES B LAWRENCE I would suggest carcinoma of the splenic flexure with complications

DR CATTELL That is a definite possibility, but the barium enema was negative

DR THOMAS J ANGLE For how many days was sulfadiazine given?

DR CASTLEMAN For six days during the last admission

DR JOSEPH ROSS Is there any implication of the report of myeloid hyperplasia at the biopsy?

DR CASTLEMAN I think it meant hyperplasia of the myeloid elements but no myeloma

DR CATTELL That was my interpretation

DR CASTLEMAN Just a shift to the left

#### CLINICAL DIAGNOSIS

Carcinoma of pancreas

#### DR CATTELL'S DIAGNOSIS

Carcinoma of body of pancreas

#### ANATOMICAL DIAGNOSES

*Retroperitoneal fibrosarcoma, bilateral, with involvement of both adrenal glands and with metastases to liver and stomach*

*Chordoma of lumbar vertebrae*

#### PATHOLOGICAL DISCUSSION

DR CASTLEMAN The clinical impression was the same as Dr Cattell's that the patient had carcinoma of the pancreas One opinion reads as follows

This sixty-two-year-old man with syphilitic heart disease has left-upper-quadrant pain of about two months' duration, associated with weight loss and occasional vomiting. All x-ray examinations have failed to disclose the site of the lesion in the abdomen, so the tail of the pancreas has been considered as the site of a neoplasm The history of constipation of two years' duration, worse in recent months, suggests a colonic lesion (carcinoma of the splenic flexure), but the barium enema was negative I agree that laparotomy is now indicated and will not be surprised to find a retroperitoneal tumor in the left upper quadrant, with possibly a lymphoma, or no intra-abdominal disease

At autopsy the patient had a retroperitoneal tumor, a very malignant tumor, and its distribution was rather unusual It involved both sides of the abdomen The larger mass was located in the region of the right adrenal gland, completely obliterating it, and extending into the liver on that side as well as invading into a portion of the terminal ileum There was a similar but smaller tumor on the left side involving a portion of the left adrenal gland and extending into the tissues around that

increase in the anteroposterior diameter of the chest. There is no detectable enlargement of the heart, and no fluid is present in the costophrenic sinuses.

Examination of the chest made five months after admission shows a slight increase in the pulmonary involvement particularly in the apical segments.

The final examination of the chest made nine months after the first admission discloses a definite progression of the pulmonary changes. The focal areas of increased density are more marked. There is more emphysema, as shown by further flattening of the diaphragm. An additional finding at this time is a slight prominence of the right ventricle as seen on the lateral film.

The films of the paranasal sinuses are of considerable interest. They show almost complete obstruction of the nasal fossa by a polypoid soft-tissue mass. Marked thickening of the mucous membrane, with polypoid change, is seen in the maxillary, ethmoid and sphenoid sinuses. The frontal sinuses remain clear.

DR ROSS: Do you think there is alveolar involvement in the final film?

DR MCCORT: There are irregular patches of density in the peripheral lung. We cannot be certain whether they are atelectatic lobules or cellular infiltration of the alveoli.

DR ROSS: In arriving at this inevitable diagnosis we get help from the family history of one infant with chronic pulmonary disease, lasting eight months and ending in death, presumably, the same disease. An eight-week-old infant dying after persistent vomiting suggests, again without proof, that one child died of meconium ileus, a condition that has been described in association with cystic fibrosis of the pancreas in the newborn period. We know that the condition is commonly a familial, congenital disease. The persistent symptoms from early childhood—the voracious appetite, with rapid growth and apparent obesity—mean, I think, that this child met the requirement for growth by eating tremendous quantities, more than the average person, although a good deal was not absorbed as evidenced by the bulky, foul stools. The final occurrence of severe, persistent respiratory disease fills out the picture. The laboratory data of low serum calcium, the osteoporosis and the low vitamin A and carotenoids all indicate poor fat absorption. The absent tryptic enzyme activity shows that there was no pancreatic juice passing into the duodenum. The enlargement

of the liver, with the suggestively positive cephalin flocculation test, also suggests the possibility of some cirrhotic changes in the liver, which have been described in pancreatic fibrosis. However, the final enlargement of the liver on the last admission suggests more to me right-sided heart failure due to prolonged pulmonary emphysema.

Pancreatic fibrosis in a thirteen-year-old child is unusual. Most of the cases previously presented in these gatherings have been in young infants or in children just above the age of infancy. There have been cases reported sporadically in the literature of older children—none older than fourteen and a half years. The striking situation here is the late onset of the alarming symptoms—the alarming symptoms being due not to nutritional deficiency but to infection of the respiratory tract.

The best that could be done with chemotherapy was to control the infection. The underlying disease of the mucous membranes indicated by polyps and progressive emphysema, with probable fibrosis in the lungs, was not controlled—the use of various chemotherapeutic agents caused the change from one pathogen to another, without finally being able to keep ahead of the disease. My diagnosis is, therefore, pancreatic fibrosis. Dr Reversbach may have some comments about our present experience with this disease.

DR GERTRUD C. REYERSBACH: We have followed a number of children with this disease. The oldest we have is twelve and a half years old, having had diarrhea since birth and respiratory symptoms for five years. The next is ten years old and has had bulky stools since birth, respiratory symptoms starting at four years. Both these children have been treated with penicillin, streptomycin, and one also with a diet and pancreatin. We wonder whether we have helped these children to survive by therapy. When we go back to the literature we find quite a number of cases exactly the same as this in which the patients survived without therapy. Thus, the question whether our therapy helps is doubtful.

Our experience with treating the respiratory infection, which seems to be the lethal factor, has been disappointing. We are able to treat the *Staph aureus*, the causative agent of the infection, generally found at first and quite successfully for a time. Then the staphylococcus is replaced by gram-negative organisms: *B. pyocyaneus*, colon bacillus and so forth. We add streptomycin in the

*Staphylococcus aureus* and beta-hemolytic streptococcus. Two duodenal aspirations showed no tryptic enzyme activity.

The temperature and cough subsided on sulfadiazine and aerosol penicillin. The appetite was good. She was discharged after one month of hospitalization.

**Second admission** (four months later). During the first month after discharge sulfadiazine was continued at home, and the patient felt well. Fol-

lowing its discontinuance her condition was stabilized for a few weeks, but gradually recurrent cough, fever, weight loss and large, foul, frothy stools, averaging three or four each day, appeared. The physical signs were similar to those on the previous admission. On aerosol penicillin and streptomycin the symptoms subsided, and she was discharged one month after admission.

**Third admission** (three months later). Complaints and findings were similar to those on the second admission. There was some improvement on aerosol penicillin. She was discharged two weeks after admission.



FIGURE 1

**Final admission** (one month later). For a few days preceding admission she became febrile, chilly, cyanotic, dyspneic and orthopneic, and she had paroxysms of productive cough. On examination she was cyanotic. There was a small area of dullness and diminished breath sounds in the right base. The chest was otherwise hyperresonant. The liver edge was palpable two fingerbreadths below the costal margin. The temperature was

#### DIFFERENTIAL DIAGNOSIS

**DR RALPH A. ROSS:** This story has all the stark, grim inevitability of a Greek tragedy. The patient had a family history of two siblings who died in infancy, one of chronic infection and the other of neonatal intestinal obstruction. The patient herself had a history of a large appetite throughout life, even in the midst of acute illness, bulky stools, with severe respiratory infection from childhood.



FIGURE 2

and with cough and nasal polyps since ten years of age. Physical examination disclosed malnutrition, a protuberant abdomen and emphysema, with clubbing, in addition to x-ray findings, which were apparently those of general pulmonary involvement leading to a sum total of what we call cystic fibrosis of the pancreas.

May we see the x-ray films?

**DR JAMES J. McCORT:** An examination of the chest made on admission shows a patchy and mottled increase in density throughout both lung fields. Within this there are numerous radiolucent areas. The diaphragm is flat, and there is an

usual picture of cystic fibrosis of the pancreas seen in infancy. Whether it is possible for the latter to develop to the stage of complete disappearance of acinar tissue I have not the experience to say. Dr Sidney Farber informs me that he does believe it is possible.

The lungs showed the characteristic picture that we see in cystic fibrosis. They were very large; the entire bronchial tree was filled with rather inspissated purulent secretion. There was emphysema beyond the obstructed bronchi and the infection had extended here and there into the alveolar lumens, but the great majority was still in the bronchi.

The organ that interested me most was the liver. This was greatly enlarged, weighing 2000 gm, which would be large for the liver of an adult and was extremely large for this child. It was very fatty (Fig 4) as one would expect to find the liver of an animal that had a total pancreatectomy and had been kept alive with insulin — the type that Chaikoff<sup>1</sup> and Best<sup>2</sup> and various others have described. There was cirrhosis but not a portal cirrhosis, which develops from the lack of pancreatic secretions but a very clear-cut, biliary cirrhosis. All the small bile ducts were filled with plugs of inspissated material tinged with bile although not consisting primarily of bile pigment (Fig 5). I feel quite sure that the actual cirrhotic process was due to plugging of the bile ducts and was biliary in type. The fat infiltration, in contrast, might be traced to deficiency of pancreatic external secretion and had nothing to do with the development of the cirrhosis.

DR BUTLER: In Best's experimental animals he got fatty livers first, and then the cirrhosis seemed to come and replace the fatty liver, so that at one stage there was fatty liver and at a later stage cirrhosis.

DR ROSS: Has this been seen in infants?

DR REYERSBACH: Yes, it has. It is of interest because the clinical pictures vary so much in infants and in children in the same family — three siblings with the same disease — one dies at six months,

the next one at six years, and the next at ten, twelve or fourteen years. Going through the autopsy reports and the literature, I happened to find that the condition described today has been found at least four times in infants as well as in children aged four or more.<sup>3</sup> Whether that is different from the usual fibrosis of the pancreas I do not know.

DR MALLORY: In the case reported by Siwe<sup>4</sup> the pancreatic lesion was apparently entirely similar to that in this case — complete replacement of



FIGURE 5

acinar cells with adipose tissue and persistence of the islands of Langerhans. He interpreted it as agenesis of the acinar tissue. His case also showed cirrhosis of the liver but as far as I can judge from his illustrations and description it was portal rather than biliary in type.

#### REFERENCES

- 1 Chaikoff I L, Connor C L and Biskind G R. Fatty infiltration and cirrhosis of liver in depancreatized dogs maintained with insulin. *Am J Path* 14:101-110, 1958.
- 2 Best C H, Channon H J and Ridout J H. Choline and diet in production of fatty livers. *J Physiol* 81:403-421, 1934.
- 3 Andersen D H. Cystic fibrosis of pancreas and its relation to celiac disease: clinical and pathologic study. *Am J Dis Child* 56:344-399, 1958.
- 4 Siwe S A. Über die exokrine Funktion des Pankreas und die Folgen ihres Wegfalles: ein Fall von fast toaler Agenesie des exokrinen Teiles des Pankreas. *Deutsches Arch f. klin. Med.* 173:559-585, 1952.

course of the disease. Often, all the organisms become drug resistant. We may have given this child help in combating the infection and may have prolonged life, but we have not made any definite changes.

DR. TRACY B. MALLORY: The experience is almost exactly similar to that of treating bronchiec-

tasis with chemotherapeutic agents. One can change the bacterial flora very readily. One gets rid of the staphylococcus only to have it replaced with the colon bacillus. Whether the agents serve any useful purpose is very doubtful.

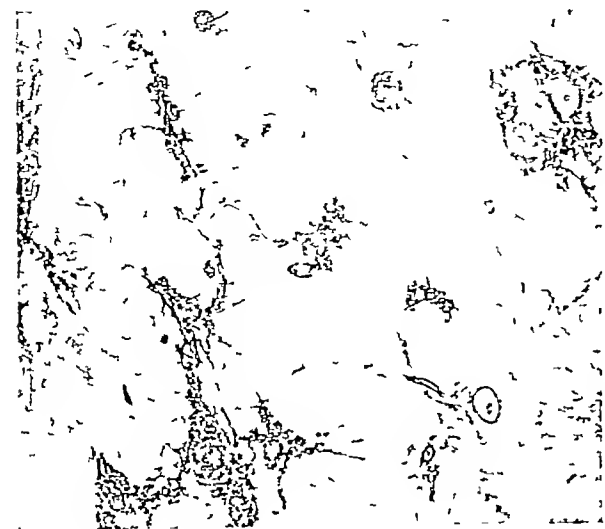


FIGURE 3

tasis with chemotherapeutic agents. One can change the bacterial flora very readily. One gets rid of the staphylococcus only to have it replaced with the colon bacillus. Whether the agents serve any useful purpose is very doubtful.

DR. ALLAN M. BUTLER: Your mention of bronchiectasis brings up the connection between a patient such as this and the group of cases Dr. Churchill's service has been interested in, characterized by nasal polyps, underdevelopment of the sinuses, chronic sinusitis, bronchiectasis and status inversus. What is the difference in the bronchiectasis of this group, who have no pancreatic fibrosis, as far as I know, and of patients with pancreatic fibrosis?

I do not know whether you found cirrhosis of the liver at post-mortem examination of this patient, but our findings on the ward made it suspect. It reminds one of the experience of Dr. Best with depancreatized dogs developing cirrhosis of the liver. Such cirrhosis could be prevented by the administration of choline or methionine. It is odd that in many patients who have no external secretions of the pancreas so little cirrhosis of the

#### CLINICAL DIAGNOSIS

Pancreatic fibrosis

#### DR. ROSS'S DIAGNOSES

Fibrosis of pancreas

Chronic pulmonary infection

Cor pulmonale?

Cirrhosis of liver?

#### ANATOMICAL DIAGNOSES

*Atrophy of acinar tissue of pancreas, complete*

*Bronchitis, chronic*

*Emphysema*

*Fat infiltration of liver, severe*

*Biliary cirrhosis of liver*

#### PATHOLOGICAL DISCUSSION

DR. MALLORY: We found very severe pancreatic disease, but there were no cysts and not a great

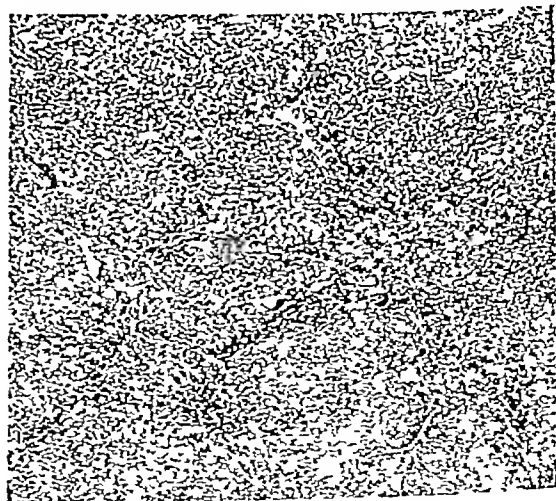


FIGURE 4

deal of fibrosis. There was a small, fibrous area close to the head of the pancreas in about the spot where the pancreatic duct should have been, but we were entirely unable to identify the pancreatic duct. The remainder of the pancreas consisted of fatty tissue (Fig. 3) and islands of Langerhans that looked normal. There were no acinar cells left, so that the microscopical appearance was essentially what one sees following ligation of the main pancreatic duct and did not resemble the

usual picture of cystic fibrosis of the pancreas seen in infancy. Whether it is possible for the latter to develop to the stage of complete disappearance of acinar tissue, I have not the experience to say. Dr Sidney Farber informs me that he does believe it is possible.

The lungs showed the characteristic picture that we see in cystic fibrosis. They were very large, the entire bronchial tree was filled with rather inspissated, purulent secretion. There was emphysema beyond the obstructed bronchi and the infection had extended here and there into the alveolar lumens, but the great majority was still in the bronchi.

The organ that interested me most was the liver. This was greatly enlarged, weighing 2000 gm., which would be large for the liver of an adult and was extremely large for this child. It was very fatty (Fig 4) as one would expect to find the liver of an animal that had a total pancreatectomy and had been kept alive with insulin — the type that Chaikoff<sup>1</sup> and Best<sup>2</sup> and various others have described. There was cirrhosis but not a portal cirrhosis, which develops from the lack of pancreatic secretions, but a very clear-cut, biliary cirrhosis. All the small bile ducts were filled with plugs of inspissated material tinged with bile, although not consisting primarily of bile pigment (Fig 5). I feel quite sure that the actual cirrhotic process was due to plugging of the bile ducts and was biliary in type. The fat infiltration, in contrast, might be traced to deficiency of pancreatic external secretion and had nothing to do with the development of the cirrhosis.

DR BUTLER: In Best's experimental animals he got fatty livers first, and then the cirrhosis seemed to come and replace the fatty liver, so that at one stage there was fatty liver and at a later stage cirrhosis.

DR ROSS: Has this been seen in infants?

DR REYERSBACH: Yes, it has. It is of interest because the clinical pictures vary so much in infants and in children in the same family — three siblings with the same disease — one dies at six months,

the next one at six years and the next at ten, twelve or fourteen years. Going through the autopsy reports and the literature I happened to find that the condition described today has been found at least four times in infants as well as in children aged four or more.<sup>3</sup> Whether that is different from the usual fibrosis of the pancreas, I do not know.

DR MALLORY: In the case reported by Siwe<sup>4</sup> the pancreatic lesion was apparently entirely similar to that in this case — complete replacement of



FIGURE 5

acinar cells with adipose tissue and persistence of the islands of Langerhans. He interpreted it as agenesis of the acinar tissue. His case also showed cirrhosis of the liver, but as far as I can judge from his illustrations and description it was portal rather than biliary in type.

#### REFERENCES

- 1 Chaikoff I L, Connor C L and Biskind G R. Fatty infiltration and cirrhosis of liver in depancreatized dogs maintained with insulin. *Am J Path* 14:101-110, 1958.
- 2 Best C H, Channon H J and Ridout J H. Choline and dietary production of fatty livers. *J Physiol* 81:409-421, 1954.
- 3 Andersen D H. Cystic fibrosis of pancreas and its relation to celiac disease: clinical and pathologic study. *Am J Dis Child* 56:344-399, 1958.
- 4 Siwe S A. Über die exokrine Funktion des Pankreas und die Folgen ihres Wegfalles: ein Fall von fast totaler Agenesie des exokrinen Teiles des Pankreas. *Deutsches Arch f klin Med* 173: 9-28, 1952.

# The New England Journal of Medicine

Formerly •

The Boston Medical and Surgical Journal

Established 1828

Official Organ of

THE MASSACHUSETTS MEDICAL SOCIETY

and

THE NEW HAMPSHIRE MEDICAL SOCIETY

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND

PUBLISHED WEEKLY UNDER THE JURISDICTION OF THE

COMMITTEE ON PUBLICATIONS

James P. O'Hare, M.D. Richard M. Smith, M.D., *Chairman*  
Oliver Cope, M.D. Conrad Wesselschoeff, M.D.  
John Fallon, M.D.

Joseph Garland, M.D., *Editor*

ASSOCIATE EDITORS

Thomas H. Laoman, M.D. Donald Munro, M.D.  
Henry Jackson, Jr., M.D.

Clara D. Davies, *Executive Editor*

Robert O'Leary, *Assistant Editor*

EDITORIAL BOARD

C. Guy Laoc, M.D.	Maxwell Finlaid, M.D.
Henry R. Viets, M.D.	James M. Faulkner, M.D.
Robert M. Greco, M.D.	Carroll B. Larson, M.D.
Dwight O'Hara, M.D.	Francis D. Moore, M.D.
Fletcher H. Colby, M.D.	C. Stuart Welch, M.D.
Robert L. Goodale, M.D.	Vernon P. Williams, M.D.
Chester M. Jones, M.D.	Benjamin Castleman, M.D.
Harvey R. Morrison, M.D.	Hugh R. Leavell, M.D.

**SUBSCRIPTION TERMS** \$7.00 per year in advance, postage paid for the United States (medical students \$4.00 per year) Canada \$8.00 per year (Boston funds) \$9.50 per year for all foreign countries belonging to the Postal Union

MATERIAL should be received not later than 0000 on Thursday, three weeks before date of publication

THE JOURNAL does not hold itself responsible for statements made by any contributor

COMMUNICATIONS including those concerning classified advertising but not those regarding other advertising should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts. Telephone KE 6-2094

NEW ENGLAND ADVERTISING REPRESENTATIVE (except for classified advertising) Edwin B. Tyler, 89 State Street, Boston, Massachusetts. Telephone LA 3-5516

## ONE WORLD

THE relations of human beings, one with another, too often represent the very extremes of human conduct. Bitterness and hate and cruelty as expressed by individuals and nations and races is thrown into sharp contrast with those great emotional surges of tenderness and compassion that at other times may animate almost all men and seem at all times to animate some of them.

The consciences and the emotions of the common people of a nation tend in the main to direct their thoughts and activities into the channels of compassion. Thus the people of this country, coldly as they may sometimes have been viewed by their fellow citizens of a world drawn closer together by mutual interdependence and swift travel, still pride

themselves on their generosity and their feeling of good will toward the common people of all other nations.

Aside from the vast gifts that national policy has dictated should be put into the hands of the Wise Men for distribution to our stricken neighbors, there has been a constant flow of more spontaneous, if lesser, offerings of good will to all those who suffer and who could be reached.

The air bridge to Berlin has carried more than food for the mouths and coal for the bins of our recent enemies and present wards, it has carried good will in a franker form to the children of that city under siege as a spontaneous expression of kindness and generosity on the part of American airmen.

Santa Claus in numerous guises and directing a variety of carriers, working in all seasons and without vacation, has delivered a continuous stream of freely offered gifts from these shores to all available quarters of the globe. And yet these earnestness of good intention on the part of a people conscious of its own favorable situation represent but one manifestation of a general good feeling that needs only the opportunity to prevail. Various religious and sociologic organizations have this year held meetings on an international plane, not the least among them being the World Council of Churches, the World Health Organization and the World Medical Association. The United Nations stand ready to hang a Christmas wreath on the door of nearly every country in the world and even, with some trepidation, to pin one upon the Iron Curtain itself.

The United States, at long last, has officially admitted and sincerely welcomed a new band of pilgrims to set foot upon her shores—at the Thanksgiving season, with fitting symbolism. May their Christmas in a new land be a happy one, and may this land fulfill the promises of freedom and opportunity that it has so far seemed to these displaced persons to offer!

Each year at this time it is well to remember that good will is communicable, that if enough people wish it "Earth shall be fair and all her people one", that through their will they may yet see peace on earth.

## MASSACHUSETTS PHYSICIANS COMMITTEE

ON NOVEMBER 22, 1948, a group of physicians from various parts of the Commonwealth met and voted to form a Massachusetts Physicians Committee for the purpose of promoting free enterprise and the preservation of a system of private practice in medicine in this country. This committee was formed not to oppose, but to assist, not to hinder but to help, not to destroy but to build up. Believing in the same health goal, if not in the methods of reaching it, that Mr Ewing has established in his report to the President — namely, the extension of the best possible medical services to all the people of the country, — it offers its assistance in helping to achieve those ends by the best possible means.

It believes that this goal can be most nearly approximated by preserving the system of private medical practice with all the reforms and safeguards for the people that experience may suggest, by the promotion and extension of voluntary prepayment plans, and by assisting government at the most effective level in furnishing the same adequate service to those who cannot afford to bear their share of the costs.

This committee is fearful of the waste and extravagance and inefficiency that may accompany an attempt at reaching the common goal by means of any system of compulsory, tax-supported or political medicine. It is fearful of the distance that such a system, however innocuous it appears at the beginning, may eventually travel.

It does not believe, as the chairman of the Committee for the Nation's Health believes, "that national health insurance does not mean regimentation of doctors or state control, and will not interfere in any way with the doctor-patient relationship." It does agree with him that "The time has come to take the politics out of health," but it does not agree that the passage of a bill for government-controlled national health insurance will achieve that end.

Working in harmony with the organized profession of medicine and with all other healthy inter-

ests, it invites the help of the physicians of the Commonwealth in studying these matters of general concern, in enlightening the public and in lending all the aid possible to the Government and the people in establishing the health care of the nation on a secure basis.

---

## UNDERGRADUATE INSTRUCTION IN ALLERGY

A COMPREHENSIVE survey has clearly demonstrated that satisfactory instruction in allergy is not being provided in the majority of the leading medical schools today. New England institutions, unhappily, prove no exception to the rule. This conclusion is based upon the results of a questionnaire<sup>1</sup> returned by sixty-six schools, less than half of which were found to have an acceptable minimal curriculum in allergy.

Should such an observation call forth the comment "why bother our students about sneezes, wheezes and itches," the answer seems clear. Few can deny that many young internists have completed their medical training with little or no contact with allergy or allergic thought.<sup>2</sup> Some medical and much lay opinion still classes allergy as a narrow specialty whose chief qualification is the ability to perform and the inability to interpret skin tests. On the contrary, altered reaction in general is the province of the allergist. Such a heading embraces the principles of sensitivity, of anaphylaxis, of immunology. It includes altered reactivity to proteins, bacteria, nonbacterial substances and drugs. Allergy is concerned with the practical management and pathogenesis of many diseases. It is closely interrelated with the fields of bacteriology, biochemistry, pathology, metabolism, circulatory disorders and psychosomatic medicine — in short, it is part and parcel of internal medicine.

No allergist can fulfill his maximum responsibility to his patients and to his specialty unless he has a background of sound medical training. In like manner, no internist should be regarded as well trained in internal medicine unless he is thoroughly

cognizant of the principles of anaphylaxis and allergy and of their application to medicine. It is high time that departments of medicine recognized the need of adequate undergraduate training in allergy. They should then take steps to obtain suitable facilities and to organize them in such a manner as to provide systematic and enlightened training.

#### REFERENCES

- 1 Swineford O Jr Undergraduate education in allergy, report of Subcommittee on Undergraduate Education in Allergy of American Academy of Allergy. *J A M A Coll* 21:265-270 1946
- 2 Barr D P Relationship of allergy to medicine. *J Allergy* 16:61-68, 1945

### GUIDE TO HEALTH SERVICES

A USEFUL key to the health services available in the Greater Boston area has been prepared by the Boston Health League and sent to all physicians practicing in the area. Arranged according to type of specialized service, the information it offers runs the scale from adoption and care of the aged to well-baby conferences, workmen's compensation and x-ray services.

The complexity of the facilities available in a great metropolitan area make such a handbook nearly indispensable. With the *Handbook for Physicians* published by the Massachusetts Department of Public Health, and the *Directory of Social Service Resources of Greater Boston*, emanating from the Greater Boston Community Council, it completes an invaluable triad of such guides.

### OBITUARY

#### ABRAHAM MYERSON (1881-1948)

The death of Dr Abraham Myerson on September 3, 1948, in his sixty-seventh year ended a distinguished medical service of more than thirty-five years in this community.

Dr Myerson graduated from Tufts College Medical School in 1908. After a period of practice in Boston he trained for a career in neuropsychiatry by serving as resident neurologist to Alexian Brothers Hospital in St. Louis, 1912-1913, and assistant physician to the Boston Psychopathic Hospital, 1913-1914. From 1914 to 1918 he was pathologist and clinical director of the Taunton State Hospital, from 1918 to 1920 he served as chief medical officer of the outpatient department of the Boston Psychopathic Hospital. Thus he acquired a background

and experience in neurology, neuropathology and intramural and extramural psychiatry. His teaching experiences began in St. Louis and were continued in Boston. He became professor of neurology at Tufts College Medical School and taught this subject in an inspiring manner to generations of medical students. He was clinical professor of psychiatry at Harvard Medical School. Throughout his life his interests encompassed both neurology and psychiatry. He was visiting neurologist to the Boston City Hospital, neuropsychiatrist to the Beth Israel Hospital and consultant in neurology or psychiatry to several other institutions.

Dr Myerson became interested in research early in his medical career, and for more than thirty-five years he made outstanding contributions to medical literature. Two of his early interests were syphilis of the nervous system and genetics, and to the end he continued to investigate and report on these subjects. The scope of his research interests widened greatly, encompassing the effects of social, environmental and internal stresses on the one hand and metabolic and biochemical changes concomitant to mental illness on the other. The first group of studies are found in books from his pen, namely, *The Nervous Housewife*, *Foundations of Personality* and *When Life Loses Its Zest*. Many papers appearing in the medical literature document other types of work. In recognition of his abilities and accomplishments a research building was erected at the Boston State Hospital, and, aided by a large grant from The Rockefeller Foundation, he became director of research of an active organization.

He was a member of many medical societies, served on many committees and was elected president of several. He published eight books and more than a hundred and fifty scientific papers.

These cold facts give no adequate picture of Abraham Myerson. His dynamic personality, his speaking ability, his quick wit and humor, his logical thinking, his friendliness and his devotion to social improvement, civic affairs and human rights are more to the point. He was a stimulating teacher, guide and friend to students. He was a leader of many younger colleagues in their research efforts. He was a most popular lecturer to lay groups and was ever ready to interpret psychiatry to the laity as well as to his medical colleagues.

He was strong in his opinions and fearless in his expression of them. Book reviews by Myerson were forthright, explicit and critical. Praise was not withheld when considered merited, but statements inimical to his point of view were brilliantly and vigorously attacked. He was a strong and articulate opponent of psychoanalysis. To do justice to the subject and express his opinion, he read everything written by Freud as well as a vast amount of other psychoanalytic literature, becoming

ing almost encyclopedic in his knowledge of literature on this subject

With great dynamic qualities of personality, with deep erudition and learning, with brilliance, wit and articulateness, with strong emotional devotion to good causes and with a great store of energy he was indeed a force in the medical world — local, national and international. Perhaps no better testimony of his influence is needed than the fact that his two sons follow his footsteps in neuropsychiatry and his daughter is training in psychiatric social work.

A final word about his strength of character and great spirit is due. For seven years he was aware that he had a progressive cardiac ailment. Never for an instant did he seek sympathy, never did his broad interest in science and literature diminish. Until his last hours he continued his intellectual efforts and only wondered how much he could accomplish in the brief interval before death would stop him.

H C S

## MASSACHUSETTS MEDICAL SOCIETY

### DEATHS

**BARTON** — Robert B. Barton, M.D., of Wellesley Hills, died on November 30. He was in his forty-eighth year. Dr. Barton received his degree from Boston University School of Medicine in 1926. He was a fellow of the American Medical Association.

His widow and two daughters survive.

**PAINE** — N. Emmons Paine, M.D., of Walpole, died on November 30. He was in his ninety-sixth year.

Dr. Paine received his degree from Albany Medical College in 1875. He was the founder of the Newton Sanatorium and was formerly superintendent of the Westboro State Hospital and a member of the staffs of Newton-Wellesley Hospital and Massachusetts Memorial Hospitals. He was professor emeritus of psychiatry at Boston University School of Medicine and was a fellow of the American College of Physicians and the American Psychiatric Association.

A son and two daughters survive.

**SCHWAGER** — Solomon Schwager, M.D., of Pittsfield, died on November 30. He was in his fifty-eighth year.

Dr. Schwager received his degree from New York University College of Medicine in 1917. He was a fellow of the American Medical Association.

His widow and two sons survive.

## CORRESPONDENCE

### DOCTOR DRAFT

To the Editor: The editorial entitled "Concerning the Doctor Draft," which appeared in the November 11 issue of the *Journal*, contains the following statements:

Congress's contemplated action will concern chiefly doctors who were trained under ASTP and V-12 at Government expense but were unable to complete their term of active duty. If they should be required to complete their contract in a few months of peace-time service, it would seem too reasonable a sacrifice to be fairly resented.

There are a few errors here.

In the first place, we completed our term of active duty as determined by the Army and Navy.

Secondly, we have no contract broken or otherwise with the Government. With the exception of those who volunteered for the inactive reserve, we all have certificates of honorable discharge — no strings attached.

Finally, most of my colleagues who are former ASTP S or V-12's do not resent being drafted if it is necessary. We do resent slander and lies concerning us, especially in the press.

Are you brave enough to print this in toto?

KENNETH BRUNS  
Senior Medical Student  
Formerly AS V-12 USNR

493½ Forest Park  
St. Louis, Missouri

NOTE: In a literal sense Mr. Bruns is exactly right, although careful examination fails to reveal any hint of disparagement or slander in the wording of the editorial. Certainly none was intended. "Contract" was broadly used in the sense of implied obligation to repay the Government's investment by a period of active duty. ASTP S and V-12's who have served the originally intended term of active duty are morally quits with the Government that paid their tuition; those who have not (through no fault of their own, as specified in the editorial) have certainly broken no contract. However, many of them, and apparently Mr. Bruns among them, are still conscious enough of an obligation to be willing to discharge it in full when and if the necessity arises. In this they show themselves to be patriotic, responsible and fair-minded citizens, differing in no way from the overwhelming majority of the medical profession. — Ed

## BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

*Headache and Other Head Pain*. By Harold G. Wolff, M.D., professor of medicine (neurology) and associate professor of psychiatry, Cornell University Medical College and attending physician, New York Hospital, New York. 8°, cloth, 642 pp., with 154 illustrations. New York: Oxford University Press, 1948. \$12.00 (Oxford Medical Publications.)

The author in this comprehensive book summarizes his studies of fifteen years on the subject of head pain, including migraine in all its aspects and relations. Selected bibliographies are appended to the various chapters. The publishing is well done. The book is recommended for all medical libraries and should prove valuable to all neurologists and other physicians interested in the subject.

*Voluntary Medical Care Insurance in the United States*. By Franz Goldmann, M.D. 8°, cloth, 228 pp. New York: Columbia University Press, 1948. \$3.50.

This book, a companion to *Public Medical Care*, describes and analyzes the development and present state of voluntary medical care insurance and appraises the most important types of organizations in the United States including profit, nonprofit and group plans. The volume is well published and should be in all medical public and insurance libraries.

## NOTICES

### ANNOUNCEMENTS

Dr. Harold I. Miller announces the opening of an office for the practice of general surgery at 311 Commonwealth Avenue, Boston.

Dr. Edward S. Stone announces the removal of his office from 276 to 314 Commonwealth Avenue, Boston, near Massachusetts Station, for the practice of ophthalmology.

cognizant of the principles of anaphylaxis and allergy and of their application to medicine. It is high time that departments of medicine recognized the need of adequate undergraduate training in allergy. They should then take steps to obtain suitable facilities and to organize them in such a manner as to provide systematic and enlightened training.

#### REFERENCES

1. Swineford, O. Jr. Undergraduate education in allergy: report of Subcommittee on Undergraduate Education in Allergy of American Academy of Allergy. *J A Am M Coll* 21:265-270, 1946.
2. Barr, D. P. Relationship of allergy to medicine. *J Allergy* 16:61-68, 1945.

#### GUIDE TO HEALTH SERVICES

A USEFUL key to the health services available in the Greater Boston area has been prepared by the Boston Health League and sent to all physicians practicing in the area. Arranged according to type of specialized service, the information it offers runs the scale from adoption and care of the aged to well-baby conferences, workmen's compensation and x-ray services.

The complexity of the facilities available in a great metropolitan area make such a handbook nearly indispensable. With the *Handbook for Physicians* published by the Massachusetts Department of Public Health, and the *Directory of Social Service Resources of Greater Boston*, emanating from the Greater Boston Community Council, it completes an invaluable triad of such guides.

#### OBITUARY

##### ABRAHAM MYERSON (1881-1948)

The death of Dr. Abraham Myerson on September 3, 1948, in his sixty-seventh year ended a distinguished medical service of more than thirty-five years in this community.

Dr. Myerson graduated from Tufts College Medical School in 1908. After a period of practice in Boston he trained for a career in neuropsychiatry by serving as resident neurologist to Alexian Brothers Hospital in St. Louis, 1912-1913, and assistant physician to the Boston Psychopathic Hospital, 1913-1914. From 1914 to 1918 he was pathologist and clinical director of the Taunton State Hospital, from 1918 to 1920 he served as chief medical officer of the outpatient department of the Boston Psychopathic Hospital. Thus he acquired a background

and experience in neurology, neuropathology and intramural and extramural psychiatry. His teaching experiences began in St. Louis and were continued in Boston. He became professor of neurology at Tufts College Medical School and taught this subject in an inspiring manner to generations of medical students. He was clinical professor of psychiatry at Harvard Medical School. Throughout his life his interests encompassed both neurology and psychiatry. He was visiting neurologist to the Boston City Hospital, neuropsychiatrist to the Beth Israel Hospital and consultant in neurology or psychiatry to several other institutions.

Dr. Myerson became interested in research early in his medical career, and for more than thirty-five years he made outstanding contributions to medical literature. Two of his early interests were syphilis of the nervous system and genetics, and to the end he continued to investigate and report on these subjects. The scope of his research interests widened greatly, encompassing the effects of social, environmental and internal stresses on the one hand and metabolic and biochemical changes concomitant to mental illness on the other. The first group of studies are found in books from his pen, namely, *The Nervous Housewife*, *Foundations of Personality* and *When Life Loses Its Zest*. Many papers appearing in the medical literature document other types of work. In recognition of his abilities and accomplishments a research building was erected at the Boston State Hospital, and, aided by a large grant from The Rockefeller Foundation, he became director of research of an active organization.

He was a member of many medical societies, served on many committees and was elected president of several. He published eight books and more than a hundred and fifty scientific papers.

These cold facts give no adequate picture of Abraham Myerson. His dynamic personality, his speaking ability, his quick wit and humor, his logical thinking, his friendliness and his devotion to social improvement, civic affairs and human rights are more to the point. He was a stimulating teacher, guide and friend to students. He was a leader of many younger colleagues in their research efforts. He was a most popular lecturer to lay groups and was ever ready to interpret psychiatry to the laity as well as to his medical colleagues.

He was strong in his opinions and fearless in his expression of them. Book reviews by Myerson were forthright, explicit and critical. Praise was not withheld when considered merited, but statements inimical to his point of view were brilliantly and vigorously attacked. He was a strong and articulate opponent of psychoanalysis. To do justice to the subject and express his opinion, he read everything written by Freud as well as a vast amount of other psychoanalytic literature, becoming

# The New England Journal of Medicine

Copyright 1948 by the Massachusetts Medical Society

Volume 239

DECEMBER 23, 1948

Number 26

## MORAL PROBLEMS IN THE PRACTICE OF MEDICINE\*

With Analogies Drawn from the Profession of the Ministry

WILLARD L. SPERRY, M A, D D, S T D, AND LITT D T

CAMBRIDGE, MASSACHUSETTS

MAY I begin what I have to say to you this afternoon by thanking Dr Means for his kind invitation to me to share your staff meeting with you. And may I add my thanks to all of you for your co-operation in the Institute of Pastoral Care, which heads up at the Massachusetts General Hospital.

The fact that I am here at all and that this institute is centered at your hospital is symptomatic of one of the most significant facts in our life today — the fact that, as in the natural sciences, so in the sciences of man and in the professions, the party walls between fields of specialization are not so high as they once were. When I began my ministry I kept bachelor's hall with a well known surgeon. Occasionally I went his rounds with him. One night he routed me out to go along with him to a hospital. He was giving oxygen to a dying patient. As we came out of the room he said, "She'll be gone before morning." I asked, "What happens to her then?" He replied, "That is your business, not mine. You and I are never in the sick room at the same time. We meet at the doorway. You come in as I go out." That would hardly be said today. Our professions may not coincide, but they do overlap.

May I continue by saying that the standards of your profession are, on the whole, higher than those of any of the other professions. I saw this without disparagement of the earnestness and the devotion of the members of my own profession. But the separation of church and state in America forbids the state to do anything whatsoever to maintain decent minimal standards for the ministry, whereas the Commonwealth can and does require of you an adequate education before you may practice medicine. Not only so, but your own professional ethics, over and above the competence required by law, maintain your usage at a very high level. Take a single instance. A professional man is not supposed to advertise. If the newspapers carried, day by day, medical parallels to the ad-

vertisements run by the churches on a Saturday and the publicity that ministers allow themselves on Monday, any doctor who sanctioned such self-advertisement would find himself charged at once with unprofessional conduct. I do not hesitate, in dealing with students in the Divinity School, to call attention to the high ethical standards that prevail in the field of medicine.

I have been asked by Dr Means to talk about certain problems that we share together — problems that are more properly moral rather than medical. We shall come to cases a little later on. But I have to warn you, as I warned him in accepting his invitation, that these problems have no single, simple solution. However, Havelock Ellis once said that the important thing is not to find a man who knows the answer to your problem, but to find a man who knows what the problem is. Were I minded to do so I could cite problems in the practice of my own profession that are, in principle, substantially those which Dr Means had in mind in inviting me here. I merely ask you to take it for granted that I am not wholly unfamiliar with the type of situation that you face.

When we talk about morals and ethics we may mean one of two things. The two words mean, linguistically, the same thing — the *mores* or the *ethos* of a society, that is, the mean high-water mark of accepted manners in a given society. Thus a recent *Handbook of Psychiatry* (Overholser and Richmond) says, "Conscience is not something that is born in the individual, but something that is acquired from the practices, the beliefs, the attitudes and the customs of the group with which the individual identifies himself. For the average individual his conscience is the crystallized attitude of his group." This is a purely naturalistic sociologic account of morals. It makes large room for relativity in the whole field of ethics, and for the changes in moral standards of which all of us are aware.

On the other hand there are persons, and these in the main professedly religious persons, who are not content to define and dismiss morality as a

\*Presented at a staff meeting of the Massachusetts General Hospital, Boston, January 19, 1948.

†Dean, Harvard Divinity School.

## GREATER BOSTON MEDICAL SOCIETY

A meeting of the Greater Boston Medical Society will be held in Building E, Harvard Medical School, on Tuesday, December 21, at 8 15 p.m. A symposium on virus diseases will be presented, with Dr. John F. Enders as chairman.

## PROGRAM

- The Diagnosis of Virus Diseases of the Respiratory Tract  
Dr. Maxwell Finland
- The Prevention and Treatment of Virus Diseases of the Respiratory Tract  
Dr. Monroe D. Eaton
- Recent Advances in the Diagnosis and Treatment of Certain Rickettsial Diseases  
Dr. John C. Snyder
- The Interpretation of Reactions Following Smallpox Vaccination  
Major Abram S. Benenson, M.D.

## AMERICAN ASSOCIATION OF SCHOOLS OF SOCIAL WORK

The American Association of Schools of Social Work will hold its thirtieth annual meeting at the Hotel Statler, Boston, on January 27, 28 and 29, 1949.

## MAINE MARITIME ACADEMY

A position of medical officer is available for the annual cruise of the Maine Maritime Academy, which begins on January 8 and continues until April 4, 1949. A straight fee of \$1000, in addition to maintenance for the three months' cruise, is usually paid.

Further information regarding qualifications may be obtained from the Superintendent, Maine Maritime Academy, Castine, Maine.

## NATIONAL FOUNDATION FOR INFANTILE PARALYSIS FELLOWSHIPS

The National Foundation for Infantile Paralysis announces that the following fellowships are available to qualified applicants: research fellowships in virology, orthopedic surgery, pediatrics, epidemiology and neurology (available to doctors of medicine, or, when appropriate, doctors of philosophy, the former having a minimum of two years of training on the residency level, of sound health, as attested by a physical examination, citizens of the United States who can present an appropriate program of study and investigation), clinical fellowships in physical medicine for physicians who wish to prepare for eligibility for certification by the American Board of Physical Medicine (available to graduates of Class A medical schools who have completed a rotating internship of not less than one year in a hospital approved by the Council on Medical Education and Hospitals of the American Medical Association, licensed to practice medicine in one or more states, citizens of the United States, forty years of age or younger and of sound health, as attested by a physical examination), and fellowships in public health for postgraduate study leading to the degree of Master of Public Health at a school of public health approved by the American Public Health Association (available to graduates of Class A medical schools who have completed not less than one year of internship in a hospital approved by the Council on Medical Education and Hospitals of the American Medical Association, licensed to practice medicine in one or more states, citizens of the United States and of sound health as attested by a physical examination).

For further information regarding the fellowships, application should be made to the National Foundation for Infantile Paralysis, 120 Broadway, New York 5, New York. Selection will be made on a competitive basis by committees composed of specialists in each field, and awards will be based on the individual needs of the applicants.

## AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY, INC.

The next written examination and review of case histories (Part I) for all candidates will be held in various cities of the United States and Canada on Friday, February 4, 1949.

Arrangements will be made so far as possible for candidates to take the Part I examination (written paper and submission of case records) at places convenient for them.

Candidates who successfully complete the Part I examination proceed automatically to the Part II examination to be held May 8 to 14 inclusive, 1949, at the Hotel Shoreland, Chicago, Illinois. Notice of the exact time and place of the Part I and Part II examinations will be sent all candidates well in advance of the examination date.

New bulletins are now available for distribution upon application and give details of all changes in Board requirements and regulations made at the annual meeting of the Board held in Washington, D. C., May 16 to May 22, 1948. These apply both to candidates and to hospitals conducting residency services for training.

Application forms and bulletins will be sent upon request made to the American Board of Obstetrics and Gynecology, Inc., 1015 Highland Building, Pittsburgh 6, Pennsylvania.

## SOCIETY MEETINGS AND CONFERENCES

## CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, DECEMBER 23

## FRIDAY, DECEMBER 24

- \*9 00-10 00 a.m. Craniopharyngioma. Ophthalmic Type due to Pituitary Tumors (Demonstration and Discussion of Cases Operated on by Transphenoidal Methods) Dr. Oscar Hirsch. Joseph H. Pratt. Diagnostic Hospital.
- \*9 00 a.m.-12 00 p.m. Combined Medical and Surgical Staff Rounds. Peter Bent Brigham Hospital.

## MONDAY, DECEMBER 27

- \*12 15-1 15 p.m. Clinicopathological Conference. Main Amphitheater. Peter Bent Brigham Hospital.
- 5 15 p.m. Staff Meeting. Harris Hall. New England Deaconess Hospital.

## TUESDAY, DECEMBER 28

- \*12 15-1 15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.
- \*1 30-2 30 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children. Massachusetts General Hospital.

## WEDNESDAY, DECEMBER 29

- \*11 00 a.m.-12 00 m. Medical Rounds. Amphitheater. Children's Hospital.
- \*12 00 m.-1 00 p.m. Clinicopathological Conference (Children's Hospital). Amphitheater. Peter Bent Brigham Hospital.
- \*2 00-3 00 p.m. Combined Clinic by the Medical, Surgical and Orthopedic Services. Amphitheater. Children's Hospital.

\*Open to the medical profession.

OCTOBER 1-MAY 20. Metropolitan State Hospital. Page 418. Issue of September 9.

NOVEMBER 17-JANUARY 26. Boston State Hospital. Psychiatric Seminar Schedule. Page 762. Issue of November 11.

DECEMBER 21. South End Medical Club. Page xiii. Issue of January 9.

DECEMBER 21. Greater Boston Medical Society. Notice above.

JANUARY 13, 1949. The Present Status of the Peptic Ulcer Problem. Dr. S. Allan Wilkinson. Pentucket Association of Physicians. 8 30 p.m. Haverhill.

JANUARY 27-29, 1949. American Association of Schools of Social Work. Notice above.

MARCH 7-9, 1949. American Academy of General Practice. Page 728. Issue of November 4.

MARCH 28-APRIL 1, 1949. American College of Physicians. Page 158. Issue of July 22.

MAY 16-19, 1949. American Urological Association. Biltmore Hotel, Los Angeles, California.

MAY 24-26, 1949. Massachusetts Medical Society. Annual Meeting. Worcester Municipal Auditorium, Worcester.

MAY 26-28, 1949. American Gopher Association. Hotel Lorraine, Madison, Wisconsin.

MAY 30-JUNE 3, 1949. International Congress on Rheumatic Diseases. Page 800. Issue of November 18.

NOVEMBER 11-17, 1949. Third Inter American Congress of Radiology. Page 158. Issue of July 22.

## DISTRICT MEDICAL SOCIETIES

## HAMPTDEN

JANUARY 25. 8 30 p.m. Academy of Medicine, Springfield. A Review of the Sterility Problem. Dr. John Rock.

## MIDDLESEX EAST

JANUARY 19.

MARCH 23.

MAY 11.

## WORCESTER NORTH

FEBRUARY 23. Burbank Hospital, Fitchburg.

APRIL 27. Annual Meeting.

# The New England Journal of Medicine

Copyright 1948 by the Massachusetts Medical Society

Volume 239

DECEMBER 23, 1948

Number 26

## MORAL PROBLEMS IN THE PRACTICE OF MEDICINE\*

With Analogies Drawn from the Profession of the Ministry

WILLARD L. SPERRY, M.A., D.D., S.T.D., AND LITT.D.†

CAMBRIDGE, MASSACHUSETTS

MAY I begin what I have to say to you this afternoon by thanking Dr. Means for his kind invitation to me to share your staff meeting with you. And may I add my thanks to all of you for your co-operation in the Institute of Pastoral Care, which heads up at the Massachusetts General Hospital.

The fact that I am here at all and that this institute is centered at your hospital is symptomatic of one of the most significant facts in our life today — the fact that, as in the natural sciences, so in the sciences of man and in the professions, the party walls between fields of specialization are not so high as they once were. When I began my ministry I kept bachelor's hall with a well known surgeon. Occasionally I went his rounds with him. One night he routed me out to go along with him to a hospital. He was giving oxygen to a dying patient. As we came out of the room he said, "She'll be gone before morning." I asked, "What happens to her then?" He replied, "That is your business, not mine. You and I are never in the sick room at the same time. We meet at the doorway. You come in as I go out." That would hardly be said today. Our professions may not coincide, but they do overlap.

May I continue by saying that the standards of your profession are, on the whole, higher than those of any of the other professions. I say this without disparagement of the earnestness and the devotion of the members of my own profession. But the separation of church and state in America forbids the state to do anything whatsoever to maintain decent minimal standards for the ministry, whereas the Commonwealth can and does require of you an adequate education before you may practice medicine. Not only so, but your own professional ethics, over and above the competence required by law, maintain your usage at a very high level. Take a single instance. A professional man is not supposed to advertise. If the newspapers carried, day by day, medical parallels to the ad-

vertisements run by the churches on a Saturday and the publicity that ministers allow themselves on Monday, any doctor who sanctioned such self-advertisement would find himself charged at once with unprofessional conduct. I do not hesitate, in dealing with students in the Divinity School, to call attention to the high ethical standards that prevail in the field of medicine.

I have been asked by Dr. Means to talk about certain problems that we share together — problems that are more properly moral rather than medical. We shall come to cases a little later on. But I have to warn you, as I warned him in accepting his invitation, that these problems have no single, simple solution. However, Havelock Ellis once said that the important thing is not to find a man who knows the answer to your problem, but to find a man who knows what the problem is. Were I minded to do so I could cite problems in the practice of my own profession that are in principle, substantially those which Dr. Means had in mind in inviting me here. I merely ask you to take it for granted that I am not wholly unfamiliar with the type of situation that you face.

When we talk about morals and ethics we may mean one of two things. The two words mean, linguistically, the same thing — the *mores* or the *ethos* of a society, that is, the mean high-water mark of accepted manners in a given society. Thus a recent *Handbook of Psychiatry* (Overholser and Richmond) says, "Conscience is not something that is born in the individual, but something that is acquired from the practices, the beliefs, the attitudes and the customs of the group with which the individual identifies himself. For the average individual his conscience is the crystallized attitude of his group." This is a purely naturalistic, sociologic account of morals. It makes large room for relativity in the whole field of ethics, and for the changes in moral standards of which all of us are aware.

On the other hand there are persons, and these in the main professedly religious persons, who are not content to define and dismiss morality as a

\*Presented at a staff meeting of the Massachusetts General Hospital, Boston, January 19, 1948.

†Dean, Harvard Divinity School.

matter of social custom. Such persons feel that the distinction between right and wrong, in whatever terms these two words may be defined, has about it a certain absolute quality. Thomas Carlyle says that the greatest moment in modern European history was that when a lonely man stood before a hostile court and said, "It is dangerous to sin against conscience." Most of us have had moments in which we were aware of that danger. In the ancient Wisdom Literature of Israel there is a verse in which God says, "Thou hast not as it were forsaken me, thou hast forsaken thyself." To "forsake oneself" is a serious business, the process may eventually become suicidal for character.

Therefore, I commend to you another account of morals by Father George Tyrrell.

The rock of irresistible reality is conscience — the sense of right and its absolute claims. No analysis, no explaining away can permanently destroy this faith or lay the ghost. Only conscience can say, "Thou shalt have no other gods before me, thou shalt not bow down to them or worship them, for I the Lord thy God am a jealous God."

The sciences of man can prove beyond all contradiction the relativity of moral judgments at any given place and time. A practice that yesterday was declared to be permissible, if not right, is today declared to be forbidden and wrong. Polygamy and human slavery are two historic instances of this proposition. The prodigal varieties of moral judgment, and the fact, which each one of us has verified in his own experience, that conscience is educable, inclines the sociologist to regard the whole matter as one of ethical relativity. But the religious man cannot abandon altogether his conviction that, whatever its particular pronouncement at any given moment, the principle of conscience has an absolute warrant. No rationalization can explain, much less explain away, this conviction, which has its origins in the belief that the life of man is lived in touch with an "Infinite Mystery" and that our attempts to distinguish between right and wrong have their ultimate origins in the nature of "The Eternal Goodness." The process of ethical culture still goes on, but the quality of an ethical conviction remains constant.

To come more closely to our immediate subject, the actual moral choices that we have to make in this world are seldom between black and white, they are between shades of gray. One of my friends, who taught the undergraduate classes in ethics at Yale, used to say that once we have chosen the lighter shade of gray, we must then, for all practical purposes, go ahead on the assumption that it becomes for us a clear white.

The narrator in Conrad's *Lord Jim* says of his tragic hero that, given his dilemma, there was only a hairbreadth, only the thickness of a sheet of paper, between right and wrong. Once again all of us have had experience of this narrow margin between our moral options.

The most serious and by far the most difficult moral decisions we have to make are those that involve two rival loyalties, each of which is wholly good on its own premises, but which cannot be easily squared. I cited you a moment ago Father George Tyrrell. There is in his autobiography a poignant passage that harks back to just such a collision of loyalties in his own early life. He had felt a call to the religious life and had decided to join a religious order. But his decision meant abandoning to their own fate a needy mother and sister who, humanly speaking, had simple prior claims upon him. Looking back on his decision he said years later:

Well I remember my last day at home, my last day with those two now hid in death's dateless night, who were my share of the world, the best this life has had for me — whom I forsook for what? in the name of all that is sane and reasonable? For a craze, an idea, a fanaticism? Or for the love of and zeal for the truth, the Kingdom of God, the good of mankind. Had I been faithful to my duty all along, had I stayed at home and supported my mother and sister and made their sad narrow lives a little wider and brighter, would not God have given me light needful for my salvation? Have I done so much good to others who had no claim on me to atone for my neglect of those who had every claim? What have I given up or forsaken for the service of God, as I suppose some would call it, except my plain duty? These are the pleasant doubts that fill my mind in the spare moments, and make me say, Surely I have lived in vain.

In his *Oxford Lectures on Poetry*, A. C. Bradley has an essay on "Hegel's Theory of Tragedy." He points out that tragedy is never a matter of a conflict between good and evil. Such a conflict is forthright and never tragic. The essence of tragedy is, as we have said, a matter of a collision of two loyalties, each of which is wholly good on its own ground.

The essentially tragic fact is the self-division and intestinal warfare of the ethical substance, not so much the war of good with evil as the war of good with good. The family claims what the state refuses, love requires what honor forbids. The competing forces are both in themselves rightful, and so far the claim of each is equally justified, but the right of each is pushed into a wrong because it ignores the right of the other.

Professor Bradley illustrates this thesis at great length from the great Greek tragedies and from those of Shakespeare. Clytemnestra has killed her husband and her king. Orestes, her son, is ordered by Apollo to avenge his father, but to kill one's mother is itself a sin against filial piety. The bond of father and son demands that which the bond of son and mother forbids. Richard Lovelace, on going to the wars, says to his *Lucasta*:

Yet this inconstancy is such  
As you shall too adore  
I could not love thee, dear, so much,  
Loved I not honour more.

This was Othello's tragedy: his passionate love of Desdemona and his duty to his honor were at the final fatal moment incompatible, so he "put out the light."

The essence of tragedy, then, is not pain or suffering. The essence of tragedy is waste. We are confronted again and again with what William James has called "a forced, momentous option." This option cannot be avoided, a choice must be made, but when it is made something good in itself is inevitably lost.

In this analysis of our moral problems we come here to an area of life where crude rules of thumb, which serve the humdrum needs of every day, are of little help. We must go to art, and perhaps to religion, to understand the nature of our dilemma and to find there some element of resignation and reconciliation.

To come to still closer grips with our problem let me take two or three instances of the tragic dilemma with which we are only too familiar. At these points the professions of medicine and the ministry constantly overlap. Please understand that what I may say hereafter provides no dogmatic resolution of the tragic dilemma. I offer merely my own reflections upon situations that are even more familiar to you than they are to me, and yet situations that, over the years, I have shared with you. For there are times when a patient asks a priest or minister or rabbi questions that he shrinks from asking his doctor.

#### TELLING THE PATIENT THE TRUTH

This issue was, you remember, one that was vigorously debated here in these very circles some years ago, when a gallantly and remorselessly sincere man urged truth telling at all costs.

One might dodge the issue by asking in turn, with Pilate of old, "What is truth?" Bacon said that Pilate was merely a jester, who would not stay for an answer. My observation is that many wise physicians and surgeons are cautious about claiming finality for their diagnoses and prognoses. In the order of nature there are run-of-the-mill diseases that, humanly speaking, must apparently go their normal course to the end. It is a matter of common knowledge that the faith-healing sects in this country have made much of their capital out of hasty and erroneous diagnoses. Some would-be truth teller, who misinterpreted the facts, has dismissed them, perhaps to the ministry of devout believers, but certainly to the *vis medicatrix naturae*. This, however, is more immediately your problem than mine. Furthermore, as one of you said to me not long ago we never know when some new treatment and possible cure may come suddenly around a corner. Years ago a little daughter of Dean Inge of St. Paul's and a son of L. P. Jacks were taken to London hospitals in the last stages of diabetes, to await the first insulin that was being flown to England from Canada. The girl, alas, died, the lad lived to get his insulin and still lives happily.

But when there is reasonable assurance as to diagnosis and prognosis, what are the doctor, and the minister who shares the doctor's opinion, to do?

Much, perhaps all, depends on a patient's temperament and mental state at the time. Resolute natures, in full possession of their wits usually want to know what we think and expect, and are able to "take it." I see no reason or warrant for withholding what we believe to be the truth from such a person. I mentioned that Yale professor a few moments ago. He had an obscure illness and died untimely, after going the rounds of specialists in both New York and Boston. He was a man of quick intellect and good courage. He once said to me in a mood of discouragement and temporary bitterness, "I no longer believe anything that any doctor says to me. They have all lied to me so consistently that I have lost all faith in them." This was a bit of deliberate overstatement on his part, but I think he meant that he was tired of being cheered up by a too facile optimism, or dismissed with deliberate perplexity.

On the other hand many persons do not even ask themselves how ill they are, let alone asking any one else. They prefer to take what comes, as it comes. The reticence of such persons should be respected. There is no occasion and no moral obligation to intrude the supposed truth upon such minds. To do so would be a bit of gratuitous cruelty. And all of us know that there is a point in the course of an illness at which nature herself mercifully dulls the mind and its power of grasping ideas begins to relax. In his Ingersoll Lecture on the Immortality of Man, given at Harvard some years ago, William Osler said that most people die as they were born, unconscious of what is happening. You doctors know this well. I have to tell my divinity students that this is so, and that at these times they are not to ask or expect anything like quick mental response to their ministry to the sick. These are not the occasions to carry on a prolonged discussion as to an afterlife.

In short this whole question of truth telling seems to me to depend upon the temperament and the mental state of a patient. No single categorical rule can be laid down, we have to trust our instinctive knowledge of human beings and be guided accordingly.

#### PROLONGATION OF LIFE AND EUTHANASIA

Regarding the first of these questions there seems to be little question. There is a point beyond which the mere artificial prolongation of the life of a body that seems marked down for death is not merely useless but also even an unkindness. One might even defend the thesis that it is a perverted conception of goodness and of ethics. When Shakespeare says, "She should have died hereafter," he meant not that her death was premature but rather that she was going to die some time and in any case

When we are actually in sight of that time it seems to be right to accept the fact. I have never come across on the part of the laity any difference of opinion about the medical conduct of a case once this situation is accepted.

The question of euthanasia is more difficult. There is, as you know, much vocal medical opinion in its favor in England. And the matter is often discussed privately here. It is an open question. As to the act itself, many a suffering person has begged for it, many kinsfolk have been willing to accept it, and I suspect that many a doctor has been sorely tempted at this point. I have a friend who, with the connivance of her doctor, gave her husband, who was suffering from a cruelly painful and fatal disease, a heavy overdose of morphine. She said she had no scruples about doing so and had never had a single regret. You must know many more such examples than I know. She was either more resolute or more fortunate than most human beings. A few years ago I watched my Scottish terrier being put away. He was old and blind and sick. But even so I didn't like it. It seemed to me that the veterinarian and I were taking a great responsibility and one perhaps to which we were not morally entitled. How much more so in the case of a human life!

If euthanasia were ever to be legalized no single medical man could be or should be empowered to make such a decision alone. A panel of doctors would probably have to be set up by the state to make any such decision. Public medicine of any kind raises all sorts of valid questions. It is not easy to foresee a panel of state officials charged with this task, nor is it easy to envisage the doctor who would accept this responsibility as the major, if not the sole, form in which he practiced his profession. Whatever the warrant of a given emergency may be, the legal validation of euthanasia seems to cut against the whole basis and practice of medicine. I suppose that none of us are 100 per cent psychologically sound, and one wonders what perversions might creep into the practice of euthanasia.

Albert Schweitzer, who is a doctor as well as a minister, and who has done such splendid work at Lambarene in West Africa, says of himself that journeying up river from the coast to his hospital on one occasion he was searching for some basic ethical principle.

Slowly we kept upstream, laboriously feeling for channels between the sand banks. Lost in thought I struggled to find the elementary and universal conception of the ethical which I had not discovered in any philosophy. Sheet after sheet I covered with disconnected sentences. Late on the third day at the very moment we were making our way through a herd of hippopotamuses, there flashed upon my mind, unforeseen and unsought, the phrase "Reverence for life." For all life.

His autobiography has many striking instances of his subsequent application of that principle.

This is, after all, the ethical basis of the practice of your profession as of my profession. If we forfeit that reverence we have slipped our moral moorings. And if in practice we violate that principle, we should know that we are doing so and take the responsibility for so doing. Once again, "Thou hast not as it were forsaken me, thou hast forsaken thyself." To forsake one's own self is an act that leaves its scars on the mind. Personally, I should question the wisdom of medicine's accepting as a principle, and the state's legalizing in practice, acts of euthanasia. Such a *volte face* in the whole conception of the aim of the profession would impair the conscious integrity of its members and would introduce in place of an accepted principle—which, if it is ever to be violated, should be violated soberly and wittingly—a state of ethical perplexity and painful indecision in which each case must be decided on its own merits. The effect on the public would be almost disastrous, since it would introduce into these relationships a sense of insecurity and apprehension, rather than confidence and assurance. If a doctor or a minister has never had, or having had has lost, his reverence for life and his feeling for the sacredness of life, he lacks that which in theory his profession presupposes. Unless you and I are to revise radically our conception of our common task, it is not our business to take life, only to try to save it.

#### RIVAL CLAIMS OF COMPETING INDIVIDUALS, OR OF THE CONCRETE INDIVIDUAL AND SOCIETY IN THE ABSTRACT

We come, finally, to the specific type of problem that was proposed to me. Here is a woman apparently dying of an inoperable and incurable cancer of the stomach. She is being kept alive by blood transfusions, but the blood that she needs is the rarest type, of which the blood bank has only a limited supply. The transfusions cannot save her. Is it not foolish, perhaps even wrong, to waste this precious blood on her? Ought it not to be kept for some later patient who may be helped by it, whose life perhaps may actually be saved by it? Or here is a man in the iron lung, who could not live an hour outside it and yet may live half a lifetime in it, to the exclusion of someone else who might be got around a bad corner and in due time dismissed. Ought he to be allowed his monopoly of this mechanism?

These are difficult, even heartbreaking questions. Either way, the choice is a genuinely tragic one. I do not know that I have sufficient wisdom to answer them. I can only fall back on general principles.

There are two terms that have been much to the front in recent years. They represent what are called social trends. One is the word "depersonalization," and the other the words "mass man." Both terms represent tendencies, particularly on the part of the state, to depreciate the value of the

single individual in favor of the group as a whole. These trends have found their fullest expression in countries where totalitarianism has been, or still is, the order of the day. In such societies the individual is of value only as a member of the mass, and is always regarded as expendable.

Our own country has just now fought two world wars in defense of the general idea of liberty and the rights of the individual. His liberties have had to be circumscribed in wartime, and now that the fighting is for the moment over, we are left with lives that are much less free, as far as our private affairs are concerned, than they were forty years ago. It could not have been otherwise, perhaps, and yet this steadily narrowing area in which anything like actual liberty and private initiative remains is one of the paradoxes of these years.

There is abroad a tendency to treat this doctrine of mass man as though it were a late discovery, the mature achievement of complex modern societies. I venture to point out that on the whole, it is the oldest of all our social theories. It was the appraisal of life current in all primitive societies. The individual mattered only as a member of the tribe, and all the tribal rites looked to his initiation into the tribe and his subsequent identification with it. This was true of the religion of the early Israelites. The single individual had no independent worth either in his own eyes or for his fellows or even to Jehovah. The doctrine of the worth and moral independence of the individual emerges only with the prophet Ezekiel after the return from the exile. This lead is taken up and matured in Christianity, which holds that "not a sparrow falls to the ground without your Father." However difficult the doctrine may be to understand and defend, such is the doctrine of later Judaism and Christianity — both have traditionally believed in the value of the individual. Our social institutions come into being to express him and to defend him. "The Sabbath was made for man, not man for the Sabbath."

This appraisal of the facts was, also, the premise of all modern democracies, our own in particular. The case has never been theoretically proved beyond all contradiction, or vindicated in the total practice of any society. It remains, in many respects, a bold ideal. But unless we repudiate our hereditary faith, both religious and political, it is still our ideal, and its denial would mean a radical change in the whole temper of our life.

The drift of the times, in the worlds of finance and industry, and in military policy, seems to be in the direction of the dogma of mass man. At their hands the individual is inevitably more or less depersonalized. Perhaps it cannot be otherwise, given the numbers of human beings involved and the complexity of most modern issues.

In any case it is left largely to two groups of professional persons, the doctor and the minister, to

vindicate a working faith in the value of the individual. Any lack of that faith on our part is tantamount to desertion of an ideal outpost that we have held in behalf of what we believed to be a valid cause.

The first social-settlement house in the English-speaking world, Toynbee Hall in East London, was presided over by a quiet little Anglican clergyman, Samuel Barnett. In her biography of her husband Mrs. Barnett says that any number of persons used to come down for a day from the West End of London to its dreary East End, with large blue-print plans for the redemption of those drab slums. They aired their plans, spent a pleasant evening with the warden and went away. Mrs. Barnett says that her husband came to the conclusion that the only permanent good ever done in the East End of London was done by those "who were willing to take time and trouble with individuals," and that this verdict upon the fact became his own rule of life.

A man who goes into the practice of medicine or of the ministry ought to enter his profession with that conviction and ought to do his best to vindicate it. There is a place in society for the man who wishes to devote his life to the general and all-over cause of public health. There is a place in the religious world for a man who feels he should sign on with one or another of the great reform movements of the time. The work of these men is necessary, and their contribution to society may be very great. But the practicing doctor and the parish minister are primarily concerned with individual human beings. The moment either begins to sacrifice his concern for the individual to some other hypothetical person, or to society in the abstract, he has mistaken his vocation.

He may justify his decision to himself on the grounds of a higher or broader loyalty, but he will have failed his cause at a point that it is more and more difficult to hold in the modern world. If he ceases taking time and trouble with a given individual on the ground that he can thus be of greater service to someone else he impairs to this extent the confidence of the community in himself and his profession. Once a man accepts the ministry of a parish he is under bonds to take time and trouble with the individuals who comprise it. Most of the failures that I know of in my own profession have been due to a neglect of that premise. If my analogy is valid I should suppose that once a doctor and a hospital have accepted a patient they are under bonds to see the patient through.

I agree that this may involve what will often seem a waste of precious time to no permanent good. But there is something more at stake here than the welfare of the single patient, there is also the confidence of the community in the integrity and single-mindedness of the profession itself. If

that confidence is impaired not merely the good name but also the actual effectiveness of the profession suffers in consequence

These are tragic choices. And as Bradley says, the essence of tragedy is the fact of waste that it involves. To know them as tragic and to feel their tragedy is perhaps half the battle at the outset. If a man cannot feel these tragedies in medicine and the ministry there is something wrong with him. If he is a sensitive man he will feel them more deeply as the years go on. He will always make his decisions reluctantly and with pain of heart, if not perplexity of mind. But he is the defender in church and state of certain basic principles of our society that he cannot forfeit without radically revising

the premises of his profession and to this extent impairing the whole tradition to which he belongs

\* \* \*

I have not answered Dr Means's problems, or yours. But I have tried to point out what some of the issues are. In so far as I have any answers they are, briefly

Tell the truth, but "tell the truth in love," and telling the truth in love may often mean silence rather than some hastily spoken word. Maintain at all times a sense of the sacredness of life.

Be willing to take time and trouble with individuals at the expense of that abstraction known as mass man.

## PROGNOSIS IN ESSENTIAL HYPERTENSION\*

### Eight-Year Follow-up Study of 430 Patients on Conventional Medical Treatment

ROBERT STERLING PALMER, M D,† DOROTHEA LOOFBOUROW, M D,‡ AND  
CARL R. DOERING, M D§

BOSTON

CONSCIENTIOUS interval evaluation of sympathectomy for essential hypertension by comparison with control material is progressively defining the limitations and the applicability of this procedure.<sup>1,2</sup> The same attention to control material is required when one considers the usefulness of very restrictive diets, interest in which has recently revived.<sup>3,4</sup> Before applying these diets generally and indiscriminately, we should ask ourselves what the remote effects will be on the body electrolyte economy, on work capacity and hot-weather tolerance, on resistance to infection, on the basal metabolism, on carbohydrate tolerance and on fetal health in pregnancy. Finally and practically, how often is an extremely irksome diet necessary in essential hypertension? If employed, does it actually prolong the life of the patient? Are most of the successes obtained in those patients likely to be matched in any case? To help answer these three important questions, adequate control material is the first necessity. This we believe we have and submit it herewith. In this series of cases, treatment consisted of the combination of physical rest and activity deemed

appropriate for each patient, sedative drugs and sometimes sulfocyanates, low-fat, relatively high-protein and low-salt diets, in exceptional cases low-sodium diets for short periods, the usual drugs for congestive or anginal failure and finally practical psychotherapy.

Originally, our series of patients with hypertension consisted of 1072 patients personally observed, the great majority of them between 1935 and 1940. After patients with transient nervous hypertension, those with glomerulonephritis, those who were sympathectomized and those inadequately followed had been excluded, 646 subjects remained. Observation comprised a careful history and physical examination, routine blood and urine examinations, a fractional intravenous phenolsulphonephthalein test, a urine concentration test, frequently intravenous urography or orthodiagram or seven-foot film of the heart and an electrocardiogram.

After the original observations and satisfactory follow-up study, these 646 patients were classified according to clinically recognizable organic changes in the three vital areas: the head, the heart and the kidneys. The classification depended upon the most marked change in the area or areas in which it was found. These criteria are presented below.

#### CLASSIFICATION

##### Grade I Changes

These patients have no changes or minimal changes in the fundi as represented by narrowing

\*From the Committee on Research in Diseases of the Autonomic Nervous System, Massachusetts General Hospital and the Harvard School of Public Health.

This study was supported by a grant from the Life Insurance Fund of America.

†Associate physician, Massachusetts General Hospital; consulting physician, Massachusetts Eye and Ear Infirmary.

‡Assistant in medicine, Massachusetts General Hospital.

§Assistant professor of biostatistics, Harvard School of Public Health; consultant, Cambridge Tuberculosis and Health Association.

of the arterioles, normal hearts or no more than prominence in the region of the left ventricle by x-ray study, no impairment of renal function by the tests used and normal urine examination or occasionally slight albuminuria and slight changes on microscopical examination of the sediment

### *Grade II Changes*

These cases include moderate organic changes in the fundi as represented by widening of the arteriolar light reflex, narrowing, caliber changes and arteriovenous compression. The heart exceptionally is normal by x-ray study and is usually prominent in the region of the left ventricle and sometimes more definitely enlarged but without functional impairment, the kidney is normal slight degrees of albumin and minimal numbers of formed elements are found in the sediment, or there may be slightly impaired function

### *Grade III Changes*

The fundi are rarely normal, usually showing arteriolar narrowing, caliber changes, wide light reflex and arteriovenous compression. Often, there are exudates and hemorrhages, the heart is often moderately to markedly enlarged, commonly with symptoms and signs of actual or impending congestive failure or symptoms of anginal failure. The urine frequently shows albuminuria and casts, and renal function is often impaired though actual failure (uremia) is not common, cerebral accidents sometimes occur (in 20 per cent of cases)

### *Grade IV Changes*

The cardinal—indeed, the obligatory—sign is edema of the optic disks, with or without exudates and hemorrhages and always with marked narrowing of the arterioles. Cardiac enlargement and congestive failure may be present, renal impairment and failure are common

It is emphasized again that classification is not based on one organ, such as the fundus, but on recognized changes in any area, and that the classification is mild (Grade I), moderate (Grade II), or severe benign (Grade III), according to the most advanced change whether in one or more areas. For instance, a patient who has had a cerebral thrombosis is placed in Grade III, though the heart, kidneys and fundi are normal, no classification higher than III is made if the kidneys are impaired, there is angina pectoris, and there are exudates and hemorrhages in the eyegrounds—that is, there may or may not be evidence that one or all vital areas are affected seriously. Grade IV or malignant hypertension is recognized by papilledema alone with or without other changes. In 95 per cent this sign indicates a rapidly progressive course to a fatal outcome. In Grades I and II patients must be observed a year or more for one to be sure that the course characteristically is progressing slowly,

if at all. In Grade III serious change is promptly recognized in fundi (exudate or hemorrhages, or both), in the cerebral circulation (thrombosis or hemorrhage) in the heart (marked enlargement, actual or impending congestive or anginal failure) and in the kidneys (significant impairment of function)

We are well aware that the outward signs are poorly correlated with the inward state in essential hypertension as in other aspects of man, but we must use the signs that we have. For this reason, any clinically observable sign of vascular change in one or more of the three vital areas is taken as indicative of diffuse vascular disease, however localized such a change may be on clinical examination. It is further assumed that the severity of recognizable organic change as defined in the classification is directly proportional to the severity of the disease process. The latter assumption in practice has proved fairly correct.

In 1942–1943 after an average four years of follow-up study of 50 per cent of the 646 cases, the mortality was 6 per cent in Grade I hypertension, 17 per cent in Grade II, 36 per cent in Grade III, and 80 per cent in Grade IV.<sup>1</sup> In 1946–1947 after another four years, 430 cases or 66.5 per cent of the 646, were followed. The mortality was 22 per cent in Grade I, 47 per cent in Grade II, 78 per cent in Grade III and 94 per cent in Grade IV. It is evident that this clinical classification of essential hypertension on the average indicates the severity of the disease in respect to survival.

The average and median duration of known hypertension in each grade of the 430 patients is given in Table 1. The known duration of hypertension in Grades I to III is longer in the living (twelve to fifteen years) than in the dead (seven to nine years) patients. This reminds us of three things that the actual onset of hypertension is hardly ever accurately determined that the prognosis varies with age and sex, and that present methods of clinical examination as employed by us differentiate patients who do well from those who do badly only by an average of each grade and not in an individual patient. In Grade IV hypertension 3 patients with papilledema have survived an average of nine years and two months. These cases are exceptional. Others have had a similar experience.<sup>5, 6</sup> The average duration in patients with Grade IV changes who died is three and one-fourth years owing to the long duration of apparently benign hypertension terminated by the malignant phase in some of these cases. The median known duration is just under one and a half years. The average duration of our own observation of these patients is a little over seven months and the median slightly more than four months. It is almost always apparent at once that the course of the disease in patients with Grade IV changes is intense and rapid. It is usually apparent in Grade

III that one is observing an end stage of a condition that has often been very slowly progressive In Grades I and II a number of interval observations of a year or more are needed to prove that the condition is slowly progressive or stationary We know of no infallible signs at a single examination in these patients with Grade I and II changes that will foretell the appearance of late Grade III or malignant Grade IV changes

The age distribution of the various grades is shown in Figure 1 By inspection, one can notice that the patients with Grade IV changes are younger than all the others and that those with Grade II and III changes are older than those with Grade I This suggests that Grade I, II, and III changes form a group of patients that represents a condition different from that of Grade IV

Table 2 shows the sex distribution and survival rates and demonstrates that in this sample there are

TABLE 1 *Average and Median Duration of Known Hypertension by Grades*

GRADE OF HYPERTENSION	DURATION	
	AVERAGE yr	MEDIAN yr
Living patients		
I	12.5	11.5
II	13.9	13.0
III	14.7	13.0
IV	9.2	—
Dead patients		
I	9.1	8.5
II	8.6	7.0
III	8.2	7.0
IV	3.2	1.4

more female than male patients with essential hypertension In Grades I and II the percentage of women is greater than that of men The reverse is true of Grade IV In Grade III the numbers are equal, but the percentage of the total number of each sex reveals 50 per cent men and 40 per cent women with this degree of hypertension In Grade IV the percentage of the total number of each sex reveals 17 per cent men and 9 per cent women This sex difference is considered significant statistically, suggesting that female patients tend to have the milder grades of this disease It is an important point also that the probability of survival for females is definitely superior — 82 per cent as compared with 66 per cent for the men in Grade I, and 57 per cent as compared with 42 per cent for the men in Grade II The probability of survival is somewhat better in Grade III (27 and 17 per cent for female and male patients, respectively) and also better in Grade IV (9 and 3 per cent each for female and male patients)

The onset and progress of organic change in essential hypertension is assumed to depend upon the duration, the persistence and the height of blood pressure To evaluate the factor of age, the age at

first known hypertension was calculated, and Grades I to III were grouped as follows twenty-nine years or less, thirty to thirty-nine inclusive, forty to forty-nine inclusive, and fifty or over The mortality and the average duration of known blood pressure were determined for each group This was not done in Group IV because the course of the disease was short at any age The results for Grades I to III for the different age groups are shown in

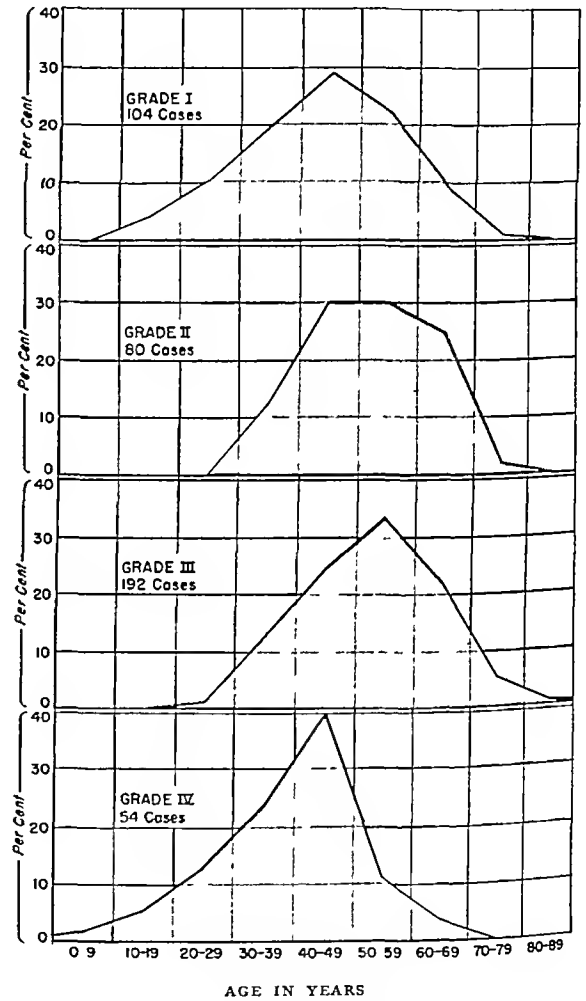


FIGURE 1 *Age Distribution by Decades*

Table 3 In these mortality figures, deaths from causes other than hypertension are excluded

From inspection of these figures it appears that an increase in age is associated with a higher mortality only in Grade I hypertension In Grades II and III the patients are older The numbers in age group twenty-nine or less are too few to be significant It is assumed that the course of the disease in many patients in Grades II and III when they were first seen was already more advanced The usually shorter known duration of hypertension in the dead patients may have been due to the cir-

cumstance that an earlier asymptomatic stage of the disease passed unnoticed. It may be that variations in the natural course of hypertension are due to constitutional, infectious, dietary, situational,

TABLE 2 Sex Distribution and Survival Rates

GRADE OF HYPERTENSION	STATUS OF PATIENT	MALE PATIENTS		FEMALE PATIENTS	
		NO	SURVIVAL %	NO	SURVIVAL %
I	Living	25		56	
	Dead	13		10	
	Totals	38	66	66	82
II	Living	11		31	
	Dead	15		25	
	Totals	26	42	54	57
III	Living	16		26	
	Dead	80		70	
	Totals	96	17	96	27
IV	Living	1		2	
	Dead	31		20	
	Totals	32	5	22	9
All grades	Living	53		115	
	Dead	139		125	
	Totals	192	28	258	48

psychologic or other unknown factors that influence its progress favorably or unfavorably.

We wish to form an estimate of the prognosis of essential hypertension treated by conventional medical management based on the observation of these 430 patients followed in some cases for as long as seventeen years, some of them for shorter

III patients and the 54 Grade IV patients as 100 per cent in each grade and plotted the survival rate in per cent after four years, and again after eight years (Fig 2). The curve for Grade IV has been drawn with a steeper slope than is apparent from the four-year follow-up study. The reasons for this are that the median duration of known hypertension in this group is about one and a half years and that the median duration of our observation of this group prior to death is only slightly more than four months. If the follow-up examination had been made at two years instead of at four years, we should probably have found just a trifle larger percentage of survivors, as in the patients examined after four years.

Tentatively we have used a method of prediction that is both rough and speculative, by which one

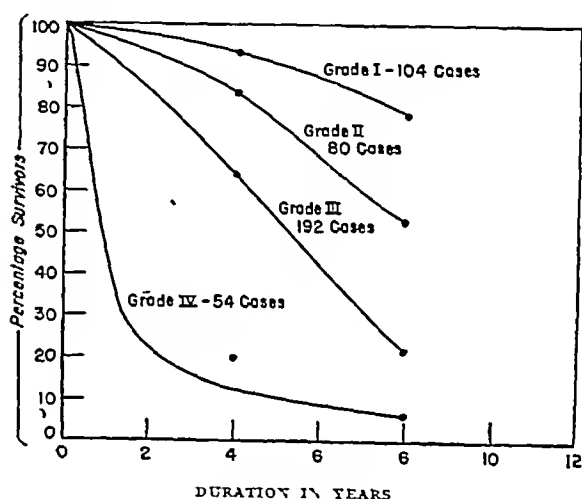


FIGURE 2 Survival according to Duration of Hypertension

TABLE 3 Mortality and Average Duration of Hypertension according to Age at Onset

AGE	MORTALITY	AVERAGE DURATION	
		LIVING PATIENTS	DEAD PATIENTS
yr	%	yr	yr
Patients with Grade I changes			
29 or less	12.5	12.5	14.0
30-39	12.0	12.8	9.0
40-49	19.0	11.1	6.2
50 and over	40.0	13.3	9.7
Patients with Grade II changes			
29 or less	—	20.0*	—
30-39	44.0	15.4	14.1
40-49	48.0	11.4	8.9
50 and over	42.0	11.9	6.6
Patients with Grade III changes			
29 or less	82.0	—†	11.3
30-39	78.5	15.6	8.7
40-49	68.0	15.8	9.1
50 and over	80.0	11.3	6.9

\*Includes only 6 patients

†Only 2 living patients, both of whom are included under group 50-59 years of age

periods, the average being eight years, and many of them with known hypertension long before our time of observation. We have taken the 104 Grade I patients, the 80 Grade II patients, the 192 Grade

might estimate the probable percentage of survivors at twelve years in Grade I as 58 per cent, in Grade II as 24 per cent, in Grade III as less than 2 per cent and in Grade IV as almost zero. Three years hence we hope to have the actual percentages.

### DISCUSSION

From our data, the quickest and clearest demonstration of the effectiveness of any therapeutic program will be to show survival of 20 per cent or more of a significant number of patients with Grade IV or malignant hypertension for five or more years. This criterion has been satisfied by Peet's<sup>7</sup> experience with dorsal sympathectomy.

The next most definite criterion of effectiveness of any given program will be to demonstrate the survival of two thirds of a significant number of patients with Grade III hypertension for more than five years.

The therapeutic effectiveness of any program in Grade I and Grade II hypertension will be doubtful until a significant number of patients have been

followed for ten years. At present we may say that considerably more than 80 per cent should be surviving after eight years in Grade I, and 60 per cent or more in Grade II to demonstrate therapeutic superiority. Consideration should be given to the sex incidence in these two grades, and allowance made for the uniformly better prognosis in female patients.

We urge that responsible clinical investigators interested in the study of essential hypertension agree upon terms and criteria for a clinically applicable classification of hypertension for the purpose of establishing the prognosis and the effectiveness of treatment in this, one of the most serious threats to life of civilized man.\*

\*The classification here used is based on that of Keith, Wagener and Kernohan,<sup>10</sup> whose work in this field since 1920, particularly in establishing the clinical syndrome of malignant hypertension is gratefully acknowledged.

## REFERENCES

- 1 Rogers W T, and Palmer R S. Essential hypertension: prognosis and comparison of medical and surgical treatments. *Am. Practitioner* 1:459-465 1947
- 2 Palmer R S. Medical evaluation of surgical treatment of hypertension. *J A M A* 134:914 1947
- 3 Kempner W. Compensation of renal metabolic dysfunction treatment of kidney disease and hypertensive vascular disease with rice diet. *North Carolina M J* 6:61-72 1945
- 4 Grollman A et al. Sodium restriction in diet for hypertension. *J A M A* 129:533-537 1945
- 5 Keith N M and Wagener H P. Acute vasospastic hypertension case with signs of cerebral irritation and severe retinitis with remission. *Am J M Sc* 190:454-459 1935
- 6 Fishberg A M. *Hypertension and Nephritis*. Fourth edition. 779 pp. Philadelphia: Lea & Febiger 1939. P 315
- 7 Peet M M and Ishberg, E M. Surgical treatment of essential hypertension. *J A M A* 130:467-473 1946
- 8 *Idem*. Problem of malignant hypertension and its treatment by splanchnic resection. *Ann Int Med* 28:755-767 1948
- 9 Keith N M, Wagener H P and Barker N W. Some different types of essential hypertension: their course and prognosis. *Am J M Sc* 197:332-343 1939
- 10 Wagener H P and Keith N M. Diffuse arteriolar disease with hypertension and associated retinal lesions. *Medicine* 18:317-430 1939

## RECENT CONCEPTS REGARDING THE SPREAD AND TREATMENT OF POLIOMYELITIS\*

ROBERT B. LAWSON, M.D.†

WINSTON-SALEM, NORTH CAROLINA

THE essential questions asked about poliomyelitis today are, "How is it spread?" "How can you prevent the disease?" and "How can you cure it?" Although the answers to these questions are not known, a vast amount of knowledge about poliomyelitis, which is beginning to fit together, may furnish these answers in the next few years. At present there are glaring gaps in understanding of this disease, but the definite advances that are being made are filling some of these gaps.

### EPIDEMIOLOGY

Poliomyelitis is a worldwide disease affecting all races and classes of people. It is recognized to be most important as an epidemic disease, however, in North America, the Scandinavian countries, Great Britain and elsewhere in Europe. Until recently it was assumed to be very uncommon in the other sections of the world. Recent investigations by Paul et al.<sup>1,2</sup> have shown that, although epidemics of paralytic poliomyelitis are uncommon in the countries of the Middle East and the Far East, nonparalytic and nonepidemic infections are probably widespread in these and similar countries. This was clearly brought out by the experience of British and American troops stationed in the Middle East and Far East respectively. For, although there were only a few cases of poliomyelitis recognized in the native populations, the inci-

dence of poliomyelitis among the foreign military personnel was significantly higher than that in their home countries.

It is noteworthy that recognized epidemics are of recent occurrence and date back little more than sixty years in this country and in Scandinavia. During this period the age incidence of recognized cases has changed. Whereas the disease primarily involved infants and young children at first, there was a gradual extension into the older age groups here and in Scandinavia after the passage of years. Japan, on the other hand, had its first large epidemic in 1939 and, interestingly enough, is having the same younger age incidence that was seen in the early epidemics in the United States. Ninety per cent of the cases reported in Japan were in children under five years of age, whereas only 36 per cent of the patients were under five years in recent epidemics in this country.<sup>1</sup> It seems that there is a higher immunity in the older age groups in these native populations than is apparent in the population of the United States. This can be attributed to a more widespread dissemination of the virus in infancy in these countries, which, with the lower reported incidence of the disease, are also the countries of poor sanitation, so that it has been postulated that poor sanitation leads to wide dissemination of poliomyelitis virus among the young infants, which is not attended with a high rate of paralysis. On the other hand, as a country's sanitation is improved, it seems that more persons escape exposure to the virus in the early years and therefore remain

\*Presented at the annual meeting of the Massachusetts Medical Society, Boston, May 25, 1948.

From the Department of Pediatrics, Bowman Gray School of Medicine of Wake Forest College.

†Associate professor of pediatrics, Bowman Gray School of Medicine of Wake Forest College.

susceptible to a later and possibly more serious infection

The spread of poliomyelitis from patient to patient may go on by different routes. It is possible to infect experimental animals and presumably man through three routes: the nose and olfactory bulbs, the skin, and the gastrointestinal tract. It is well accepted that the usual and almost exclusive mode of entry in man is by the oropharynx through the mouth or nose. Virus leaves the human body by two routes, the oropharynx and the lower intestinal tract in the feces. Oropharyngeal swabbings contain virus in as many as 50 per cent of patients, especially for two to three days before the onset of the clinical disease to three to five days after the onset.<sup>3</sup> Stools have been found to contain virus in an even higher percentage of cases, especially in the first two weeks of the disease, but also as long as nineteen days before clinical evidence of infection<sup>4</sup> and six weeks or longer after the onset of disease in some cases.<sup>5</sup> The possible pathways of the virus from the oropharyngeal secretions or feces of the apparently healthy carrier or the clinical case to the new, susceptible person are shown in Figure 1. Virus may be transmitted directly by

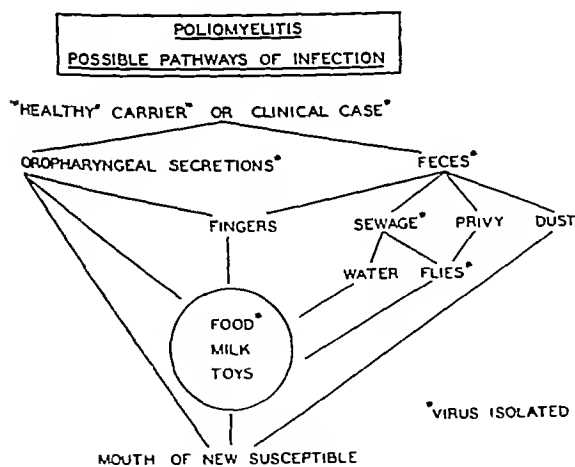


FIGURE 1

inhalation and ingestion of infected oropharyngeal droplets. Infected oropharyngeal secretions may also be passed by means of fingers and toys or food during the intimate play of children. Fecal virus may be transmitted directly as fecal dust or through the medium of toys among children, just as pinworm ova are spread so widely. Direct fecal contamination of food, including milk, may occur in the same way that typhoid spreads from a carrier, or fecal contamination of food or water may occur indirectly, transported by flies from exposed feces in privies or toilet bowls or from contaminated sewage. All these routes and others are possible and even probable, but there is no agreement on

which one is the most important in the actual transmission of the disease. The marked summer incidence of the disease and the finding of the virus in pools of flies caught during epidemics make the theory of fly transmission very attractive. I believe, however, that the fly plays only a minor role.

At present, the most convincing evidence indicates that close contact between human carriers of the virus plays the important role. During any epidemic only a small percentage of people carrying the virus are recognized since the vast majority of carriers do not have a typical illness. There is a serious lack of an easy and economical epidemiologic tool, such as the serologic tests for syphilis or the skin test for tuberculosis, that will pick up these inapparent infections. However, there are several small studies that show the importance of contact. Brown, Francis and Pearson<sup>1</sup> studied a boy's camp in Detroit after the appearance of poliomyelitis in a camper. One week after this case, they found poliomyelitis virus in the throat or feces of 5 of the remaining 7 boys in the same cabin, whereas no virus was found in the 10 boys living in the next cabin. Another interesting point was brought out — namely, that nineteen days later one of these boys carrying the virus developed typical poliomyelitis following severe exertion. A similar study was done by Gear and Mundel<sup>6</sup> in Johannesburg. After the appearance of paralytic poliomyelitis in a two-year-old child they tested the other members of the household and found virus in the stools of an eight-year-old brother. Twelve days later he developed poliomyelitis. Subsequently 2 children whom he had visited just before he became ill developed poliomyelitis, and their father had the virus in his stool. These 3 children and 12 others were at a birthday party together, of this group tests on 8 subjects revealed that 5 were harboring the virus. One of these carriers had an illness compatible with nonparalytic poliomyelitis. In summary, 1 paralytic case was followed by 3 other paralytic infections, 1 nonparalytic infection and 5 carrier states among 14 healthy contacts tested. Casey and his co-workers<sup>7</sup> have carried out extensive studies, also pointing out the importance of contact.

From these studies one can conclude that poliomyelitis virus has a world-wide distribution, that clinically recognized epidemics of poliomyelitis infections are of relatively recent origin and have been particularly prominent in the countries with high sanitation (this may mean that in countries of poorer sanitation, infections are occurring in the younger age groups with resulting immunity, but not associated with the usual signs of poliomyelitis), that close personal contact between apparently healthy carriers or clinical cases and susceptible hosts plays an important role in this widespread dissemination of the virus, and that

something happens during the summer in the temperate zones to increase this dissemination of virus (this may be explained by insect transmission, but other possibilities such as changes in the host or the virus itself may prove to be more important)

### PREVENTION

The epidemiology of poliomyelitis is important, for it leads to a discussion of prevention. The first approach is to try to prevent the dissemination of the virus. Although the most important pathway of infection is not known, the foregoing discussion suggests certain steps to minimize the transfer of the virus. Ordinary contact in schools, movies and churches may play some role, but intimate contact between children during epidemics appears to be the most dangerous factor in the spread of the virus, and should be reduced to a minimum. Foods commonly eaten raw should be washed, and all milk should be pasteurized. In addition, the possibilities of transfer of virus by flies should be minimized by fly-abatement programs and screening of all food in stores, restaurants and kitchens. Screening flies away from exposed feces in privies and toilets should be done, and further studies should be encouraged on ways to inactivate the virus present in sewage.

The second approach is to try to reduce the number of paralyzing infections among susceptible persons who have become carriers of the virus. There is evidence that exhaustion, severe chilling, coincident gastrointestinal infections and operations on the nose and throat may make the difference between a carrier state, or nonparalytic infection, and a case of paralysis. For this reason these conditions should be avoided during epidemic periods.

The third approach is to produce artificial immunity to poliomyelitis. Because of ignorance of the exact mode of transmission of the virus and because of the practical difficulties of applying what is known about it, the immunization of children against poliomyelitis is the greatest need in this field. Attempts in the past have met with failure either because the vaccines used did not produce immunity or because they were too dangerous by reason of containing live virus. New approaches to this problem are being made, and a satisfactory vaccine may be developed. If it can be proved that the people of the more unsanitary countries actually acquire immunity without demonstrable infection from exposure to the virus in early infancy, this may lead to an immunization procedure by the oral administration of virus. This idea has appealed to many people, but obviously it cannot be undertaken lightly.

### TREATMENT

The treatment of poliomyelitis is still hampered by the lack of a specific viricidal agent. The temporary popularity of serum from convalescent

patients has waned, and few people believe that it has any beneficial effect. In the present state of ignorance the treatment resolves itself around nonspecific measures aimed at the relief of complications during the acute stage, making the patient comfortable, limiting spasm and contracture of the muscles, muscle re-education and the correction of resulting deformities.

Almost all the deaths from poliomyelitis are due to bulbar or respiratory involvement so that improved treatment for this form of the disease is particularly important. Some of these deaths have resulted from complicating pneumonia, which may be prevented or treated by the judicious use of chemotherapy or antibiotic therapy (sulfonamides, penicillin). The early recognition and treatment of atelectasis may prevent some of the deaths. A more recent development is the early use of tracheotomy and oxygen therapy in selected cases described by a team of workers at the University of Minnesota,<sup>8</sup> who have shown that many patients with bulbar involvement have difficulty getting a good respiratory exchange even in the respirator. By the use of tracheotomy, alone or in conjunction with the respirator, and by the liberal use of oxygen they believe that they have pulled many patients through who would otherwise have died. Their criteria for tracheotomy were "Respiratory distress as evidenced by recurrent cyanosis, coarse rales in the chest and laryngeal stridor, excitement and unmanageability causing the patient to resist pharyngeal aspiration, stupor of a degree sufficient to make the patient oblivious of the accumulation of secretion in his airway, inability to cough effectively, pharyngeal pooling of mucus, vocal cord paralysis (or intralaryngeal hypesthesia demonstrable by laryngoscopy)."<sup>9</sup>

Another annoying and occasionally serious complication is paralysis of the bladder. Recent experience has shown that most of these patients can be relieved by the use of one of the new parasympatheticomimetic drugs, furmethide (furfuryltrimethylammonium iodide).<sup>10</sup> This is given subcutaneously in doses of 1.5 to 5.0 mg according to age, and is usually followed by voiding in five to ten minutes. The drug may have to be repeated, but spontaneous voiding is usually re-established after the first dose. In a short series of cases it has been found that catheterization, with its discomfort and attendant danger of urinary infection, can be avoided in the majority of cases.

The main treatment of poliomyelitis is symptomatic and at present is usually some modification of the Kenny technic. It is not necessary to dwell on Miss Kenny's theories regarding the therapy that she has gradually evolved, for these theories are not accepted as being tenable.

It has been pointed out that all her therapeutic measures of positioning in bed, hot applications and early muscle re-education have been described

before and used extensively in one clinic or another. It is not fair to Miss Kenny, however, to claim that nothing is new in her scheme of treatment, for it is quite apparent that these methods had given way in previous years to prolonged immobilization in splints or casts, followed by late muscle re-education. A few physicians never adopted the prolonged use of casts and splinting, but the majority had done so before Miss Kenny's appearance. Now very little of this type of immobilization is being practiced.

The chief differences in the Kenny regime and so-called "orthodox" treatment are that muscle re-education, including passive motion of the extremities, is started earlier in the Kenny program, that immobilization is much more complete in the "orthodox" method, and that Miss Kenny treats contractures by application of heat and tendon stretching rather than by corrective appliances.<sup>11, 12</sup>

There are many minor variations in the technique of treatment, of course, but it does not seem that many of them are important. Many different methods of treatment between these two extremes have been used for the past thirty years. Some men carried out a program of treatment very similar to Miss Kenny's for years before her advent. At the present time most medical centers have adopted treatment schemes that are very similar to the Kenny method, without its rigid barriers to modification.

It is of interest to compare, if possible, the results of treatment by these various methods. One cannot be dogmatic about such a comparison, for each investigator has a different method of evaluating results. However, a review of all the available articles that include specific figures shows very similar therapeutic results. Mortality rates over the past thirty years have varied, and there has been some variation in end results, but there appears to be no really significant difference in results obtained by the various methods.<sup>13</sup>

The first fairly satisfactory statistics from the Kenny Institute fail to prove any superiority for this method of therapy. I for one, however, would not go back to the period of long immobilization in casts. It is impossible to agree with Miss Kenny's pseudoscientific reasoning, but it does seem that her method of treatment is more comfortable for the patient and probably makes the recovery of muscle function easier, since the peripheral tissues are kept in better tone.

The only other new developments in therapy during the past few years have been the use of prostigmine and curare for the relief of muscle spasm. In the absence of proved value the latter is too dangerous for use at the present time, although it does warrant further study. The value of prostigmine also is not well proved. Because of the variability of this disease, many better controlled studies will have to be made before one can assess the worth of either of these drugs. Fortunately, most children with poliomyelitis will escape paralysis regardless of the method of treatment employed, and even those who are paralyzed will improve their muscular co-ordination and efficiency if treated over long periods by experienced personnel.

### CONCLUSION

In conclusion it may be noted that the picture is confused, but it is getting clearer. Newer theories regarding epidemiology, prevention and therapy have the support of well controlled clinical observation and experimentation. The outlook is better already, and investigators may well be on the brink of new discoveries that will allow conquest of this disease.

### REFERENCES

- 1 Paul J. R. Poliomyelitis in Japan. *Am. J. Hyg.* 45:205-218, 1947.
- 2 Paul J. R., Havens W. P. Jr. and Van Rooven C. E. Poliomyelitis in British and American troops in Middle East: isolation of virus from human faeces. *Brit. M. J.* 1:841-843, 1944.
- 3 Howe H. A., Bodian D. and Wenner H. A. Further observations on presence of poliomyelitis virus in human oropharynx. *Bull. Johns Hopkins Hosp.* 76:19-24, 1945.
- 4 Brown G. C., Francis T. Jr. and Pearson H. E. Rapid development of carrier state and detection of poliomyelitis virus in stool nineteen days before onset of paralytic disease. *J. A. M. A.* 129:121-123, 1945.
- 5 Horstmann D. M., Ward R. and Melnick, J. L. Persistence of virus excretion in stools of poliomyelitis patients. *J. A. M. A.* 126:1061, 1944.
- 6 Gear J. H. S. and Mundel B. Studies in poliomyelitis: study of outbreak of poliomyelitis occurring in suburb of Johannesburg. *South African M. J.* 20:106-140, 1946.
- 7 Casey A. E., Fishbein W. I. and Bundesen H. V. Transmission of poliomyelitis by patient to patient contact. *J. A. M. A.* 129:1141-1145, 1945.
- 8 Minnesota Poliomyelitis Research Commission. Bulbar form of poliomyelitis. II. Therapeutic measures based on pathologic and physiologic findings. *J. A. M. A.* 135:425-428, 1947.
- 9 Priest R. E., Boies L. R. and Goltz V. F. Tracheotomy in bulbar poliomyelitis. *Ann. Otol. Rhin. & Laryng.* 56:250-263, 1947.
- 10 Lawson R. B. Use of formaldehyde (furfuryltrimethylammonium iodide) for paralysis of bladder from poliomyelitis. *South M. J.* 41:251-255, 1948.
- 11 Key J. A. Reasons why orthodox is better than Kenny treatment of poliomyelitis. *Surg. Gynec. & Obst.* 77:389-396, 1943.
- 12 Pohl J. F. Kenny concept and treatment of infantile paralysis: report of five year study of cases supervised by Miss Elizabeth Kenny in America. *Journal-Lancet* 65:265-271, 1945.
- 13 Lawson R. B. Treatment of acute anterior poliomyelitis. *Aortic Carolina M. J.* 8:26-29, 1947.

### ADDITIONAL REFERENCE

- Ward, R. Poliomyelitis: review of its natural history. *Physiotherapy Rev.* 27:213-218, 1947.

something happens during the summer in the temperate zones to increase this dissemination of virus (this may be explained by insect transmission, but other possibilities such as changes in the host or the virus itself may prove to be more important)

### PREVENTION

The epidemiology of poliomyelitis is important, for it leads to a discussion of prevention. The first approach is to try to prevent the dissemination of the virus. Although the most important pathway of infection is not known, the foregoing discussion suggests certain steps to minimize the transfer of the virus. Ordinary contact in schools, movies and churches may play some role, but intimate contact between children during epidemics appears to be the most dangerous factor in the spread of the virus, and should be reduced to a minimum. Foods commonly eaten raw should be washed, and all milk should be pasteurized. In addition, the possibilities of transfer of virus by flies should be minimized by fly-abatement programs and screening of all food in stores, restaurants and kitchens. Screening flies away from exposed feces in privies and toilets should be done, and further studies should be encouraged on ways to inactivate the virus present in sewage.

The second approach is to try to reduce the number of paralyzing infections among susceptible persons who have become carriers of the virus. There is evidence that exhaustion, severe chilling, coincident gastrointestinal infections and operations on the nose and throat may make the difference between a carrier state, or nonparalytic infection, and a case of paralysis. For this reason these conditions should be avoided during epidemic periods.

The third approach is to produce artificial immunity to poliomyelitis. Because of ignorance of the exact mode of transmission of the virus and because of the practical difficulties of applying what is known about it, the immunization of children against poliomyelitis is the greatest need in this field. Attempts in the past have met with failure either because the vaccines used did not produce immunity or because they were too dangerous by reason of containing live virus. New approaches to this problem are being made, and a satisfactory vaccine may be developed. If it can be proved that the people of the more unsanitary countries actually acquire immunity without demonstrable infection from exposure to the virus in early infancy, this may lead to an immunization procedure by the oral administration of virus. This idea has appealed to many people, but obviously it cannot be undertaken lightly.

### TREATMENT

The treatment of poliomyelitis is still hampered by the lack of a specific viricidal agent. The temporary popularity of serum from convalescent

patients has waned, and few people believe that it has any beneficial effect. In the present state of ignorance the treatment resolves itself around nonspecific measures aimed at the relief of complications during the acute stage, making the patient comfortable, limiting spasm and contracture of the muscles, muscle re-education and the correction of resulting deformities.

Almost all the deaths from poliomyelitis are due to bulbar or respiratory involvement so that improved treatment for this form of the disease is particularly important. Some of these deaths have resulted from complicating pneumonia, which may be prevented or treated by the judicious use of chemotherapy or antibiotic therapy (sulfonamides, penicillin). The early recognition and treatment of atelectasis may prevent some of the deaths. A more recent development is the early use of tracheotomy and oxygen therapy in selected cases described by a team of workers at the University of Minnesota,<sup>8</sup> who have shown that many patients with bulbar involvement have difficulty getting a good respiratory exchange even in the respirator. By the use of tracheotomy, alone or in conjunction with the respirator, and by the liberal use of oxygen they believe that they have pulled many patients through who would otherwise have died. Their criteria for tracheotomy were "Respiratory distress as evidenced by recurrent cyanosis, coarse rales in the chest and laryngeal stridor, excitement and unmanageability causing the patient to resist pharyngeal aspiration, stupor of a degree sufficient to make the patient oblivious of the accumulation of secretion in his airway, inability to cough effectively, pharyngeal pooling of mucus, vocal cord paralysis (or intralaryngeal hypesthesia demonstrable by laryngoscopy)."<sup>9</sup>

Another annoying and occasionally serious complication is paralysis of the bladder. Recent experience has shown that most of these patients can be relieved by the use of one of the new parasympatheticomimetic drugs, furmethide (furfuryltrimethylammonium iodide).<sup>10</sup> This is given subcutaneously in doses of 15 to 50 mg according to age, and is usually followed by voiding in five to ten minutes. The drug may have to be repeated, but spontaneous voiding is usually re-established after the first dose. In a short series of cases it has been found that catheterization, with its discomfort and attendant danger of urinary infection, can be avoided in the majority of cases.

The main treatment of poliomyelitis is symptomatic and at present is usually some modification of the Kenny technic. It is not necessary to dwell on Miss Kenny's theories regarding the therapy that she has gradually evolved, for these theories are not accepted as being tenable.

It has been pointed out that all her therapeutic measures of positioning in bed, hot applications and early muscle re-education have been described

dentally at the age of 44, was the darkest of the family, but so far as is known he was not diabetic.

Physical examination revealed a bronze-gray cast of the exposed areas, the unexposed portions showing merely a peculiar dirty-blue pallor. The scleras were white. The mucosas were normal. The retinas were not remarkable. Occasional extrasystoles were noted, but the heart tones were of good quality. The liver was firm, smooth and nontender. It was enlarged four fingerbreadths and presented a rounded edge. The tip of the spleen was palpable. Angiomas and xanthomas were not present. The axillary and pubic hair were normal, but the genitalia showed mild atrophy. The rectal sphincter tone was good, and the prostate normal. Pedal pulses were present.

The blood pressure was 120/80.

The laboratory procedures are best enumerated as functional groups.

**Hepatobiliary system.** The albumin-globulin figures were 3.8:3.2 gm. The alkaline phosphatase was 10.2 Bodansky units. The cephalin flocculation was + + +, and the thymol turbidity, 0 units. The prothrombin time was normal. The bromsulfalein test, 5 mg per kg of body weight per 45 minutes, showed about 10 per cent retention of the dye (serum, opaque), the total cholesterol was 208 mg, and the cholesterol esters, 68 mg per 100 cc. The total serum lipids were 1057 mg per 100 cc, and the lipochrome index, 26 units. A Graham-Cole test showed nonvisualization



FIGURE 3 Liver Needle Section, Showing Hemochromatotic Cirrhosis (Low-Power, Hemosiderin and Eosin Stain)

of the gallbladder after the administration of nine "prodax" tablets. Duodenal drainage then revealed normal "A" bile, but "B" bile could not be obtained.

**Pancreas.** Pancreatic lipase and amylase were present in normal amounts in the duodenal contents. The stool fat and fatty acid content was not abnormal (Sudan III). Fatty acid crystals were not seen, nor were undigested fibers observed.

**Kidneys.** Urinalysis showed a trace of protein, but no formed elements. The urine concentration reached 1015 after 15 hours' abstinence from fluids. The phenolsulfonephthalein excretion after adequate fluids was 40 per

cent in 15 minutes, and totaled 50 per cent at the end of 2 hours. The serum phosphorus was 3.6 mg, and the blood urea nitrogen, 14 mg per 100 cc.

**Adrenal glands.** The serum sodium was 318 mg, and the serum potassium, 11.4 mg per 100 cc. A Kepler-Power water test<sup>6</sup> showed a night volume of 280 cc, the largest hourly day specimen measuring 90 cc. The quotient, how-



FIGURE 4 Portion of the Liver Needle Section, Showing Hemosiderin Granules within the Liver Cells, the Bile-Duct Epithelium and the Fibrous Stroma (High-Power, Ferrocyanide Technique)

ever, was 30 according to Procedure II and, therefore, negative.

**Hematopoietic system.** The hematocrit was 40 per cent. The red-cell count was 3,800,000, and the hemoglobin 11.2 gm (photometric technique). No macrocytosis was evident. The gastric contents were acid after histamine. Bone-marrow smears obtained from the iliac crest showed a marked increase in erythropoiesis, mild myeloid maturation arrest and hemosiderosis of fixed cells. Pathological sections of the clotted marrow showed that it was moderately fatty. Increased amounts of hemosiderin were present within the reticular and the sinus epithelial cells (Fig. 1).

A skin biopsy obtained from the dorsum of the hand revealed slight to moderate amounts of hemosiderin about the sweat glands (Fig. 2).

Liver needle biopsy showed a well established portal cirrhosis with moderate bile-duct proliferation. Abundant pigment was present within the fibrous stroma, and smaller amounts were found within the hepatic cells proper, as well as within the bile duct epithelium (Fig. 3 and 4). No active degenerative changes were evident.

The hemosiderin present in all three locations exhibited the ferrocyanide reaction characteristic for this pigment.

## DISCUSSION

The clinical picture in this case was sufficiently characteristic to make its discussion unnecessary. The lipemia, however, warrants some consideration. Since it most probably reflects primary digestive-organ impairment, the interrelated functions of the liver, the pancreas and the gastrointestinal tract are involved to a variable degree. Of course, lipemia is a feature of the nephrotic syndrome, but this need not be considered here.

The gastrointestinal tract is probably not at fault. This is a postabsorptive lipemia. As such, it is somewhat more logical to assume that this mani-

## LIPEMIA IN HEMOCHROMATOSIS\*

## Report of a Case

ALFRED R. LENZNER, M.D.,† AND BYRON D. BOWEN, M.D.‡

BUFFALO, NEW YORK

THE occurrence of lipemia in hemochromatosis has not been described in the literature, to our knowledge. The recognition, therefore, of an opaque serum taken from an otherwise typical patient in the fasting state was quite surprising. But so are several variants of hemochromatosis reported since Trousseau's first casual allusion to this syndrome in 1865<sup>1</sup>. For example, of the

etiology per se, they are of as much aid as those for the total iron content would be. The present circumstance, however, does give occasion for careful reconsideration of the causes of postabsorptive lipemia.

## CASE REPORT

A 56-year-old fireboat deckhand was admitted to the hospital in July, 1947, with the chief complaint of failure to gain weight. Diabetes mellitus had been diagnosed 18 months previously, after he had noted polyuria for 8 weeks. These symptoms were accompanied by a 30-pound weight loss. His physician had placed him upon 35 units of protamine insulin daily. No change in weight had followed this regimen. Four months before admission, he had entered another hospital because of painful feet and nocturia. Hepatomegaly, diabetes and pigmentation had been noted by a medical student acting as a subintern. Roentgenograms of the legs had revealed a moderate amount of arterial calcification and mild osteoporosis of the bones of the feet. The first fasting blood glucose had been 211 mg per 100 cc, a cephalin flocculation test had been ++, and the fasting serum collected



FIGURE 1 Section of Bone Marrow Aspirated from the Iliac Crest, Showing Increased Amounts of Hemosiderin in Reticular and Sinus Epithelial Cells (High-Power, Hemosiderin and Eosin Stain)

triad of cirrhosis of the liver, diabetes mellitus and pigmentation, cirrhosis only seems to be constant. In some cases diabetes has been proved not to have been present.<sup>2,3</sup> Others<sup>4</sup> have been unable to demonstrate intradermal pigment, despite apparently typical pigmentation. Moreover, the pathological physiology itself is obscure. One salient fact stands forth, however: these patients do retain abnormal amounts of iron salts.<sup>5</sup> Sheldon<sup>1</sup> has estimated that the total iron content in hemochromatosis may lie between 25 and 50 gm, as compared with a normal of approximately 3 gm.

Up to the present, figures seem to matter little. Those for the increased serum fat in this case are readily available. So far as they might indicate



FIGURE 2 Sweat Gland from the Dorsum of the Hand, Showing Hemosiderin Granules within the Basement Membrane (High-Power, Ferrocyanide Technic)

for an icteric index was reported as "too cloudy" for determination. He had remained on 35 units of protamine insulin until he was admitted for evaluation of the diabetes and other studies.

The patient related that while in high school he had been nicknamed "Gypsy", that he had frequently used argyrol swabs for "colds", but that his skin had become distinctly darker during the onset of overt diabetes. Since the insulin had been started he had regained much of his former strength, there was no nocturia, and his feet had improved. He had had loss of libido and potency for 18 months. He denied alcoholism. The family history was suggestive of hemochromatosis in that his mother had also been dark skinned, but she had died at 75 years of age. His brother, killed acci-

\*From the Buffalo General Hospital and the University of Buffalo School of Medicine.

†Assistant in medicine, University of Buffalo School of Medicine.

‡Professor of clinical medicine, University of Buffalo School of Medicine.

and bone-marrow aspirations showed hemosiderin deposits. Probable factors in this lipemia are suggested, though none can be proved.

## REFERENCES

1. Trousseau. Cited by Sheldon J. H. *Hemochromatosis* 382 pp. London: Oxford University Press, 1905.
2. Butt H. R. and Wilder R. M. Hemochromatosis: report of thirty cases in which diagnosis was made during life. *Arch Path* 26:262-270, 1908.
3. Humphrey A. A., Alpinier S., and Verity L. E. Hemochromatosis: report of case and comment on methods of making definite diagnosis. *Arch Dermat & Syph* 45:1128-1132, 1942.
4. Cantarow A. and Bucher C. J. Hemochromatosis: report of case. *Arch Int Med* 67:333-344, 1941.
5. Marble A. and Smith R. M. Studies of iron metabolism in case of hemochromatosis. *Ann Int Med* 12:1592-1600, 1939.
6. Levy M. S., Power M. H. and Kepler E. J. Specificity of "water test" as diagnostic procedure in Addison's disease. *J Clin. Endocrinol* 6:607-632, 1946.
7. Thannbanser S. J. Serum lipids and their value in diagnosis. *New Eng J Med* 237:515-521, 1947.
8. Man E. B., Karun B. L., Durlacher S. H. and Peters J. P. Lipids of serum and liver in patients with hepatic diseases. *J Clin. Investigation* 24:623-645, 1945.
9. Man E. B. and Peters J. P. Serum lipids in diabetes. *J Clin. Investigation* 14:579-594, 1935.
10. Bailey C. C., Bailey O. T. and Leech, R. S. Alloxan diabetes with diabetic complications. *New Eng J Med* 230:553-556, 1944.
11. Goldner M. G. and Gomori, G. Alloxan diabetes in dog. *Endocrinology* 33:297-308, 1943.
12. Kendall F. E., Meyer W., Lewis L. and Victor J. Alloxan diabetes in rabbits: Production of hypercholesterolemia, hyperlipemia and adrenal cortical lesions. *Proc Soc Exper Biol & Med* 60:190-195, 1945.
13. Bauman L. and Whipple A. O. Diagnostic value of pancreatic function tests in 47 surgically treated cases. *Am. J. M. Sc* 281:290-294.

## THE MEDICAL EXAMINER AND THE PRACTICING PHYSICIAN\*

RICHARD FORD, M.D.

BOSTON

IN THE Commonwealth of Massachusetts, medical examiners and associate medical examiners are county officers appointed for a term of seven years for the purpose of investigating certain classes of deaths. Chapter 38 of the *General Laws* of the Commonwealth (as amended by Chapter 632 of *Acts and Resolves* of 1945) states:

When any person in the Commonwealth is supposed to have died by violence or by the action of chemical, thermal or electrical agents or following abortion, or from diseases resulting from injury or infection relating to occupation, or suddenly when not disabled by recognizable disease, or when any person is found dead, it shall be the duty of any person having knowledge of such death to notify the medical examiner of the district of the county wherein the body lies of the known facts concerning the time, place, manner, circumstances, and cause of such death. A physician who, having knowledge of such a death, fails to notify the medical examiner shall be punished by a fine of not more than one hundred dollars.

In brief, the six categories of deaths to be investigated are violent, chemical, thermal or electrical, deaths resulting from induced abortion, occupational deaths resulting from injury or infection, sudden deaths in the absence of recognizable disease, and persons found dead.

On receipt of notification of a death, there are three courses open to the medical examiner. He may decline jurisdiction over the case, referring it to the attending physician or to a board-of-health physician (if there is one) for certification regarding the cause of death. He may assume jurisdiction, scrutinize available information, make a *visu* of the body (external examination) and certify the cause of death himself. Or he may view the body and then perform an autopsy or cause one to be performed.

When may a medical examiner decline jurisdiction? He may decline when, after ascertaining the available facts, he is satisfied that the death was caused by disease not related to the six categories outlined above.

Who shall certify a death when the medical examiner declines? The attending physician shall certify if he is available and if he attended the decedent at least twice, the last visit being within two weeks before death. If the physician who attended the decedent during his terminal illness is not available or if there has been no attending physician, a board-of-health physician may certify. Thus, board-of-health physicians (in areas where they are appointed) certify the deaths of those disabled by recognized disease not related to the six categories of medical-examiner cases when the attending physician has not seen the decedent within two weeks or when he is absent. Either the mother's physician or a board-of-health physician may certify stillbirths if there has been obstetric or general medical care prior to the birth, and if there is no question of violence, illegitimacy or birth injury.

What are the rules requiring that cases be reported to the medical examiner? The rules of practice vary somewhat among the medical-examiner districts and are evolved usually by collaboration between the medical examiner and the local board of health. In most districts the following cases should be reported:

Any death thought to fall into one of the six categories established by the *General Laws*.

Any hospital death within twenty-four hours of admission.

Any hospital death when the decedent was unconscious on admission and remained so.

\*From the Department of Legal Medicine, Harvard University and the Office of the Associate Medical Examiners, Suffolk County, Massachusetts.

†Research fellow in pathology and legal medicine, Harvard Medical School; associate medical examiner, Suffolk County.

festation reflects an inadequacy of assimilation rather than excessive absorption. Before assaying the contributory roles of the liver and the pancreas, however, an examination of the physical and chemical characteristics of this lipemia may be helpful.

The term "lipemia" as it is used here is a clinical one—that is, it refers to visible amounts of fat in the fasting serum or plasma. The opacity is due to fats in their neutral phase. According to Thannhauser,<sup>7</sup> this is usually but not necessarily always accompanied by hypercholesteremia. Conversely, markedly elevated serum cholesterol and phospholipid levels are exhibited in the perfectly transparent serums of patients with primary biliary "xanthomatous" and cholangiolitic types of cirrhosis. These patients do not have lipemia, however, for their neutral fats are normal in amount. In this case excess neutral fats were not accompanied by an increase in either phospholipids or cholesterol (Table 1).

This fat pattern is a key consideration. It immediately eliminates idiopathic hyperlipemia,

TABLE 1 Serum Fat Analysis \*

	PATIENT mg per 100 cc	NORMAL CONTROL mg per 100 cc
Total fatty acids	599	200-400
Neutral fat	370	0-150
Total phospholipids	151	150-250
Total cholesterol	219	150-260
Cholesterol esters	139 (64%)	70% of total

\*Reported through the courtesy of Dr. Siegfried J. Thannhauser of Boston.

which is characterized by elevated cholesterol and phospholipid levels, in addition to the high neutral fats shown here.

The liver, moreover, is apparently not the prime mover in this lipemia. For although previous laboratory data had shown hepatic dysfunction, the essentially normal phospholipid, cholesterol and cholesterol-ester relations indicated that the hepatic phase of fat metabolism was unremarkable. Man et al.<sup>8</sup> concluded from similar fat studies that a "hypolipemia" usually exists in cirrhosis. The neutral fat seldom exceeded the upper limit of normal, the cholesterol and lipid phosphorus were either normal or decreased, and the cholesterol esters were often decreased. Aside from the pigment present in this liver, the process here is identical with that in Man's cases, and should not per se produce a hyperlipemia of this type. Although some of Thannhauser's cases exhibited mild elevations of neutral fat, these apparently occurred with depressed hepatic function, as shown by manifestly poor cholesterol esterization. Such a depression of function was not observed in the case reported above.

The pancreas, however, may be responsible for this lipemia, by virtue of either islet-cell or even acinar-cell dysfunction. Primary diabetes under control should not logically produce a persistent

postabsorptive neutral hyperlipemia. Man and Peters<sup>9</sup> concluded that "abnormalities of the serum lipoids are related loosely, if at all, to diabetes." When lipemia and hypercholesteremia did occur, these could not be correlated with the "inherent severity of the (islet cell) disease as measured by any recognized criteria." Alloxan diabetes in rabbits<sup>10</sup> and in dogs,<sup>11</sup> moreover, when controlled by insulin, failed to produce a hyperlipemia (total serum lipids). But high lipids and cholesterol accompanied fatal alloxan diabetes in all of Kendall's<sup>12</sup> animals.

The patient in the case reported above is a "fragile" diabetic. On 50 units of protamine zinc insulin daily his blood glucose levels have always been low (less than 100 mg per 100 cc), with rather high postprandial values (more than 240 mg per 100 cc) and glycosuria. There has been no ketosis, however, and the transiently elevated glucose levels should not furnish cause for this lipemia. He has never exhibited clinical shock. Islet-cell diabetes, therefore, does not strike one as being the causative agent here.

Finally, the acinar tissue of the pancreas should be mentioned. The presence of adequate duodenal pancreatic ferments, together with normal stool findings, seems to absolve the acini. Perhaps these tests are too gross for this type of disease. Nevertheless, even the technic of Bauman and Whipple<sup>13</sup> proved more helpful in obstructive pancreatic disease than in the sclerosing type characteristic of hemochromatosis. The evidence against the pancreatic acini is only circumstantial, to be sure, and yet one has the feeling that the pancreas is more guilty than the liver in this case.

Most studies of the pancreas in fat metabolism mention fat accumulations in the liver. It should be pointed out that the remaining liver parenchyma and its regenerates here are not fatty. This is true despite the lipemia and probably pancreatic insufficiency—a combination that might be considered ideal for the production of fatty liver. Here, as also in "idiopathic hyperlipemia," the liver is kept free from fat accumulations in an "environment of plenty," so to speak. One cannot, therefore, identify the specific reason for this lipemia with certainty.

At present, more than two years since his diabetes was first discovered, and despite a gradually increasing lipemia, the patient works every day. The fasting urine remains sugar free on 50 units of protamine zinc insulin. But the underlying lesion apparently continues unabated, for a dermal scar at the site of the liver biopsy has developed the gun-metal pigmentation often associated with hemochromatosis.

#### SUMMARY

A case of lipemia associated with hemochromatosis is reported. Skin biopsy, liver needle sections

An almost equally important function is to assist in the protection of public health from epidemic disease and industrial hazards. An incidental function is to investigate and furnish official records of deaths resulting from trauma of any sort, thereby protecting the rights of employee and employer, policyholder and insurer, civil claimant and defendant in all claims and suits for damages.

In metropolitan areas friction sometimes exists between the resident staffs of the hospitals and the medical examiner's office. It is apparently the firm belief of many of the younger physicians that the medical examiner acts in an ignorant, capricious and indifferent manner, especially with respect to performing autopsies. It is hoped that the exposition of the duties and limitations of power of the office presented above may eliminate this impression. Such critics, if they grant that the medical examiner must certify the cause and manner of death of certain cases without the right to autopsy, complain that bodies are removed from the hospitals by the medical examiner merely for viewing at a mortuary or undertaking establishment without allowing medical attendants the opportunity to seek permission for post-mortem examination by the hospital pathologist. The major cause for removal of bodies solely for view is the inadequacy of information furnished by the hospital to the medical examiner. Frequently, when the reporting hospital is unavoidably limited in information the medical examiner's office must seek out police reports or the records of other hospitals, or per-

haps initiate a police investigation. In the interim, after enduring delays due to locating witnesses and reaching hospital record rooms (open from 9 in the morning to 5 in the afternoon except Saturday afternoon and Sunday), the family has selected an undertaker, and the medical examiner has no right to delay the funeral further to enable the attending physicians to have additional time to solicit permission for autopsy. Sometimes the co-ordination between the administrative and professional staffs of a given hospital is at fault. A case may be declined by the medical examiner and the administration of the hospital notified, but no word is sent to the professional staff that the way is open to request permission.

Often there are limits to the physical capacity of the medical examiner to fulfill his prescribed duties. If during a twenty-four-hour period 10 medicolegal deaths are reported, with between 1 and 5 autopsies necessary in the public interest, it is obviously impossible to travel from place to place to view bodies under trying circumstances. There is, however, a solution to the difficulty. If each hospital were to designate a single physician with the experience and authority necessary to ensure complete and accurate reporting of medicolegal deaths and to facilitate the prompt viewing of bodies at the hospital, more cases would be available for hospital autopsy. No medical examiner, pathologist or general practitioner will deny that autopsy is desirable for the common good.

Any death pronounced by a physician other than the attending physician

Any death when the patient was not attended by a physician within two weeks

All such cases should be reported, but many will be declined at the time of reporting, and others after a preliminary investigation. For example, a man who collapsed at home or in his office and died fifteen minutes after hospital admission may be found to have been treated by the referring physician for a myocardial infarction five days previously. In another case in which a woman dies within twenty-four hours of admission to a hospital in coma the medical examiner may infer from the excessive obesity of the patient, from a positive history of hypertension and from a negative history of trauma that death was due to natural causes. Such cases may be declined by the medical examiner if he is satisfied that there are no reasonable grounds for suspecting that the death was caused or contributed to by physical or chemical injury or occupation.

What is the limit of time between injury and death within which a death must be reported to the medical examiner? There are no limits if the reporting physician believes that the injury caused or contributed to the death. Although the passage of time between injury and death may eliminate criminal responsibility, prevent tort action (damage suit) and make insurance claims contestable, intricacies of law, as when the damage was recognized, make it imperative that the medical examiner make an official record of the circumstances. Where there is not a clearly demonstrable relation between injury and death, the medical examiner may apply the British rule and decline such cases having a time interval in excess of a year and a day.

When may a medical examiner perform an autopsy? According to Chapter 38 of the *General Laws*, as amended

If on view of the dead body and after personal inquiry into the cause and manner of death, the medical examiner considers a further examination necessary in the public interest [he] on his own authority may make or cause to be made in his presence, an autopsy on the aforesaid body

In other words, medical examiners are required to perform an autopsy only if it appears to be necessary in the public interest. A death that is a police matter is apt to require post-mortem examination, either to exonerate a suspect or to substantiate a suspicion. In general, cases likely to reach the criminal courts require autopsy. A death thought to be the result of virulent contagious disease may well require post-mortem confirmation because of the possible hazard to public health. A death related to occupation in industry, as a result of either injury or infection, may require autopsy

in the public interest if others in that industry are exposed to the same hazard. Post-mortem examination of the body of an unknown person found dead may be desirable first, to determine the cause of death and, second, to provide information about the presence of chronic disease, the nature of past surgical procedures, old injuries, and any other anatomic fact that might add to the description of the unknown.

When the circumstances have established that an autopsy may reasonably be required in the public interest, the second criterion should be met—namely, that post-mortem dissection is necessary to establish either cause or manner of death. The body of a man who was seen by reliable witnesses to slip, fall and strike his head and who subsequently died in a hospital with x-ray films showing extensive fractures of the skull does not ordinarily require autopsy. If, on the other hand, a man were found unconscious on the street and subsequently died in a hospital without regaining consciousness and with signs of severe head trauma it would be necessary to perform a postmortem examination to determine to the fullest extent the nature of the injuries. Thus, it is in the public interest to establish whether there was one or multiple impacts, the size and the shape of the object that produced injury, and the presence or absence of disease or intoxication that may have predisposed the deceased to accident or assault. In essence, then, an official autopsy is necessary in cases in which precise detail regarding cause is of value, such as those destined for criminal courts, those in which the manner of death may be ascertained in part or in entirety by determination of the nature of injuries and those in which information contributing to identification may be acquired.

Under certain circumstances a medical examiner is required to perform an autopsy when so instructed

[The medical examiner] if he be so requested by the district attorney or the attorney general, shall make or cause to be made in his presence, an autopsy on the aforesaid body. Upon written order of the district attorney of the district where the body lies, or of the attorney general, a medical examiner shall also make, or cause to be made in his presence, an autopsy of any dead body within this county.

In simpler wording, on request—verbal or written—of either the attorney general or the district attorney, a medical examiner is required to perform an autopsy.

It should now be clear that a medical examiner does not act according to whim. He declines jurisdiction, or accepts and views a case, or performs an autopsy according to certain rules, which are derived from the *General Laws* of the Commonwealth. The most important function of the medical examiner is to protect the public by the acquisition of accurate medical evidence in deaths known or suspected to have resulted from criminal action.

An almost equally important function is to assist in the protection of public health from epidemic disease and industrial hazards. An incidental function is to investigate and furnish official records of deaths resulting from trauma of any sort, thereby protecting the rights of employee and employer, policyholder and insurer, civil claimant and defendant in all claims and suits for damages.

In metropolitan areas friction sometimes exists between the resident staffs of the hospitals and the medical examiner's office. It is apparently the firm belief of many of the younger physicians that the medical examiner acts in an ignorant, capricious and indifferent manner, especially with respect to performing autopsies. It is hoped that the exposition of the duties and limitations of power of the office presented above may eliminate this impression. Such critics, if they grant that the medical examiner must certify the cause and manner of death of certain cases without the right to autopsy, complain that bodies are removed from the hospitals by the medical examiner merely for viewing at a mortuary or undertaking establishment without allowing medical attendants the opportunity to seek permission for post-mortem examination by the hospital pathologist. The major cause for removal of bodies solely for view is the inadequacy of information furnished by the hospital to the medical examiner. Frequently, when the reporting hospital is unavoidably limited in information the medical examiner's office must seek out police reports or the records of other hospitals, or per-

haps initiate a police investigation. In the interim, after enduring delays due to locating witnesses and reaching hospital record rooms (open from 9 in the morning to 5 in the afternoon except Saturday afternoon and Sunday), the family has selected an undertaker, and the medical examiner has no right to delay the funeral further to enable the attending physicians to have additional time to solicit permission for autopsy. Sometimes the co-ordination between the administrative and professional staffs of a given hospital is at fault. A case may be declined by the medical examiner and the administration of the hospital notified, but no word is sent to the professional staff that the way is open to request permission.

Often there are limits to the physical capacity of the medical examiner to fulfill his prescribed duties. If during a twenty-four-hour period 10 medicolegal deaths are reported, with between 1 and 5 autopsies necessary in the public interest, it is obviously impossible to travel from place to place to view bodies under trying circumstances. There is, however, a solution to the difficulty. If each hospital were to designate a single physician with the experience and authority necessary to ensure complete and accurate reporting of medicolegal deaths and to facilitate the prompt viewing of bodies at the hospital, more cases would be available for hospital autopsy. No medical examiner, pathologist or general practitioner will deny that autopsy is desirable for the common good.

## MEDICAL PROGRESS

## BAL\*

RAYMOND V RANDALL, M D, AND ALBERT O SEELER, M D †

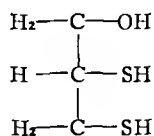
BOSTON

THE discovery of BAL (2,3-dimercaptopropanol) by Peters and his co-workers<sup>1</sup> in England was the result of an intensive search for a substance that would be effective in treating severe burns caused by contact with certain arsenical war gases such as lewisite. The name BAL is an abbreviation of "British Anti-Lewisite," a term applied to this substance after it had proved to be effective against lewisite. It was soon found that this compound was of value not only in treating the local effects of arsenical war gases but also in combating the systemic disturbances following their absorption. Moreover, BAL proved to be effective in the treatment of toxic reaction caused by arsenical drugs used in the therapy of syphilis. Further investigation showed that the substance was of value in the treatment of poisonings from a number of other metals.

The studies on BAL and related compounds have not only led to the development of a valuable therapeutic agent but also contributed to an understanding of the mode of action of various metals.

CHEMISTRY AND PROPERTIES<sup>2-4</sup>

The chemical name for BAL is 2,3-dimercaptopropanol. It contains two thiol groups (also known as sulfhydryl [-SH] groups) and consequently 2,3-dithiopropanol is a commonly used synonym. Its structural formula is



BAL has a molecular weight of 124.2 and a specific gravity of 1.21, and is an oily, colorless liquid with a skunklike odor. In common with a number of closely related dithiols, the compound is a sluggish, nonautooxidizable, oxidation-reduction system, easily oxidized in the presence of a number of catalysts, especially copper and iron porphyrins. BAL reacts with a number of metals to form BAL-metal complexes. Colored complexes are formed with iron, lead, bismuth, tin, copper, cobalt, nickel,

antimony and selenium. Zinc, cadmium and mercury combine with BAL to give white precipitates, and magnesium and manganese form colorless, soluble complexes. BAL instantaneously converts methemoglobin to oxyhemoglobin in the presence of oxygen.

BAL is soluble in water to the extent of 6 per cent (weight/volume). Because it is readily oxidized, aqueous solutions are unstable and must be prepared immediately before use. The compound is relatively stable in peanut oil, but soluble in this vehicle only to the extent of 5 per cent (weight/volume). However, when it is mixed with benzyl benzoate in the ratio of 1 part of BAL to 2 parts of benzyl benzoate it is miscible with peanut oil in all proportions. Such preparations are homogenous but become cloudy at icebox temperatures. This cloudiness readily disappears when the preparation is warmed to room temperature. Commercial preparations of BAL contain 10 per cent BAL and 20 per cent benzyl benzoate (weight/volume) in peanut oil and are suitable for intramuscular use only. Sterilization of such preparations by autoclaving at 120°C for twenty minutes may cause the loss of as much as 15 per cent of the available sulfhydryl groups by oxidation. If, however, these preparations are placed under nitrogen they may be autoclaved without significant decomposition.

## MODE OF ACTION OF HEAVY METALS AND BAL

During the past twenty-five years, the concept has arisen that heavy metals owe their toxicity, at least in large part, to their ability to combine with sulfhydryl groups of the protein fractions of enzymes. Studies that ultimately led to this concept and to the development of BAL began in 1923 when Voegtlin, Dyer and Leonard<sup>5</sup> showed that glutathione, as well as other monothiols (substances containing one thiol or sulfhydryl group), could counteract the toxic action of arsenoxides on trypanosomes both in vitro and in vivo. They further showed that glutathione delayed the onset of symptoms and death in rats given a lethal dose of arsenoxide. On the basis of these findings, they postulated that arsenoxide could be regarded as a specific poison affecting the sulfhydryl groups of some essential protoplasmic constituent. The addition of the monothiols presumably supplied extra sulfhydryl groups, which united with and thereby counteracted the toxicity of the arsenic. The au-

\*From the Department of Industrial Hygiene, Harvard School of Public Health.

This study was aided by a grant from the Medical Advisory Committee of the American Petroleum Institute.

†Assistant professor of industrial medicine, Harvard School of Public Health.

thors also assumed that the union between the arsenic and the added sulfhydryl groups was not stable—otherwise glutathione would have prevented rather than merely delayed death in rats given lethal doses of arsenic. Further evidence of the relation of sulfhydryl groups to the toxicity of arsenic was the observation of Walker<sup>6</sup> in 1928 that *Colpidium colpoda*, a unicellular organism, could be temporarily revived after arsenic poisoning by the addition of sodium thioglycollate.

Similarity in the mode of action of arsenic, bismuth and mercury compounds was demonstrated in 1939 by Eagle,<sup>7</sup> who showed that various sulfhydryl-containing substances abolished the anti-spirochetal action in vitro of bismuth and mercury as well as of arsenic. He found that thiamine chloride and methionine, which contain sulfide (—S—) rather than sulfhydryl (—SH) groups did not have a similar inhibitory effect on these heavy metals.

Studies on proteins and enzyme systems have also been carried out in an attempt to discover the mode of action of arsenic. Szent-Györgyi,<sup>8</sup> in 1930, showed that arsenic strongly inhibited the respiration of minced liver tissue. Voegtlin, Rosenthal and Johnson<sup>9</sup> found that glutathione added to rat tissue slices prevented the reduction in oxygen consumption caused by arsenic alone. These findings also suggested that sulfhydryl groups were intimately concerned with tissue respiration, and that the action of arsenic upon living tissue was primarily through the tissue's sulfhydryl compounds. Further evidence in support of these views was forthcoming in 1932, when Rosenthal<sup>10</sup> showed that although arsenic combined with proteins containing sulfhydryl groups, it did not combine with proteins in the absence of these groups.

In the course of studies on arsenical war gases, Peters, Sinclair and Thompson<sup>11</sup> found the enzyme pyruvate oxidase to be sensitive to small concentrations of arsenic or lewisite. Since none of the coenzymes known to be concerned with the pyruvate oxidase system were sensitive to lewisite, it was concluded that the point of attack of arsenic was upon a protein component of the enzyme system. It was soon demonstrated that a protein containing sulfhydryl groups was essential for the function of pyruvate oxidase and that blockage of these groups would inactivate the enzyme.<sup>12</sup> These findings indicated that the toxic action of arsenic was due, not to some nonspecific denaturant or coagulant effect upon cellular constituents, but to enzyme inhibition.

In contrast to the work mentioned above, wherein it had been found that monothiol afforded protection against various arsenic compounds, Sinclair (as quoted by Peters et al.<sup>11</sup>) found that monothiols, even when present in large excess, failed to protect pyruvate oxidase from the toxic action of lewisite. It, therefore, seemed important to re-

investigate the nature of the union between arsenic and protein sulfhydryl groups. Since it was impossible to obtain an arsenic-sensitive enzyme, such as pyruvate oxidase, in a purified state, Stocken and Thompson<sup>13</sup> studied kerateine, a derived protein containing many sulfhydryl groups. They found that at least 75 per cent of the arsenic in the lewisite-protein complex was in combination with two sulfhydryl groups. Additional findings made it seem probable that the arsenic had combined with two sulfhydryl groups closely placed on the same protein molecule to form a ring. On physicochemical grounds it was predicted that



FIGURE 1 Ring Structure FIGURE 2 Open-Chain Structure

a ring compound (Fig 1) would be more stable than an open-chain structure formed by the union of arsenic with two monothiol molecules (Fig 2). On the basis of this reasoning, it appeared that a substance capable of competing successfully with tissue proteins for arsenic must also be capable of forming a ring compound as stable as, and preferably more stable than, that formed between arsenic and the proteins. Supporting this view was the work cited above<sup>5-7</sup> showing that monothiols delayed but did

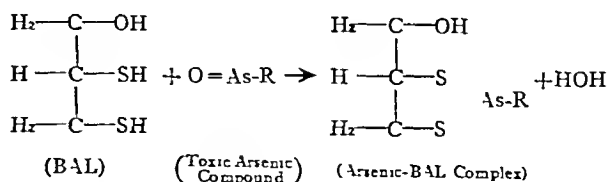


FIGURE 3 Reaction Between Arsenic and BAL

not always prevent the death of animals poisoned with arsenic.

Stocken and Thompson<sup>14</sup> decided to experiment with various dithiols because they believed that these compounds with their two sulfhydryl groups might be capable of forming stable cyclic combinations with arsenic. Numerous dithiols were tested, some with as many as 12 carbon atoms between the two sulfhydryl groups, and a number were found to react with arsenic to form a stable ring structure. However, not all the latter compounds were satisfactory on pharmacologic grounds, and it was only after extensive animal studies that BAL was selected as the most promising compound.

## MEDICAL PROGRESS

### BAL\*

RAYMOND V RANDALL, M D, AND ALBERT O SEELER, M D †

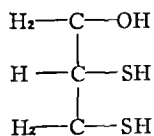
BOSTON

THE discovery of BAL (2,3-dimercaptopropanol) by Peters and his co-workers<sup>1</sup> in England was the result of an intensive search for a substance that would be effective in treating severe burns caused by contact with certain arsenical war gases such as lewisite. The name BAL is an abbreviation of "British Anti-Lewisite," a term applied to this substance after it had proved to be effective against lewisite. It was soon found that this compound was of value not only in treating the local effects of arsenical war gases but also in combating the systemic disturbances following their absorption. Moreover, BAL proved to be effective in the treatment of toxic reaction caused by arsenical drugs used in the therapy of syphilis. Further investigation showed that the substance was of value in the treatment of poisonings from a number of other metals.

The studies on BAL and related compounds have not only led to the development of a valuable therapeutic agent but also contributed to an understanding of the mode of action of various metals.

#### CHEMISTRY AND PROPERTIES<sup>2-4</sup>

The chemical name for BAL is 2,3-dimercaptopropanol. It contains two thiol groups (also known as sulfhydryl [-SH] groups) and consequently 2,3-dithiopropanol is a commonly used synonym. Its structural formula is



BAL has a molecular weight of 124.2 and a specific gravity of 1.21, and is an oily, colorless liquid with a skunklike odor. In common with a number of closely related dithiols, the compound is a sluggish, nonautoxidizable, oxidation-reduction system, easily oxidized in the presence of a number of catalysts, especially copper and iron porphyrins. BAL reacts with a number of metals to form BAL-metal complexes. Colored complexes are formed with iron, lead, bismuth, tin, copper, cobalt, nickel,

antimony and selenium. Zinc, cadmium and mercury combine with BAL to give white precipitates, and magnesium and manganese form colorless, soluble complexes. BAL instantaneously converts methemoglobin to oxyhemoglobin in the presence of oxygen.

BAL is soluble in water to the extent of 6 per cent (weight/volume). Because it is readily oxidized, aqueous solutions are unstable and must be prepared immediately before use. The compound is relatively stable in peanut oil, but soluble in this vehicle only to the extent of 5 per cent (weight/volume). However, when it is mixed with benzyl benzoate in the ratio of 1 part of BAL to 2 parts of benzyl benzoate it is miscible with peanut oil in all proportions. Such preparations are homogenous but become cloudy at icebox temperatures. This cloudiness readily disappears when the preparation is warmed to room temperature. Commercial preparations of BAL contain 10 per cent BAL and 20 per cent benzyl benzoate (weight/volume) in peanut oil and are suitable for intramuscular use only. Sterilization of such preparations by autoclaving at 120°C for twenty minutes may cause the loss of as much as 15 per cent of the available sulfhydryl groups by oxidation. If, however, these preparations are placed under nitrogen they may be autoclaved without significant decomposition.

#### MODE OF ACTION OF HEAVY METALS AND BAL

During the past twenty-five years, the concept has arisen that heavy metals owe their toxicity, at least in large part, to their ability to combine with sulfhydryl groups of the protein fractions of enzymes. Studies that ultimately led to this concept and to the development of BAL began in 1923 when Voegtlin, Dyer and Leonard<sup>5</sup> showed that glutathione, as well as other monothiols (substances containing one thiol or sulfhydryl group), could counteract the toxic action of arsenoxides on trypanosomes both in vitro and in vivo. They further showed that glutathione delayed the onset of symptoms and death in rats given a lethal dose of arsenoxide. On the basis of these findings, they postulated that arsenoxide could be regarded as a specific poison affecting the sulfhydryl groups of some essential protoplasmic constituent. The addition of the monothiols presumably supplied extra sulfhydryl groups, which united with and thereby counteracted the toxicity of the arsenic. The au-

\*From the Department of Industrial Hygiene, Harvard School of Public Health.

This study was aided by a grant from the Medical Advisory Committee of the American Petroleum Institute.

†Assistant professor of industrial medicine, Harvard School of Public Health.

blood pressure is common, but this soon gives way to vascular collapse<sup>22</sup>

Undiluted BAL applied directly to the skin and mucous membranes causes localized redness, edema and capillary injury<sup>23, 24</sup>

Electroencephalograms taken during BAL-induced convulsions in rabbits have revealed that they are not cortical in origin. Studies following transection of the thoracic cord further showed that the convulsions do not arise in the cord. The exact site of origin has not been established. Sodium pentobarbital controlled these convulsions, but death from vascular collapse usually occurred<sup>22</sup>

In moderate doses, BAL is a respiratory stimulant. Large doses stimulate respiration initially, but severe depression of the respiratory center follows<sup>22</sup>

BAL causes an initial arteriolar constriction resulting in a rise in blood pressure. This effect is not mediated through the central nervous system, but is the result of a direct action upon the vessel walls. Subsequently, BAL may cause extensive capillary damage, which can lead to irreversible shock<sup>25, 26</sup>

In dogs, an intramuscular, lethal dose of BAL (100 mg per kilogram of body weight) has produced early hyperglycemia with glycosuria and subsequent preterminal hypoglycemia. Convulsions occurring in these animals were not hypoglycemic because they began while the blood sugar was still elevated. Histologic examination of the liver failed to reveal any evidence of hepatic-cell damage<sup>22</sup>. However, fatty degeneration and occasional necrosis have been found in the livers of dogs given daily intramuscular doses of 15 to 30 mg per kilogram of body weight for four days<sup>27</sup>. The possibility that the clinical use of BAL might be contraindicated in some cases of hepatic damage has been raised by the finding that animals with livers damaged by carbon tetrachloride showed toxic signs after doses of BAL that were ordinarily well tolerated<sup>28</sup>. However, BAL has been used in a number of patients with so-called postarsenical hepatitis, and there is no mention of extraordinarily toxic manifestations occurring in these persons.

Although the anticoagulant effect of BAL *in vitro* is pronounced, doubling the prothrombin time of human plasma, it has not been reported to produce hemorrhagic tendencies *in vivo*. Fantl and Nance<sup>29</sup> found that rabbits given BAL intramuscularly showed no changes in prothrombin time or coagulation time.

In general, histologic studies of animals receiving both single and repeated doses of BAL have failed to reveal conspicuous morphologic changes except in those dying from acutely lethal doses. Such animals show pulmonary hemorrhages and edema, which are probably the results of the marked vascular action of BAL. Isolated instances of thickening of alveolar walls and renal tubular degeneration have been seen, but it is impossible to correlate

these rare findings with the administration of BAL<sup>22</sup>. As noted above, liver damage has been observed to follow large doses.

### *Action on Man*

All clinicians who have written about the therapeutic uses of BAL warn of the undesirable side effects that may occur. Eagle and Magnuson<sup>30</sup> have reported the incidence of toxic manifestations following the intramuscular administration of BAL to 60 normal subjects and 61 patients with arsenical poisoning. At a dose level of 2.5 mg per kilogram of body weight, less than 1 per cent of injections were followed by mild toxic signs and symptoms. At a level of 4 mg per kilogram, mild to moderate reactions were noted in about 15 per cent of cases, and at a level of 5 mg 50 to 60 per cent had reactions. Localized pain at the site of injection was not uncommon, but it was no more severe than that seen after the intramuscular administration of a number of other therapeutic agents. The usual toxic manifestations were nausea, vomiting, headache, burning sensations of the mouth and eyes, lacrimation, profuse salivation, rhinorrhea, muscular aches, tingling of the extremities, sweating of the forehead and hands, pain in the teeth, a sense of constriction in the chest, anxiety and general agitation. Transient elevation of blood pressure was common. The symptoms began about ten to twenty minutes after the injections, reached a maximum in twenty to thirty minutes, and disappeared within fifty to ninety minutes. These findings are in accord with those of Modell et al<sup>31</sup> who, in addition, observed that single doses of 8 mg per kilogram of body weight almost invariably produced marked symptomatology. They also found that doses of 5 mg per kilogram could be repeated every three hours for twenty-four hours without significant cumulative effects.

Woodruff and Kometani<sup>32</sup> reported the case of a child who received two overdoses of BAL of 25 mg per kilogram each. Thirty minutes after the first overdose the child developed anorexia, vomiting and restlessness, all subsiding in an hour. Ten minutes after the second overdose (given three hours later) examination showed cutaneous flushing, mild hyperpyrexia, tachycardia, hypertension, a generalized convulsion lasting for three minutes and coma and stupor lasting for an hour. After the coma the child appeared to be normal, and recovery was uneventful.

Localized abscesses at the site of injection occur occasionally<sup>30</sup>. They seem to occur most frequently in cases of arsenical dermatitis in which the intramuscular needles have passed through infected tissues, and, therefore, are probably the result of secondary infection rather than a direct action of BAL upon the tissues.

Application to the skin can cause varying degrees of localized reactions ranging from mild erythema

It now seems clear that the antidotal action of BAL lies in its ability to unite with arsenic to form a relatively stable cyclic compound and thus to compete successfully with the sulfhydryl groups of tissue proteins for arsenic. This action is both prophylactic and therapeutic, because BAL can unite with arsenic before it enters into combination with the tissues (Fig 3) as well as wrest arsenic away from the tissues (Fig 4).

## PHARMACOLOGY

### Action on Enzymes

In an attempt to arrive at an understanding of the toxicity of BAL, Webb and van Heyningen<sup>15</sup> studied its action on a large number of enzyme

### Absorption, Metabolism and Excretion<sup>17-21</sup>

Studies with radioactive BAL (BAL containing radioactive sulfur) have shown that it is slowly absorbed through the skin but rapidly dispersed once it penetrates the cutaneous barrier. Radioactive BAL given intramuscularly has disappeared rapidly from the site of injection, with no radioactivity remaining at the site after six hours. Within five minutes after instillation into the conjunctival sac of the rabbit, BAL has been recovered from the aqueous of the anterior chamber.

Experiments with rabbits given intramuscular injections of radioactive BAL have shown that 80 per cent of the injected BAL entered the circulation and was distributed throughout the body within

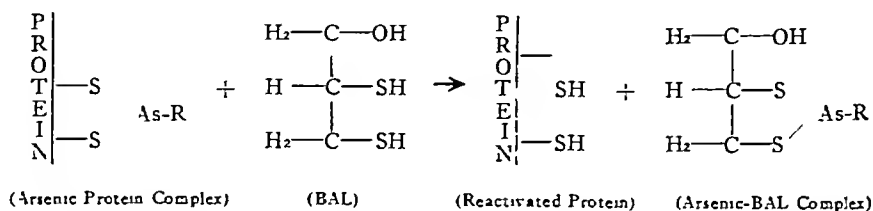


FIGURE 4 BAL Reactivation of an Arsenic-Poisoned Tissue Protein

systems. They found seven enzymes to be strongly inhibited by BAL: polyphenol oxidase, carbonic anhydrase, catalase, peroxidase, aldehyde mutase, phosphorylase and glyoxalase. Of these, four are known to be metal-containing enzymes: polyphenol oxidase (copper), carbonic anhydrase (zinc), catalase (iron), and peroxidase (iron). In view of the fact that BAL forms complexes with these metals,<sup>3</sup> it is likely that it inhibits the enzymes by combining with their metal radicals. In further support of this hypothesis is the finding that the addition of a copper salt to polyphenol oxidase inhibited by BAL restores the activity of this copper-containing enzyme. Cytochrome oxidase is the only metal-containing enzyme that was examined and found not to be inhibited by BAL. This was thought to be due to a rapid oxidation and inactivation of BAL when it comes in contact with this enzyme. No explanation is offered for the inhibition of aldehyde mutase and phosphorylase, although it is pointed out that these, too, may be metallic enzymes. It is believed that glyoxalase, which does not contain a metal but does contain glutathione (a monothiol), is inhibited by BAL, because the BAL can compete successfully with the monothiol for a position in the enzyme structure.

Barron et al.<sup>16</sup> found that BAL decreased the respiration of tissue slices and inhibited cytochrome C and succinoxidase. They also noted that BAL destroyed the activity of insulin by reduction of its —S—S— linkages.

an hour of injection. A fairly uniform blood level was maintained for two hours. This level was halved by the third hour, and fell to a third of the original value by the seventh hour. Aside from somewhat higher concentrations in the kidney and intestine, BAL was diffusely distributed throughout the body.

Only minute amounts of BAL have been found to be excreted by the respiratory tract although its skunklike odor may be detected in the expired air. Studies have shown that the major portion of absorbed BAL is rapidly metabolized and excreted in the urine. After single injections of radioactive BAL, 45 per cent of the total radioactivity could be recovered from the urine within six hours, and 81 per cent within twenty-four hours. Only a small proportion of the radioactive substances recoverable from the urine was in the form of unchanged BAL.

### Action on Animals

In general, the signs and symptoms of BAL toxicity are ushered in by an initial period of apathy accompanied by lacrimation, blepharospasm and conjunctival edema. With increasing dosage, one finds in addition to the above muscle tremors of gradually increasing intensity, inco-ordination, ataxia, especially of the hind limbs, dyspnea, and finally generalized clonic convulsions, coma and death. Only an occasional animal recovers once convulsions have begun. An early transient rise in

blood pressure is common, but this soon gives way to vascular collapse<sup>22-23</sup>

Undiluted BAL applied directly to the skin and mucous membranes causes localized redness, edema and capillary injury<sup>23-24</sup>

Electroencephalograms taken during BAL-induced convulsions in rabbits have revealed that they are not cortical in origin. Studies following transection of the thoracic cord further showed that the convulsions do not arise in the cord. The exact site of origin has not been established. Sodium pentobarbital controlled these convulsions, but death from vascular collapse usually occurred<sup>22</sup>

In moderate doses, BAL is a respiratory stimulant. Large doses stimulate respiration initially, but severe depression of the respiratory center follows<sup>22-23</sup>

BAL causes an initial arteriolar constriction resulting in a rise in blood pressure. This effect is not mediated through the central nervous system, but is the result of a direct action upon the vessel walls. Subsequently, BAL may cause extensive capillary damage which can lead to irreversible shock<sup>25-26</sup>

In dogs, an intramuscular lethal dose of BAL (100 mg per kilogram of body weight) has produced early hyperglycemia with glycosuria and subsequent preterminal hypoglycemia. Convulsions occurring in these animals were not hypoglycemic because they began while the blood sugar was still elevated. Histologic examination of the liver failed to reveal any evidence of hepatic-cell damage<sup>22</sup>. However, fatty degeneration and occasional necrosis have been found in the livers of dogs given daily intramuscular doses of 15 to 30 mg per kilogram of body weight for four days<sup>27</sup>. The possibility that the clinical use of BAL might be contraindicated in some cases of hepatic damage has been raised by the finding that animals with livers damaged by carbon tetrachloride showed toxic signs after doses of BAL that were ordinarily well tolerated<sup>28</sup>. However, BAL has been used in a number of patients with so-called postarsenical hepatitis, and there is no mention of extraordinarily toxic manifestations occurring in these persons.

Although the anticoagulant effect of BAL *in vitro* is pronounced, doubling the prothrombin time of human plasma, it has not been reported to produce hemorrhagic tendencies *in vivo*. Fantl and Nance<sup>29</sup> found that rabbits given BAL intramuscularly showed no changes in prothrombin time or coagulation time.

In general, histologic studies of animals receiving both single and repeated doses of BAL have failed to reveal conspicuous morphologic changes except in those dying from acutely lethal doses. Such animals show pulmonary hemorrhages and edema, which are probably the results of the marked vascular action of BAL. Isolated instances of thickening of alveolar walls and renal tubular degeneration have been seen, but it is impossible to correlate

these rare findings with the administration of BAL<sup>23</sup>. As noted above, liver damage has been observed to follow large doses.

#### *Action on Man*

All clinicians who have written about the therapeutic uses of BAL warn of the undesirable side effects that may occur. Eagle and Magnuson<sup>30</sup> have reported the incidence of toxic manifestations following the intramuscular administration of BAL to 60 normal subjects and 61 patients with arsenical poisoning. At a dose level of 2.5 mg per kilogram of body weight, less than 1 per cent of injections were followed by mild toxic signs and symptoms. At a level of 4 mg per kilogram mild to moderate reactions were noted in about 15 per cent of cases, and at a level of 5 mg, 50 to 60 per cent had reactions. Localized pain at the site of injection was not uncommon, but it was no more severe than that seen after the intramuscular administration of a number of other therapeutic agents. The usual toxic manifestations were nausea, vomiting, headache, burning sensations of the mouth and eyes, lacrimation, profuse salivation, rhinorrhea, muscular aches, tingling of the extremities, sweating of the forehead and hands, pain in the teeth, a sense of constriction in the chest, anxiety and general agitation. Transient elevation of blood pressure was common. The symptoms began about ten to twenty minutes after the injections, reached a maximum in twenty to thirty minutes, and disappeared within fifty to ninety minutes. These findings are in accord with those of Modell et al,<sup>31</sup> who, in addition, observed that single doses of 8 mg per kilogram of body weight almost invariably produced marked symptomatology. They also found that doses of 5 mg per kilogram could be repeated every three hours for twenty-four hours without significant cumulative effects.

Woodv and Kometani<sup>32</sup> reported the case of a child who received two overdoses of BAL of 25 mg per kilogram each. Thirty minutes after the first overdose the child developed anorexia, vomiting and restlessness, all subsiding in an hour. Ten minutes after the second overdose (given three hours later) examination showed cutaneous flushing, mild hyperpyrexia, tachycardia, hypertension, a generalized convulsion lasting for three minutes and coma and stupor lasting for an hour. After the coma the child appeared to be normal and recovery was uneventful.

Localized abscesses at the site of injection occur occasionally<sup>30</sup>. They seem to occur most frequently in cases of arsenical dermatitis in which the intramuscular needles have passed through infected tissues, and, therefore, are probably the result of secondary infection rather than a direct action of BAL upon the tissues.

Application to the skin can cause varying degrees of localized reactions ranging from mild erythema

to severe whealing and capillary damage<sup>19</sup> Sulzberger<sup>33</sup> was able to create skin sensitization with repeated applications of a 5 per cent BAL ointment to normal skin. Sixteen of 88 human subjects (19 per cent) developed localized reactions varying from faint erythema with pinhead-sized, papulo-urticarial lesions to marked erythema with confluent urticarial and papular lesions lasting up to five days. These relatively persistent lesions should be distinguished from the erythema and whealing frequently noted after topical application of BAL, which disappear in fifteen minutes to two hours. When applied to skin previously damaged by mustard gas, BAL caused a definite dermatitis in 35 out of 53 subjects (66 per cent).

Epinephrine has been used successfully to alleviate the undesirable side effects of BAL. 0.6 of 1 cc of 1:1000 epinephrine hydrochloride solution gave rapid and complete relief. Oral or parenteral administration of 25 mg of ephedrine sulfate half an hour before the administration of BAL prevented the onset of symptoms.<sup>34</sup>

### COMPOUNDS RELATED TO BAL

Although many compounds related to BAL have been studied, only two are of particular interest — namely, the ethyl ether of BAL and BAL glucoside.

The ethyl ether of BAL is more toxic than BAL. Whereas the initial toxic manifestations of this compound are similar to those produced by BAL, death, when it occurs, is not acute but is almost invariably delayed for days or weeks. Even doses forty times greater than those necessary to produce mild symptoms do not kill immediately. In spite of its comparatively great toxicity the ethyl ether of BAL is of interest because it is more effective than BAL in the treatment of arsine poisoning in animal experiments.<sup>24, 35</sup>

BAL glucoside (BAL-intrav) is much less toxic than BAL and has the advantage of being freely water soluble. Doses as large as 100 mg per kilogram of body weight have been given intravenously to man without apparent ill effects, whereas BAL itself may produce symptoms when given intramuscularly in doses of 4 mg per kilogram. Unfortunately, there are not sufficient data to permit a quantitative comparison of the therapeutic activity of BAL glucoside with BAL, but the limited information available suggests that the former has a more satisfactory therapeutic index than the latter.<sup>36-38</sup>

### BAL IN SPECIFIC POISONINGS

Although the immediate interest at the time BAL was developed was the treatment of arsenical war-gas poisoning, it soon became apparent that the compound was of value in the therapy of arsenical poisoning in general. Investigation of its value in other heavy-metal poisonings indicated that BAL could not be used indiscriminately in the treat-

ment of all because in some cases it not only was valueless but also actually appeared to enhance the toxicity of a metal. The concluding section of this progress report will be devoted to a discussion of the role of BAL in the treatment of specific metal poisonings, and mention will also be made of the effects of BAL on the action of alloxan and phenylthiourea.

(To be concluded)

### REFERENCES

- Peters R. A., Stocken L. A. and Thompson R. H. S. British anti-lewisite (BAL). *Nature* 156 616-619 1945
- Waters L. L. and Stock, C. BAL (British anti-lewisite). *Science* 102 601-606 1945
- Barroo E. S. G. Miller Z. B. and Kalnitsky, G. Oxidation of dithiols. *Biochem J* 41 62-68 1947
- Eagle, H. Magnuson H. J. and Fleischman, R. Clinical uses of 2,3-dimercaptopropanol (BAL). I. Systemic treatment of experimental arsenic poisoning (mapharsen lewisite phenyl arsenoxide) with BAL. *J Clin Investigation* 25 451-466 1946
- Voegtlin C., Dyer H. A., and Lennard C. S. On mechanism of action of arsenic upon protoplasm. *Pub Health Rep* 38 1881 1912 1923
- Walker E. Chemical constitution and toxicity. *Biochem J* 22 291-305 1928
- Eagle H. Effect of sulphydryl compounds on antispasmodic action of arsenic, bismuth and mercury compounds in vitro. *J Pharmacol & Exper Therap* 66 436-448 1939
- Szent-Györgyi A. Action of arsenite on tissue respiration. *Biochem J* 24 1723-1727 1930
- Voegtlin C. Rosenthal S. M. and Johnson J. M. Influence of arsenicals and crystalline glutathione on oxygen consumption of tissues. *Pub Health Rep* 46 339 354 1931
- Rosenthal S. M. Action of arsenic upon fixed sulphydryl groups of proteins. *Pub Health Rep* 47 241 256 1932
- Peters R. A., Sinclair, H. M. and Thompson, R. H. S. Analysis of inhibition of pyruvate oxidation by arsenicals in relation to enzyme theory of vesication. *Biochem J* 40 516-524 1946
- Peters R. A., and Wakelin R. W. Observations upon relation between sulphydryl groups and pyruvate oxidation in brain tissue. *Biochem J* 40 513 516 1946
- Stocken L. A. and Thompson R. H. S. British anti-lewisite. I. Arsenic derivatives of thiol proteins. *Biochem J* 40 529 535 1946
- Idem. British anti-lewisite. 2. Dithiol compounds as antidotes for arsenic. *Biochem J* 40 535-548 1946
- Webb E. C. and van Heyningen R. Action of British anti-lewisite (BAL) on enzyme systems. *Biochem J* 41 74-78 1947
- Barron E. S. G. Miller Z. B. and Meyer J. Effect of 2,3-dimercaptopropanol on activity of enzymes and on metabolism of tissues. *Biochem J* 41 78-82 1947
- Young L. Canadian researches on BAL (British anti-lewisite). *Science* 103 439, 1946
- Peters R. A. et al. Use of British anti-lewisite containing radioactive sulphur for metabolism investigations. *Biochem J* 41 370 373 1947
- Sulzberger M. B. Baer R. L. and Kanof A. Clinical uses of 2,3-dimercaptopropanol (BAL). III. Studies on toxicity of BAL on percutaneous and parenteral administration. *J Clin Investigation* 25 474-479 1946
- Adler F. H. Leopold I. H. Steele, W. H. S. and Crandall A. S. Cited by Hughes W. F. Jr. Clinical uses of 2,3-dimercaptopropanol (BAL). IX. Treatment of lewisite burns of eye with BAL. *J Clin Investigation* 25 541-548 1946
- Wexler J. et al. Clinical uses of 2,3-dimercaptopropanol (BAL). II. Effect of BAL on excretion of arsenic in normal subjects and after minimal exposure to arsenical smoke. *J Clin Investigation* 25 467-473 1946
- Durlacher S. H. et al. Toxicological action of 2,3-dimercaptopropanol (BAL). *J Pharmacol & Exper Therap* (Supp) 87 28-32, 1946.
- Madell W. Chenneth M. B. and Krop, S. Toxicology of 2,3-dimercaptopropanol (BAL) in cats. *J Pharmacol & Exper Therap* (Supp) 87 33-40 1946
- Fitzhugh O. G. et al. Toxicities of compounds related to BAL (2,3-dimercaptopropanol) with note on their relative therapeutic efficiency. *J Pharmacol & Exper Therap* (Supp) 87 13-27, 1946.
- Chenneth M. B. Cardio-vascular actions of 2,3-dimercaptopropanol (BAL). *J Pharmacol & Exper Therap* (Supp) 87 41-54 1946.
- Hitchcock P. Effect of dithiols and other enzyme inhibitors on blood vessels. *J Pharmacol & Exper Therap* (Supp) 87 55 59 1946
- MacNider W. de B. Liver injury in dog following use of 2,3-dimercaptopropanol (BAL). *Proc Soc Exper Biol & Med* 66 444-446 1947
- Cameron, Burgess and Trenwith. Cited by Peters et al.
- Faoth, P. and Nance M. H. Influence of 2,3-dimercaptopropanol (BAL) on blood coagulation. *Nature London* 159 777 1947

- 30 Eagle H and Magnuson H J Systemic treatment of 227 cases of arsenic poisoning (encephalitis dermatitis blood dyscrasias jaundice fever) with 2,3-dimercaptopropanol (BAL) *Am J Syph Gonor & Ven Dis* 30 420-441 1946
- 31 Modell W Gold H and Cattell McK Clinical uses of 2,3-dimercaptopropanol (BAL) IV Pharmacologic observations on BAL by intramuscular injection in man *J Clin Investigation* 25 480-487 1946
- 32 Woody N C and Kometani J T BAL in treatment of arsenic ingestion of children *Pediatrics* 1 372-378 1948
- 33 Sulzberger M B Baer R L and Kanof A Clinical uses of 2,3-dimercaptopropanol (BAL) V Skin sensitization to BAL *J Clin Investigation* 25 488-496 1946

- 34 Tye M and Siegel J M Prevention of reaction to BAL *J A M A* 134 1477 1947
- 35 Chenoweth M B Modell W and Riker W F Jr Pharmacology of several dithiols related to 2,3-dimercaptopropanol (BAL) *J Pharmacol & Exper Therap* (Supp) 87 6-22 1946
- 36 Danielli J F, Danielli M and Mitchell P D Development of chemotherapy for systemic arsenical poisoning *Nature London* 157 217 1946
- 37 Danielli J F et al BAL-Intrav new non toxic thiol for intravenous injection in arsenical poisoning *Biochem J* 41 325-335 1947
- 38 McCance R A and Widdowson E M Observations on administration of BAL-intrav to man *Nature London* 157 837 1946

## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

TRACY B MALLORY, M D, *Editor*

BENJAMIN CASTLEMAN, M D, *Associate Editor*

EDITH E PARRIS, *Assistant Editor*

### CASE 34521

#### PRESENTATION OF CASE

A fifty-five-year-old man entered the hospital because of abdominal cramps and distention.

Three weeks before admission the patient noted the gradual onset of an illness characterized by abdominal swelling and diffuse abdominal cramps. He felt bloated constantly and, in addition, had spasmodic, doubling, abdominal pains, which lasted about a minute and which he could not localize. There was a slight reduction in the number of bowel movements but no change in the character of the stools was noticed. There was no obstipation or passage of bloody, tarry or clay-colored stools. Though the patient's appetite remained good, he ate infrequently because his capacity for food was greatly reduced. A normal-sized meal nauseated him, but he never vomited. The urine was brown as it had been for several years. The legs and ankles became moderately swollen.

The patient had had diabetes for five years. He had been taking 10 units of protamine insulin daily until admission. For three years he had been subject to anginal attacks precipitated by exercise and relieved by nitroglycerin. There had been several episodes of ankle edema, orthopnea and nocturnal dyspnea. He had felt weak and tired since an attack of "virus pneumonia" five months before admission. He thought he had lost weight since that time but did not know how much. About four years before admission he had been jaundiced and felt weakness and malaise for three weeks. There had never been any previous episodes of abdominal symptoms.

The patient's father had died of diabetes, and a brother had the disease.

Physical examination showed a patient who appeared chronically ill and in moderate distress. The skin of the extremities and back had a dusky, cyanotic tinge. The tongue was thickly coated, and the breath fetid. The abdomen was distended, tympanic and nontender. There were shifting dullness and a fluid wave. No organs or masses were palpable. There was a soft, apical, systolic murmur. The lungs were clear. There was moderate pitting edema extending halfway up the leg, and slight pressural edema.

The temperature was 99°F, the pulse 80, and the respirations 20. The blood pressure was 130 systolic, 70 diastolic.

Examination of the blood disclosed a red-cell count of 4,400,000, with a hemoglobin of 16 gm, and a white-cell count of 8000, with 70 per cent neutrophils. The urine had a specific gravity of 1.012. The sediment was normal, and a test for bile was negative. There was a green sugar reaction. The stools were brown, formed and guaiac negative. The blood chemical values on admission were as follows: sugar 200 mg, nonprotein nitrogen 20 mg, and protein 5.8 gm per 100 cc, bilirubin 0.7 mg per 100 cc direct, 1.1 mg indirect, and carbon dioxide 31 milliequiv and chloride 88 milliequiv per liter. X-ray studies of the chest and abdomen showed both leaves of the diaphragm to be high, with haziness in the costophrenic sinuses. There was marked gaseous distention of the bowel, which could not be localized but was thought to affect both colon and small bowel. The peritoneal markings were not clear, indicating the presence of the fluid.

In the hospital the patient had a daily temperature between 100 and 102°F. A barium enema on the second hospital day showed delay of retrograde flow in the region of the splenic flexure, though barium passed into the dilated gas-filled and fluid-filled transverse colon. No definite lesion could be made out. The small intestine was also dilated. The urine reaction remained green on 10 units of regular insulin daily. The patient had a shaking chill on the third hospital day.

An exploratory laparotomy was performed on the sixth hospital day.

#### DIFFERENTIAL DIAGNOSIS

DR JAMES H TOWNSEND May we see the x-ray films?

These x-ray films are very impressive. We were not told about all this tubing, but there it is.

DR STANLEY M. WYMAN: We have only a few films from the original examination. Some of them were lost, apparently. The heart is definitely enlarged, chiefly toward the left, probably in the region of the left ventricle. The aorta is tortuous, and there is some calcification. There appears to be a small quantity of fluid in the left costophrenic angle and possibly on the right also. The lung fields reveal no definite intrinsic disease. The appearance of the chest is consistent with hypertensive arteriosclerotic heart disease, with probable fluid in both pleural spaces. This film of the abdomen with a Miller-Abbott tube in place was taken the day following the barium enema examination. The barium enema was done with the Miller-Abbott tube in place and quite a way down, as you see from the spot films. The patient was not prepared, and the examination, I gather from the record, was unsatisfactory. The fluoroscopist, in running the barium into the descending colon, arrived at the splenic flexure, where he had difficulty in forcing the barium farther. He took a number of spot films, which show barium passing into the distal transverse colon, where there is considerable fluid and retained material. The spot films of the area reveal no evidence of intrinsic filling defect, no definite kinks and no definite constriction by adhesions. I can say only from the films available that there was delay in the barium column at this point without a definite organic lesion. To go back to the plain film of the abdomen, there is a haziness that suggests fluid in the abdomen. This has to be taken with skepticism because this is a grid film.

DR TOWNSEND: From the data given I am sure that I shall be unable to make a precise diagnosis. However, there are certain possibilities that I can discuss.

To summarize the positive features, this fifty-five-year-old man, who was known to have had diabetes for five years, had an episode described as jaundice, which I think must always be taken with reservation. Four years before he had had what was called angina. For three years he had had a number of episodes of ankle edema, orthopnea and nocturnal dyspnea. Five months before admission he had what was called "virus pneumonia," and which easily could have been something else, perhaps pulmonary embolism or some other circulatory disturbance in the chest. He was brought to the hospital by an illness of three weeks' duration, characterized by abdominal cramps and swelling of the abdomen and of the ankles, and while in the hospital he had fever.

The physical examination showed a dusky color, apparently cyanosis, although there may have been something else about the color, a coated tongue, definite ascites and fever. From the laboratory evidence there was mild jaundice, elevated plasma

bilirubin, both direct and indirect, a slight reduction in serum protein, with a slight alkalosis and slight hypocalcemia, possibly associated with diet. I assume that since this man had cardiac failure he may well have been on a diet low in sodium chloride, which may have a bearing on the chloride of 88 milliequiv per liter. It is noteworthy that he did not have anemia and that the nonprotein nitrogen was normal. The blood sugar was high enough to prove the diabetes but not strikingly high. He did not have bile demonstrated in the urine. He apparently had normal amounts of bile in the stools. X-ray films suggest fluid in the pleural cavities and in the abdomen and gas-filled loops of bowel, which the x-ray people could not interpret entirely. They could not tell whether the whole intestine was dilated — paralytic ileus — or whether examination showed an obstructing lesion.

What are some of the possibilities? If we try to put them all together and put them on a cardiac basis, there seems little reason to doubt that this fifty-five-year-old man with diabetes had coronary-artery disease manifested by angina pectoris and symptoms of congestive failure. He also had a somewhat enlarged heart, and we wonder if the blood pressure had not been higher in the past than at present. We have no electrocardiographic evidence. I think we might say that he undoubtedly had coronary-artery disease and that he probably had some congestive failure. Could the cardiac condition have led to abdominal symptoms? Could he have had a mesenteric thrombosis or other thrombosis in the abdominal cavity? Yet if he had real mesenteric embolus, such as might come from thrombosis within the heart, one would hardly expect him to live three weeks. The episode would have been much more critical, and he would have died or been in serious trouble within a few hours as a rule. Is there anything about the cardiac condition that might lead to jaundice and ascites? Yes. Jaundice is not common in cardiac failure, although it may occur. Ascites may occur in most types of heart failure associated with right-sided heart failure, such as that seen with adhesive pericarditis or tricuspid lesions or with long-standing, definite, congestive failure, in which the nutmeg type of liver and, possibly, slight jaundice occur. However, this does not sound like that sort of history.

Are there any abdominal conditions that are part and parcel of the diabetes? There are at least three types of abdominal conditions that can produce abdominal symptoms and have diabetes as a feature. One is chronic pancreatitis, with enough destruction of islet tissue to produce diabetes, and I think it is possible that this patient could have had chronic recurrent pancreatitis. Jaundice and ascites can occur with it. This is a possibility, but I can see no way to prove it. The second abdominal condition associated with diabetes is a special form of liver cirrhosis, pigment cirrhosis. Hemochroma-

tos is associated with diabetes, usually from pancreatic fibrosis from pigment. This is seldom associated with jaundice, but I recall a case given to me a year or so ago in which four years before death the patient showed evidence of cirrhosis, including jaundice and ascites, and at that time on biopsy showed early Laennec's cirrhosis. Four years later, at the time of death from liver failure, there were extensive pigment deposits of the type called hemochromatosis. That is a possibility, but we have very little evidence, and I do not see how one can make the diagnosis.

Another possibility is cholesterol disease. We are not given the value of the blood cholesterol, but there is a condition of hypercholesterolemia which can be associated with deposits of cholesterol with fibrosis in the pancreas sufficient to cause diabetes. This also may be associated with enlarged liver and occasionally with jaundice. However, I doubt very much that it would lead to ascites, at least, I have never seen it. It can also be associated with coronary-artery disease and frequently terminates with coronary thrombosis.

What other possibilities should we consider? Ordinary liver cirrhosis, I think, is entirely possible. We are not given the usual battery of liver tests. We are told nothing about the prothrombin time, the cephalin flocculation test or the phosphatase level. We do know that he had ascites and jaundice, and that combination is always suggestive of Laennec's cirrhosis of the liver.

What about gallstones? There is a history of an attack of jaundice, without pain, four years ago. This time there were pain and jaundice. However, there seems to be very little to suggest that the patient was troubled with cholelithiasis, and it would be rather hard to explain the terminal picture on that basis.

What about the possibility of carcinoma of the pancreas? I think the possibility of neoplasm in the last few weeks of his life cannot be excluded. It could have been in the pancreas (it can be almost anywhere). I doubt that there is sufficient evidence to make a diagnosis without looking inside, which we are going to do vicariously in a minute.

One other possibility. Could he have had a spontaneous thrombosis of some radicle of the portal vein? Such things do occur. They are very difficult to diagnose in life and very apt to be associated with crampy, abdominal pain of indefinite character. They can be rapidly followed by the development of ascites and edema and large enough to result in a large area of gangrene of the bowel, but this man would not have lived three weeks if that had occurred. Of all possibilities, I think this is the least likely. If I were to list my diagnoses, I would say, of course, diabetes mellitus, coronary-artery disease and, I think, intra-abdominal thrombosis, probably in the portal system, possibly in some way related to cirrhosis of the liver.

DR WILLIAM DOCK I think these dusky legs make one think of hemochromatosis. That is an odd thing to have — cyanosis of the legs — without cyanosis of the lips, ears and fingers. With cyanosis of the back and legs it sounds as if he may have had an odd color, not merely diabetes with cyanosis, and it makes one suspicious. I think it is an important point. Patients with cirrhosis occasionally have bouts of fever and abdominal conditions unexplained by positive blood cultures or anything else. It may be that there was some intercurrent disease. However, I think this is a case in which terminal pyelophlebitis ought to be thought of. I should think he might have had carcinoma in the tail of the pancreas. I would be inclined to guess that he had bronze diabetes and got into new troubles superimposed on his cirrhosis, so that he came in on the Surgical rather than the Medical Service.

#### CLINICAL DIAGNOSES

Large bowel obstruction,<sup>2</sup> carcinoma  
Diabetes mellitus  
Angina pectoris

#### DR TOWNSEND'S DIAGNOSES

Diabetes mellitus  
Coronary-artery disease  
Cirrhosis of liver  
Intra-abdominal thrombosis

#### ANATOMICAL DIAGNOSES

*Hemochromatosis, liver, pancreas, skin and lymph nodes*  
*Hepatoma, with extension into hepatic and portal veins*  
Esophageal varices  
Ascites  
Splenomegaly  
Operations: exploratory laparotomy, bilateral femoral-vein ligation  
Thrombosis, left common femoral vein  
Hydrothorax  
Pulmonary congestion  
Chronic cholecystitis

#### PATHOLOGICAL DISCUSSION

DR JOHN B STANBURY The patient did come in on the Surgical Service. It was thought when he was first seen that there was distention of the small bowel, and enough possibility of small-bowel obstruction to justify surgical exploration. That was done. No obstruction was found, but a nodular liver was observed from which a biopsy was taken. It showed a marked grade of cirrhosis with a great deal of hemosiderin deposit, and a diagnosis of hemochromatosis was made. The patient was then transferred to the Medical Service, and the prognosis seemed so hopeless that they were not very

These x-ray films are very impressive. We were not told about all this tubing, but there it is.

DR STANLEY M. WYMAN: We have only a few films from the original examination. Some of them were lost, apparently. The heart is definitely enlarged, chiefly toward the left, probably in the region of the left ventricle. The aorta is tortuous, and there is some calcification. There appears to be a small quantity of fluid in the left costophrenic angle and possibly on the right also. The lung fields reveal no definite intrinsic disease. The appearance of the chest is consistent with hypertensive arteriosclerotic heart disease, with probable fluid in both pleural spaces. This film of the abdomen with a Miller-Abbott tube in place was taken the day following the barium enema examination. The barium enema was done with the Miller-Abbott tube in place and quite a way down, as you see from the spot films. The patient was not prepared, and the examination, I gather from the record, was unsatisfactory. The fluoroscopist, in running the barium into the descending colon, arrived at the splenic flexure, where he had difficulty in forcing the barium farther. He took a number of spot films, which show barium passing into the distal transverse colon, where there is considerable fluid and retained material. The spot films of the area reveal no evidence of intrinsic filling defect, no definite kinks and no definite constriction by adhesions. I can say only from the films available that there was delay in the barium column at this point without a definite organic lesion. To go back to the plain film of the abdomen, there is a haziness that suggests fluid in the abdomen. This has to be taken with skepticism because this is a grid film.

DR TOWNSEND: From the data given I am sure that I shall be unable to make a precise diagnosis. However, there are certain possibilities that I can discuss.

To summarize the positive features, this fifty-five-year-old man, who was known to have had diabetes for five years, had an episode described as jaundice, which I think must always be taken with reservation. Four years before he had had what was called angina. For three years he had had a number of episodes of ankle edema, orthopnea and nocturnal dyspnea. Five months before admission he had what was called "virus pneumonia," and which easily could have been something else, perhaps pulmonary embolism or some other circulatory disturbance in the chest. He was brought to the hospital by an illness of three weeks' duration, characterized by abdominal cramps and swelling of the abdomen and of the ankles, and while in the hospital he had fever.

The physical examination showed a dusky color, apparently cyanosis, although there may have been something else about the color, a coated tongue, definite ascites and fever. From the laboratory evidence there was mild jaundice, elevated plasma

bilirubin, both direct and indirect, a slight reduction in serum protein, with a slight alkalosis and slight hypocalcemia, possibly associated with diet. I assume that since this man had cardiac failure he may well have been on a diet low in sodium chloride, which may have a bearing on the chloride of 88 milliequiv per liter. It is noteworthy that he did not have anemia and that the nonprotein nitrogen was normal. The blood sugar was high enough to prove the diabetes but not strikingly high. He did not have bile demonstrated in the urine. He apparently had normal amounts of bile in the stools. X-ray films suggest fluid in the pleural cavities and in the abdomen and gas-filled loops of bowel, which the x-ray people could not interpret entirely. They could not tell whether the whole intestine was dilated — paralytic ileus — or whether examination showed an obstructing lesion.

What are some of the possibilities? If we try to put them all together and put them on a cardiac basis, there seems little reason to doubt that this fifty-five-year-old man with diabetes had coronary-artery disease manifested by angina pectoris and symptoms of congestive failure. He also had a somewhat enlarged heart, and we wonder if the blood pressure had not been higher in the past than at present. We have no electrocardiographic evidence. I think we might say that he undoubtedly had coronary-artery disease and that he probably had some congestive failure. Could the cardiac condition have led to abdominal symptoms? Could he have had a mesenteric thrombosis or other thrombosis in the abdominal cavity? Yet if he had real mesenteric embolus, such as might come from thrombosis within the heart, one would hardly expect him to live three weeks. The episode would have been much more critical, and he would have died or been in serious trouble within a few hours as a rule. Is there anything about the cardiac condition that might lead to jaundice and ascites? Yes. Jaundice is not common in cardiac failure, although it may occur. Ascites may occur in most types of heart failure associated with right-sided heart failure, such as that seen with adhesive pericarditis or tricuspid lesions or with long-standing, definite, congestive failure, in which the nutmeg type of liver and, possibly, slight jaundice occur. However, this does not sound like that sort of history.

Are there any abdominal conditions that are part and parcel of the diabetes? There are at least three types of abdominal conditions that can produce abdominal symptoms and have diabetes as a feature. One is chronic pancreatitis, with enough destruction of islet tissue to produce diabetes, and I think it is possible that this patient could have had chronic recurrent pancreatitis. Jaundice and ascites can occur with it. This is a possibility, but I can see no way to prove it. The second abdominal condition associated with diabetes is a special form of liver cirrhosis, pigment cirrhosis. Hemochroma-

Laboratory study revealed a serum van den Bergh of 1.8 mg per 100 cc direct and 2.0 mg per 100 cc indirect and an amylase of 116 units per 100 cc. The hemoglobin was 11 gm, and the white-cell count 6000. The specific gravity of the urine was 1.003, but examination was otherwise negative.

In the hospital the patient had another acute attack of pain, from which she was allowed to recover before operation. In the meantime she was given penicillin, streptomycin and three blood transfusions. On the twelfth hospital day a cholecystectomy and choledochostomy were done. One large and several small stones were found in the common duct, which was noted to be very large but soft. She convalesced well and was discharged on the tenth postoperative day. A cholangiogram done two days before discharge showed good filling of the biliary radicles, both intrahepatic and extrahepatic. There was some dilatation of the whole system, but the dye passed readily into the duodenum.

*Final admission* (two months later) In the interval the patient had been followed in the clinic and was very well when last seen, approximately six weeks before the present admission. She had continued to be up and about feeling well until two days before admission, when she noted the onset of anorexia and abdominal discomfort. On the following day she went to bed and had nausea and vomiting of blood of an unknown amount. She was also said to have passed blood by rectum. On the morning of the day of admission she was found unresponsive. It was also noted that the skin was yellowish. She was admitted in a state of coma.

Physical examination revealed a comatose, emaciated woman breathing heavily. The skin and conjunctivas showed jaundice. The lungs were clear. Abdominal and neurologic examinations were essentially negative. Rectal examination was negative.

The temperature was 98.6°F, the pulse 100, and the respirations 20. The blood pressure was 130 systolic, 90 diastolic.

Laboratory examination revealed a serum van den Bergh of 8.5 mg per 100 cc direct and over 12.5 mg per 100 cc indirect and a nonprotein nitrogen of 42 mg per 100 cc. The carbon dioxide was 22 milliequiv per liter, and the sugar 76 mg per 100 cc. Determination of the prothrombin time was attempted, but the blood did not clot even after 120 seconds with a control of 16 seconds. The hemoglobin was 15 gm, and the white-cell count 9000, with 81 per cent neutrophils. The urine

showed a ++ test for bile. A stool was guaiac negative.

On the following morning the patient's respirations were more rapid, and the jaundice deeper. Later that day respirations ceased, and she died.

#### DIFFERENTIAL DIAGNOSIS

DR GRANTLEY W. TAYLOR This is an extraordinary case. There are several points of considerable interest. First of all, this woman had a carcinoma of the colon at the age of fifty-five, which was cured apparently. At the age of sixty-seven she entered again with a carcinoma of the esophagus, which was an epidermoid, Grade III. This must represent one of the rare, very early cures of carcinoma of the esophagus because seven years later, when the gall bladder was operated on, I think it would have been remarked if she had shown any evidence of intra-abdominal extension or recurrence of carcinoma. She lived long enough to justify the original diagnosis of gall-bladder disease because when she came back on the eighth admission she had gallstones.

When the patient came in on the eighth admission she was a sick woman with frequent attacks of sharp pain, nausea, vomiting, gaseous eructations and questionable icterus, and she was in poor shape. The only extraordinary thing in this admission is the amylase of 116 units, which, if true, is certainly extreme. It makes one wonder if she had pancreatitis. Pancreatitis is certainly an overwhelming disease. She had an attack of pain but was not in any acute discomfort, and I am inclined to think that the amylase determination was an error. She was treated with penicillin, streptomycin and blood transfusions—again, a method of therapy consistent with the assumption that she had pancreatitis or something of that sort. Nothing was done until the twelfth day, when gallstones were removed and the common duct drained. A cholangiogram was done before discharge, which means that she had a T-tube in place and the idea was to carry out a protracted drainage of the biliary tree. That is what I get out of it. At readmission nothing is said about a biliary sinus or a biliary catheter. However, she was followed in the Out-Patient Department and did very well until just before the final admission, when she had an overwhelming onset of the final illness—an episode of anorexia, abdominal discomfort, nausea, vomiting and bleeding by rectum—and lapsed within two days into a state of

much interested in doing any great battery of liver-function tests. The bromsulfalein test showed 40 per cent retention of the dye, and the thymol turbidity was 7 units.

DR TRACY B MALLORY The patient died in two weeks. There was an episode suggesting pulmonary embolism following which the leg veins were ligated on both sides. From that time on there was constant seepage of fluid through the wounds where the veins had been ligated that could not be stopped. The peritoneal fluid evacuated at operation reaccumulated rapidly.

At autopsy we found that the liver weighed 3400 gm and was very grossly nodular, with two types of nodules, quite sharply distinct in color. In cutting across the liver we found in the central portion a large tumor similar in appearance and color to one of the types of nodules. Also, many thrombi were found in both the hepatic and portal veins. So the diagnosis of primary hepatoma with invasion of the venous system of the liver was made. There was also a thrombotic occlusion of the portal vein behind the tumor thrombus. There was moderate involvement of the adrenal glands and pancreas, and the lymph nodes in the porta hepatis were deeply pigmented.

DR TOWNSEND Was any reason found for the rather sudden decline of the patient three weeks before entry?

DR MALLORY I imagine that represents the rapid progress of the hepatic carcinoma, which spread very quickly throughout the venous system of the liver.

DR TOWNSEND Do you often find hepatic carcinoma developing on the basis of hemochromatosis?

DR MALLORY I have the impression that I have seen it disproportionately often in hemochromatosis. I have seen figures saying that that is not so. Considering the rarity of hemochromatosis, I think a surprising number of patients die with hepatoma.

DR JOHN B QUINBY What did the heart show?

DR MALLORY Mild atherosclerosis of the coronary arteries without narrowing and no infarction. The kidneys showed nothing remarkable.

### CASE 34522\*

#### PRESENTATION OF CASE

*First admission* A fifty-one-year-old unmarried woman was admitted to the hospital because of

severe epigastric pain. A diagnosis of gall-bladder disease was made. The symptoms subsided almost completely, and she was discharged on the fifth hospital day.

*Fourth admission* (four years later) In the interval the patient had two admissions for recurrent bouts of epigastric pain. During the last she underwent an exploratory laparotomy and appendectomy. The abdominal organs, including the gall bladder, were grossly normal. During this admission the patient was found to have an adenocarcinoma of the sigmoid colon, and a Mikulicz operation was subsequently done. She was discharged on the sixty-second hospital day.

*Seventh admission* (approximately twelve years later) In the interval the patient had been admitted on two separate occasions for a ventral hernia and for closure of the colostomy wound, the last admission being ten years before this one. At this time she was admitted because of increasing difficulty in swallowing and some weight loss. A roentgenogram showed findings consistent with carcinoma of the lower third of the esophagus. A biopsy showed epidermoid carcinoma, grade III. An esophagectomy and esophagostomy were done, and the patient discharged on the forty-third hospital day.

*Eighth admission* (seven years later) In the interval the patient had been seen more or less regularly in the Tumor Clinic, and no evidence of recurrence of either the esophageal or the sigmoid cancer noted. Approximately one month before admission she began to have frequent attacks of sharp, stabbing pain in the right upper quadrant. This pain was severe and accompanied by nausea, vomiting and gaseous eructations. The pain radiated to the back but not into the shoulder. She denied any change in the stools or urine but admitted to being jaundiced with several of the attacks. The present episode had begun four days before admission.

Physical examination revealed a poorly nourished woman in no acute discomfort. The scleras and skin were questionably icteric. The lungs were clear. The abdomen was flat, and numerous dilated veins were seen coursing under the skin. There appeared to be a considerable amount of voluntary spasm. The right upper quadrant was tender to deep palpation, but neither liver nor gall bladder could be felt. The spleen was not palpable.

\*Presented at a meeting of the New England Cancer Society held at the Massachusetts General Hospital.

Laboratory study revealed a serum van den Bergh of 1.8 mg per 100 cc direct and 2.0 mg per 100 cc indirect and an amylase of 116 units per 100 cc. The hemoglobin was 11 gm, and the white-cell count 6000. The specific gravity of the urine was 1.003, but examination was otherwise negative.

In the hospital the patient had another acute attack of pain, from which she was allowed to recover before operation. In the meantime she was given penicillin, streptomycin and three blood transfusions. On the twelfth hospital day a cholecystectomy and choledochostomy were done. One large and several small stones were found in the common duct, which was noted to be very large but soft. She convalesced well and was discharged on the tenth postoperative day. A cholangiogram done two days before discharge showed good filling of the biliary radicles, both intrahepatic and extrahepatic. There was some dilatation of the whole system, but the dye passed readily into the duodenum.

*Final admission* (two months later). In the interval the patient had been followed in the clinic and was very well when last seen, approximately six weeks before the present admission. She had continued to be up and about feeling well until two days before admission, when she noted the onset of anorexia and abdominal discomfort. On the following day she went to bed and had nausea and vomiting of blood of an unknown amount. She was also said to have passed blood by rectum. On the morning of the day of admission she was found unresponsive. It was also noted that the skin was yellowish. She was admitted in a state of coma.

Physical examination revealed a comatose, emaciated woman breathing heavily. The skin and conjunctivas showed jaundice. The lungs were clear. Abdominal and neurologic examinations were essentially negative. Rectal examination was negative.

The temperature was 98.6°F, the pulse 100, and the respirations 20. The blood pressure was 130 systolic, 90 diastolic.

Laboratory examination revealed a serum van den Bergh of 8.5 mg per 100 cc direct and over 12.5 mg per 100 cc indirect and a nonprotein nitrogen of 42 mg per 100 cc. The carbon dioxide was 22 milliequiv per liter, and the sugar 76 mg per 100 cc. Determination of the prothrombin time was attempted, but the blood did not clot even after 120 seconds with a control of 16 seconds. The hemoglobin was 15 gm, and the white-cell count 9000, with 81 per cent neutrophils. The urine

showed a ++ test for bile. A stool was guaiac negative.

On the following morning the patient's respirations were more rapid, and the jaundice deeper. Later that day respirations ceased, and she died.

#### DIFFERENTIAL DIAGNOSIS

DR GRANTLEY W TAYLOR. This is an extraordinary case. There are several points of considerable interest. First of all, this woman had a carcinoma of the colon at the age of fifty-five, which was cured apparently. At the age of sixty-seven she entered again with a carcinoma of the esophagus, which was an epidermoid Grade III. This must represent one of the rare, very early cures of carcinoma of the esophagus because seven years later, when the gall bladder was operated on, I think it would have been remarked if she had shown any evidence of intra-abdominal extension or recurrence of carcinoma. She lived long enough to justify the original diagnosis of gall-bladder disease because when she came back on the eighth admission she had gallstones.

When the patient came in on the eighth admission she was a sick woman with frequent attacks of sharp pain, nausea, vomiting, gaseous eructations and questionable icterus, and she was in poor shape. The only extraordinary thing in this admission is the amylase of 116 units, which if true, is certainly extreme. It makes one wonder if she had pancreatitis. Pancreatitis is certainly an overwhelming disease. She had an attack of pain but was not in any acute discomfort, and I am inclined to think that the amylase determination was an error. She was treated with penicillin, streptomycin and blood transfusions — again a method of therapy consistent with the assumption that she had pancreatitis or something of that sort. Nothing was done until the twelfth day, when gallstones were removed and the common duct drained. A cholangiogram was done before discharge, which means that she had a T-tube in place and the idea was to carry out a protracted drainage of the biliary tree. That is what I get out of it. At readmission nothing is said about a biliary sinus or a biliary catheter. However, she was followed in the Out-Patient Department and did very well until just before the final admission, when she had an overwhelming onset of the final illness — an episode of anorexia, abdominal discomfort, nausea, vomiting and bleeding by rectum — and lapsed within two days into a state of

coma On examination she was breathing heavily and was jaundiced Obviously she had severe derangement of the bleeding tendency when she came back because the blood taken for prothrombin time did not clot, even after two hours The blood hemoglobin was 15 gm, perhaps owing to hemoconcentration The white-cell count was normal, the urine showed bile, and the stool was guaiac negative — a contradiction to the history of hematemesis and melena

As I studied this case the question was obviously whether or not this was a complication of the former carcinoma in the form of hepatic metastases It seems extremely unlikely that two months after cholecystectomy, at which time presumably the liver was not manifesting hepatic metastases, metastatic disease involving the liver from either of the previous carcinomas would occur Of course the interesting thing is how rarely we see jaundice in cases of metastases involving the liver Then the question is whether she was suffering from a complication of the cholecystectomy We have been known to injure the common duct, even in this hospital, so that she could very well have had such a complication Against that is the fact that following cholecystectomy she did well for two months The terminal illness was abrupt — two days — and of severe onset Were one large and several small stones removed and one that descended to cause another acute episode of obstructive mechanical jaundice left? I think that is rather unlikely The lapse of the patient into coma, with a protracted prothrombin time such as that described here, sounds to me as if she had a profound visceral derangement of the liver, and that the terminal episode was one of liver failure — due to what, I cannot tell you It is consistent with severe hepatitis or acute yellow atrophy or something of that sort

What else could she have had? A hemorrhagic pancreatitis? At the final episode she complained of anorexia and of abdominal discomfort but nothing suggestive of the overwhelming onset of abdominal distress of pancreatic apoplexy That is as far as I can go

DR GEORGE LEVENE Is the pain radiating back into the shoulder suggestive of pancreatitis?

DR TAYLOR On the eighth admission she probably had something for which she was kept in the hospital for twelve days and given penicillin, streptomycin and transfusions We have very few data

given here, but everything was normal except for the elevated amylase It must have been thought that she had a pancreatitis secondary to biliary-tract disease because biliary drainage was instituted, a T-tube put in place and a cholangiogram taken before she went home Nothing is said about the state of the pancreas or the abdominal findings

DR LOUIS P HASTINGS Dr Taylor, did she have plasma transfusions a few months previously? What is the possibility of homologous serum hepatitis here?

DR TAYLOR I think it is possible We know that some of these patients have tremendously severe jaundice supervening on that basis We certainly do not expect it with transfusion of whole blood as commonly as we do with plasma

#### CLINICAL DIAGNOSIS

Homologous serum hepatitis

#### DR TAYLOR'S DIAGNOSIS

Hepatitis, with liver failure

#### ANATOMICAL DIAGNOSIS

*Homologous serum hepatitis*

#### PATHOLOGICAL DISCUSSION

DR BENJAMIN CASTLEMAN At autopsy this patient had a very small liver, weighing 700 gm, it was soft, flabby, and brownish red, more so on the right side, with small, yellowish to grayish-white areas here and there These grayish-white areas represented portal areas, and the reddish-brown areas represented the central parts of the lobule In the central parts of the lobule the liver cells were wiped out completely and replaced by blood This case represents an acute hepatitis of a fulminant variety and quite consistent with homologous serum jaundice The patient had received three transfusions, and I have asked Dr Soutter, who is in charge of the Blood Bank, to comment on the possible causes of the hepatitis

DR LAMAR SOUTTER This case was of great interest to us because of our desire to avoid this complication The possible source of homologous serum jaundice could have been from a needle or from a transfusion For the past half year, at least, all hypodermic and intravenous needles in the hospital have been autoclaved so that the possibility of receiving hepatitis from another patient through the means of the needle is almost nonexistent In

this case the other possible source is the transfusions. Out of 50,000 whole-blood transfusions from our Blood Bank this is the first case of homologous jaundice. Undoubtedly, there may be others in which the diagnosis was not made or the patient had a light case of jaundice not attributed to this source. It is possible for a person to have hepatitis or jaundice and not know about it—or not remember about it. We do not have any idea how long one is capable of carrying the virus before transmitting it to someone else. We do know that the incidence of homologous serum jaundice following whole-blood transfusion is infrequent as compared with that after dry plasma.

We investigated the donors of the three transfusions in this case. The first donor was a Negro boy, a professional donor of this hospital. He had been used before, and I am sure, after questioning him carefully, that he had no knowledge of ever having had any disease similar to jaundice or hepatitis. The second donor was a Red Cross volunteer, whose blood was sent to us by the Red Cross. I talked to him and found that there was no history of hepatitis or jaundice. The third blood came from an institution that establishes a credit in this hospital from which it can draw blood when needed. Unfortunately, although we believed that that institution had standards comparable to our own and observed the state and federal regulations regarding histories and physical examinations for donors, we found that it had collected blood at a prison but had neglected these matters. We assume that the blood that infected this patient came from that source, but of course there is no proof. The moral is obvious—a careful screening of donors must take place to keep down the incidence of the disease. I do not mean screening by the mere process of a

technician asking the donor if he has had jaundice. But if a doctor will ask the donor if he has had “yellow jaundice” of the skin or scleras and will go into the symptoms of hepatitis, we may cut down on this unfortunate complication.

DR RICHARD B. CATTELL: Dr. Castleman, have you ever observed this same picture in the liver in deaths following extensive disease with long common-duct obstruction due to stone?

DR CASTLEMAN: No, we never see it with stones. The liver, if involved, would be large, not small.

DR CATTELL: I mean following operation for common-duct stones.

DR CASTLEMAN: Not so rapidly as this. The patient died within three days of the onset of symptoms. It was a fulminating form of liver disease. I do not believe I have seen obstruction that fast. Have you?

DR CATTELL: No.

DR JOHN FALLON: What did you find in the pancreas?

DR CASTLEMAN: Nothing. The common duct was not dilated, and there were no residual stones.

DR TAYLOR: The tube had been taken out after the final cholecystogram?

DR CASTLEMAN: Yes. A note was made to that effect in the Out-Patient Department record.

DR TAYLOR: I did not make out why, on the eighth admission, the patient was kept for twelve days on penicillin, streptomycin and transfusions—in preparation for a gall-bladder operation.

DR CASTLEMAN: It was thought that she had acute cholecystitis. She was very sick before operation.

DR SOUTTER: The cardiologists spent five days getting her ready for operation.

# The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal  
Established 1828

Official Organ of

THE MASSACHUSETTS MEDICAL SOCIETY  
and

THE NEW HAMPSHIRE MEDICAL SOCIETY

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND  
PUBLISHED WEEKLY UNDER THE JURISDICTION OF THE  
COMMITTEE ON PUBLICATIONS

James P. O'Hare, M.D. Richard M. Smith, M.D., Chairman  
Oliver Cope, M.D. Conrad Wesselhoeft, M.D.  
John Fallon, M.D.

Joseph Garland, M.D., Editor

Thomas H. Lanman, M.D. Associate Editors Donald Munro, M.D.  
Henry Jackson, Jr., M.D.

Clara D. Davies, Executive Editor  
Robert O. Leary, Assistant Editor

## EDITORIAL BOARD

C. Gray Lane, M.D. Maxwell Finland, M.D.  
Henry R. Viets, M.D. James M. Faulkner, M.D.  
Robert M. Green, M.D. Carroll B. Larson, M.D.  
Dwight O'Hara, M.D. Francis D. Moore, M.D.  
Fletcher H. Colby, M.D. C. Stuart Welch, M.D.  
Robert L. Goodale, M.D. Vernon P. Williams, M.D.  
Chester M. Jones, M.D. Benjamin Castleman, M.D.  
Harvey R. Morrison, M.D. Hugh R. Leavell, M.D.

SUBSCRIPTION TERMS: \$7.00 per year in advance, postage paid for the United States (medical students \$4.00 per year). Canada, \$8.00 per year (Boston funds), \$9.50 per year for all foreign countries belonging to the Postal Union.

MATERIAL should be received not later than noon on Thursday three weeks before date of publication.

THE JOURNAL does not hold itself responsible for statements made by any contributor.

COMMUNICATIONS, including those concerning classified advertising but not those regarding other advertising, should be addressed to the New England Journal of Medicine, 8 Fenway, Boston 15, Massachusetts. Telephone KE 6-2094.

NEW ENGLAND ADVERTISING REPRESENTATIVE (except for classified advertising): Edwin B. Tyler, 89 State Street, Boston, Massachusetts. Telephone LA 3-5516.

## IN UNION STRENGTH

THE proposal of the Blue Cross and Blue Shield plans to form a joint national association for more effective interstate operation has met with vigorous though not unexpected opposition. The proposed organization, under the name of Blue Cross-Blue Shield Association, Inc., was to have been a non-profit membership corporation for the purpose of providing mechanisms for facilitating plan enrollment activities, collecting and interpreting experience data for all plans, basic underwriting and actuarial service for all plans, and the organization of Blue Cross-Blue Shield Health Service, Inc., as a stock insurance company. The object of the Health Service was to furnish coverage to employees of national firms where approved plans do not exist,

and excess coverage where necessary, a central agency through which enrollment, billing and collection could be handled for nationally enrolled groups, uniform rates and benefits for all employees of nationally enrolled groups regardless of place of residence, and uniform regulations regarding enrollment, membership and administration of benefits. These provisions were to provide its sole purpose for existence.

Opposition to it was based on the fear that in union there is too much strength, that centralization of organization entails centralization of authority, that this country's cherished heritage of free enterprise would be placed in jeopardy, and that an organization for the control of medical practice would be ready at hand for the Government to take over at will.

Here there was present the usual basis of controversy — not between clear right and clear wrong — but between two arguments, each of which contains or seems to contain points in its favor.

Despite the dangers that were so clearly set forth by the opponents of the proposed association, it had to be borne in mind by the medical profession that the probable alternative to the acceptance of some larger and well organized voluntary prepayment plan for medical service would be a determined attempt at Government control as outlined in Mr. Ewing's recently publicized ten-year program. It seemed also apparent to many observers of modern political trends that the motto *E pluribus unum*, adopted at one time with a reasonable show of enthusiasm, may still have its virtue. The remark attributed to Benjamin Franklin after the signing of the Declaration of Independence that the signers would do well to hang together unless they wanted to hang separately, indicates only that the advantages of united effort may sometimes outweigh its disadvantages.

The Blue Cross and Blue Shield Commissions were directed by the Los Angeles Conference of Blue Cross and Blue Shield plans in April, 1948, to revise the original proposals for a national association and submit them to the conference of plans to be held in October at French Lick Springs. This was done, the Blue Shield plans voted to submit the whole matter to the House of Delegates at its

meeting this month at St. Louis, and the Blue Cross voted to adopt the proposals but to defer action until after the same meeting.

The House of Delegates, giving as a main reason for its decision the possibility of Department of Justice action against a national company, voted to disapprove the association, favoring instead a national enrollment agency to co-operate in coordinating all prepaid health insurance plans. Such an agency would not be limited to sponsoring Blue Cross and Blue Shield plans alone.

The clear duty of the physicians of the country is now to support the actions and the decisions of their representative body, disregarding any differences of opinion that may previously have existed. The problems that lie ahead can be satisfactorily solved only by complete co-operation, and by recognition of the authority with which the House of Delegates of necessity speaks.

---

### "FORSAKE NOT THYSELF"

THREE moral obligations implicit in the ministry of the physician are the subject of Dean Willard L. Sperry's talk before the staff of the Massachusetts General Hospital, published elsewhere in this issue of the *Journal*, they concern the practice of medicine, but they present also logical points of contact with the profession of ministering to the mind and to the soul. They are to tell the truth, but so kindly that silence may sometimes take the place of words, to maintain at all times a sense of the sacredness of life, and to consider the individual at the expense of that abstraction known as mass man.

Judgment, as Hippocrates said, is difficult, and often the definition of a problem may be more stubborn than its answer. Moral judgments in particular may be relative, and the right of yesterday may be the wrong of today. Ethics can quickly change for the worse as well as for the better, and the change can be easily accepted, as was shockingly demonstrated during the years of Hitler's leadership in Germany. The principle of conscience, however, according to Dean Sperry's thesis "has an absolute warrant and cannot change."

Often the moral choice that confronts the physician is not between black and white, where the just course is plainly marked, but between two shades of gray. Having chosen what seems to be the lighter shade he must go ahead "on the assumption that it becomes a clear white." Tragedy is not a matter of a conflict between good and evil, but "a matter of a collision of two loyalties, each of which is wholly good on its own ground." This conflict has been tersely phrased by Richard Lovelace, whom Dean Sperry quotes:

"I could not love thee, dear, so much  
Loved I not honour more."

The ethics of truth-telling must be tempered with discrimination. Falsehood is not to be condoned, but as a matter of mercy and of what might be called the greater honesty, the absolute truth or what it seems to be, may sometimes need to be withheld. Time, too, may suddenly so change the apparent facts that what was held to be the truth becomes an error.

The problem of euthanasia does not immediately or openly concern the physician, but it involves a principle on which he must take his stand. This must be settled for the physician as for the minister on the basis of a profound reverence for life. A deviation on the part of medicine from its basic principle of saving life must constitute a crack in its armor. "If we forfeit that reverence we have slipped our moral moorings—it is not our business to take life, only to try to save it."

In the face of mass evaluations of strong nationalistic and group trends, of the principle of the greatest good to the greatest number, the physician in partnership with the minister must continue to have faith in the value of the individual.

---

### THE MEDICOLEGAL DEATH

Few physicians, in all probability, are entirely clear in their minds as to the exact nature of their obligations to the state in the matter of death reports. Their medicolegal obligations, at least so far as these relations in the Commonwealth of Massachusetts are concerned, are admirably presented in the article by Ford published elsewhere in this issue of the *Journal*.

Certain categories of death, as set forth, must come under the jurisdiction of the medical examiner. These and certain others—hospital deaths within twenty-four hours of admission, hospital deaths when the decedent was unconscious on admission and remained so, any death pronounced by a physician other than the attending physician and any death when the patient was not attended by a physician within two weeks—must be reported to the medical examiner for his decision as to jurisdiction.

Deaths so reported in which the medical examiner declines authority may be certified by the attending physician if he is available and attended the decedent at least twice, one of which visits was within two weeks of death. Otherwise the board-of-health physician may make the certification.

The interest of the public is in discovering and solving crime and in protecting the public health where it may be endangered by virulent communicable disease, by industrial hazards or otherwise.

The friction that sometimes exists in metropolitan areas between the resident staffs of hospitals and the medical examiner's office over the performance of autopsies could be largely eliminated by a proper understanding by the former of the duties of the latter. These difficulties could largely be eliminated, as Dr. Ford says, "if each hospital were to designate a single physician with the experience and authority necessary to ensure complete and accurate reporting of medicolegal deaths and to facilitate the prompt viewing of bodies at the hospital." If this were done, more cases would be available for hospital autopsy.

---

## THE WASHINGTONIAN HOSPITAL

IN SPITE of many difficulties, the Washingtonian Hospital is carrying on. As the oldest hospital of its kind in the United States, it is continuing to make its contribution to the treatment of alcoholism. Because of its obscure location and quiet work, few people realize that behind its ancient façade patients with acute and chronic alcoholism are continuously being treated by psychotherapy and reflex conditioning. Alumni of the hospital

have formed a "conditioning club" that meets semimonthly for group therapy with the medical director.

Last year 941 inpatients and 106 outpatients were given treatment. The average daily census is about 25. The bed capacity is 35.

Since its reorganization some ten years ago, it has continued its relation with the Community Fund. It maintains friendly relations with the Alcoholics Anonymous groups, but its main support comes from patients referred for treatment by private practitioners.

The Washingtonian Hospital, an institutional member of the American Hospital Association, is unique in offering the following services: treatment of acute alcoholic psychoses, acute intoxication without psychoses, cirrhosis of the liver, alcoholic neuritis, vitamin deficiency and malnutrition. It also institutes withdrawal procedures for certain alcohol and drug addicts. Other functions emphasized are efforts to rehabilitate alcohol addicts by psychotherapy, including some patients who require part-time hospitalization with working arrangements and social case work. Public education through addresses given to professional and lay groups is also emphasized. Consultative advice to social agencies and community leaders interested in problem drinkers is given.

In spite of the rising costs of medical care, the hospital is carrying on, mainly because a real need for it exists and because physicians practicing in Massachusetts know of its long service record and the accomplishments it has demonstrated in this uphill work.

---

## MEDICOLEGAL ABSTRACT

**Liability for Malpractice — Administration of narcotics.** A recent Massachusetts case involved questions of such general interest in connection with the liability of physicians for their administration of narcotics that a brief was filed in the case in behalf of the Massachusetts Medical Society.

The testimony in the case was wholly contradictory on the essential questions of how much morphine was given and under what circumstances it was given. The evidence in its aspect most favorable to the patient, who sued the doctor, was that on December 25, 1939, she was suffering from

nausea but without pain, that the defendant, without any complaint of pain by her and without any physical examination or questions regarding medical history, gave her a hypodermic injection of morphine, which was repeated twice that day, that early in 1940 the defendant gave her another injection in similar circumstances, that in 1941 the defendant gave her occasional injections until by July she was receiving about two injections a week, that by the end of August he was giving her an injection every day, in September twice a day, and in October three times or more a day until the patient's husband ordered the defendant from the house and threatened to "clean him up", that thereafter the patient became "jumpy and nervous", and that two days later, after telephoning about every doctor in the town for morphine, the patient experienced a complete black-out and was taken to a hospital suffering from morphine addiction and described as "one-quarter of the way along to confirmed addiction." The patient testified in effect that she had never stated that she had pain until after the defendant had ceased giving her the injections. There was medical testimony that it was not proper medical practice to administer morphine to a patient who complained of nausea but not of pain, or over a period in which there was no pain involved, or to continue giving morphine in the absence of a diagnosis of a condition that could not be cured.

There was evidence that another physician had given the patient codeine from 1939 on and during the period in which the defendant was treating her. There was also evidence that the patient had taken quantities of phenobarbital at some time, although it was not shown that she had taken phenobarbital during the period when she was receiving frequent injections of morphine from the defendant. Therefore, the question was presented whether the patient's condition when she was taken to the hospital was caused by morphine administered by the defendant or by other drugs. The court held that there was ample evidence, presumably the diagnosis of her condition as morphine addiction, to indicate that her condition was proximately caused by morphine administered by the defendant.

The court does not explain in what sense the injections given by the defendant caused the patient's condition. The court presumably meant that the jury could have believed that the injections given by the defendant were sufficient by themselves to account for the patient's condition or that the defendant's treatments would have caused some kind of breakdown by themselves although the patient's condition may have been aggravated by the codeine and phenobarbital. There is a sense in which a doctor may be said to have caused an addiction if his patient merely learns to like the effect of a drug from his injections, and the patient, afterward satisfying her taste from other sources, be-

comes an addict. The court apparently did not regard the case before it as such a case and it did not decide what rule should be applied in such a case.

The defendant argued that the plaintiff sought the morphine she got from him, knowing the risks involved and voluntarily assuming them. The court did not deny that she would be barred from recovery if such testimony were true but rejected this argument for the reason that on the evidence the jury could have found that she did not know or assume the risks. The plaintiff herself testified that if not at first, at least eventually, she sought the injections she received from the defendant. She testified that by about the last of July, 1944, she was "beginning to get a little sneaky—starting to lie" and did not always tell the defendant the truth about her condition. She testified that she did not know what the defendant was giving her, although in July she had a "suspicion," and she knew that it was something that was relieving her and making her feel "pretty high." The court concluded

From this, together with other evidence that need not be stated, the jury could have found that she knew she was getting morphine, but they were not obliged so to find. Much less were they obliged to find that she knew at what point addiction would begin, or that at any time before addiction became a fact she had ceased to rely upon the superior knowledge of the defendant as to the amount of the drug that could safely be taken over a given period of time. There was medical evidence that a person could become addicted "without knowing it."

The court plainly implied that after addiction has become a fact the patient might not be wholly responsible for her actions in attempting to get morphine injections and might not be barred from recovery on the ground that she assumed the risks. It is obvious in this case that when the patient started lying to the defendant to obtain morphine injections she had ceased to rely on the superior knowledge of the defendant and begun to assume the risks herself. The court must have thought that the jury could find that this was after the addiction was a fact. The time of addiction, therefore, becomes an important issue in cases such as this.

It was argued in the case that the patient by "lying" to obtain morphine injections was guilty of a criminal offense, which should prevent her from holding the doctor liable. However, the court held that the statute, which applied only to lying "for the purpose of procuring a prescription for, or the delivery of, a narcotic drug," was not applicable to a case of misrepresentation for the purpose of obtaining an injection personally administered by the doctor, such an injection not being a "delivery" within the meaning of the statute.

The court held that on this evidence, the jury could render a verdict for the plaintiff, even if they need not have done so. Reassuring the medical profession the court said

This decision rests upon evidence of improper and unprofessional conduct on the part of the defendant leading to addiction in the plaintiff. Nothing contained herein need cause anxiety to an honest physician who administers narcotics to a patient in accordance with the prevailing standards of medical practice.

This reassurance must be read in the light of the practical difficulties of proof that may be involved. In any case an honest doctor takes the risk that his testimony may not be believed. For example, in the case before the court, if the defendant's records and testimony had been believed, he would have appeared to be an honest physician administering narcotics to a patient in accordance with the prevailing standards of medical practice. The jury, however, apparently believed the patient's testimony, and this required the court to view the defendant's conduct in a different light (*King v Solomon*, 1948 Mass Adv Sh 1005).

## CORRESPONDENCE

### UNIVERSITY OF ROCHESTER TRAINING PROGRAM IN PSYCHOTHERAPY

To the Editor: I have read with great interest the article entitled "Medical Schools and the Quality of Medical Care," by Dr. F. Richard Weirnerman, which appeared in the November 25 issue of the *Journal*. I think that you are doing the profession a great service by publishing articles (and editorials!) on the subject of modern medical training and its socio-economic aspects. This is a timely reminder for those of us who, as students, find ourselves confronted with a maze of material in clinical medicine and who may therefore lose sight of the other implications of disease.

Nevertheless, for the sake of the record, I should like to point out that at the University of Rochester, under the expert guidance of Dr. John Romano, a well integrated program of training in psychotherapy has been initiated. This program began two years ago and now applies to students in all years. A new building has recently been erected for the hospitalization of patients with mental illness, and students in their third and fourth years are receiving intensive training in this new clinic. The course given here not only includes the study of basic psychiatry but also considers the ancillary disciplines of sociology and economics, as presented in lectures by persons who head the social service at the Strong Memorial Hospital.

Most of the students realize the great importance of this aspect of medical training — and not only of medical training but of medical living and thinking, if I may call it that.

Articles like Dr. Weirnerman's are therefore highly welcome and I hope that others on this vital topic will be forthcoming in your splendid *Journal*.

ERNEST J. LEVINER  
Third-Year Student

University of Rochester School of Medicine

## BOOK REVIEWS

*Unipolar Lead Electrocardiography. Including standard leads, unipolar extremity leads and multiple unipolar precordial leads.* By Emanuel Goldberger, B.S., M.D. 8°, cloth, 182 pp., with 88 illustrations. Philadelphia: Lea and Febiger, 1947. \$4.00.

Dr. Goldberger's book is really the first devoted almost exclusively to the subject of unipolar leads. Although these leads were studied and described by Wilson many years ago, they have come into general use only recently. The literature on this subject is growing rapidly but there has been a real need for a textbook to explain the theory and define the uses

and limitations of unipolar leads. Dr. Goldberger's book fills this requirement in part.

The presentation of material is an orderly one, beginning with an explanation of underlying theory, continuing with detailed instructions for taking leads and ending with a discussion of their clinical application.

Reasonable objections can be raised to the rather dogmatic way in which the subject matter is presented. Nevertheless, the book serves a very useful function in placing proper emphasis upon the origin of extremity lead patterns from basic patterns in the heart itself. Dr. Goldberger's approach also serves to emphasize heart position in relation to the recording electrodes. This represents another step away from purely empirical interpretation even though one does not agree with every statement the author makes. This monograph is not intended as a complete textbook and therefore detailed evaluations of unipolar leads cannot be expected. This book is recommended to all who are interested in electrocardiography.

*The Epithelia of Woman's Reproductive Organs. A correlative study of cyclic changes.* By George N. Papanicolaou, M.D., Ph.D., Herbert F. Traut, M.D., and Andrew A. Marchetti, M.D. 4°, cloth, 53 pp., with 22 plates. New York: The Commonwealth Fund, 1948. \$10.00.

This monograph records a decade of painstaking correlative research at Cornell University Medical College, sponsored by the Commonwealth Fund and conducted by three professorial experts in the fields of microscopical anatomy, biology, physiology and gynecology. The epithelial cytology of the normal human female reproductive tract is extensively examined, and its changes intensively studied in relation to the menstrual cycle. The results are embodied not only in the text but also in a large, colored folding chart, and are amplified and presented in twenty-three full-page plates of drawings and colored photomicrographs. There is a foreword by Dr. Joseph C. Hinsey, dean and professor of anatomy at Cornell University Medical College. In their introduction the authors review the literature of the subject especially the epochal work of Rock and Hertig in the classification of the menstrual cycle, which is recorded in a bibliography of ninety titles.

This volume represents a monumental piece of research of permanent value, for it goes far to clarify and complete knowledge in the field and subject with which it deals, and was made possible by the intelligently co-ordinated and directed skills of investigators, technicians, and clinicians working harmoniously in a common enterprise toward a common objective.

## NOTICES

### POSITIONS FOR CIVILIAN DOCTORS IN PANAMA

Permanent appointments, in the Civil Service, for physicians now exist in the Panama Canal Medical Service. Salaries range from \$5599 to \$7794, with free transportation to the Canal Zone provided for physicians, their families and household goods. Return transportation is furnished upon completion of a minimum of one year's service. In addition, doctors who receive appointments get two months' paid vacation (including time lost by illness) and reduced fares on Panama Canal passenger vessels.

Requirements for position paying \$5599 to \$6540 are graduation from an approved medical school, license to practice medicine in a state, ability to pass a standard physical examination and completion of one year of internship in a hospital approved by the American Medical Association.

Requirements for positions paying \$6540 to \$7794 are the same except that a minimum of three years of post-internship experience is required.

Physicians who are interested in a position as medical officer in the Panama Canal Zone should communicate with Chief of Office, The Panama Canal, Washington, D.C. Applications may also be submitted to the United States Civil Service Commission, Washington, D.C.

(Notices concluded on page vi)

NOTICES (Concluded from page 1020)

## ANNOUNCEMENTS

Dr Samuel R Manelis announces the opening of his office for the practice of orthopedic surgery and fractures at 321 North Main Street, Fall River

Dr Eugene F McAuliffe announces the opening of offices at 1180 Beacon Street, Brookline, and 486 Adams Street, Milton, for the practice of internal medicine

## AMERICAN COLLEGE OF SURGEONS SECTIONAL-MEETING SCHEDULE

The American College of Surgeons announces that six two-day sectional meetings will be held between January 7 and April 13, 1949, for physicians and surgeons, and professional personnel of hospitals. A seventh meeting to be held in the West in the latter part of April will be announced later. The latest developments in medical science and in hospital service will be presented at each meeting. The schedule follows:

DATE	CITY	HEADQUARTERS
January 7-8	Edgewater Park, Mississippi	Edgewater Gulf Hotel
January 14-15	Houston, Texas	Rice Hotel
February 11-12	Kansas City, Mo	Hotel President
March 15-16	Washington, D. C	Statler Hotel
March 21-22	Buffalo, New York	Statler Hotel
April 12-13	Edmonton, Alberta	MacDonald Hotel

Conferences for the hospital personnel and for the medical groups will run concurrently. A joint meeting of the two groups will open at 8 30 a m each day with the showing of medical motion pictures followed by separate sessions at 10-00 a m. Luncheons for the physicians and surgeons and for the hospital representatives, respectively, will be held daily. Separate afternoon sessions beginning at 2 00 o'clock will be held for the two groups. There will be a dinner meeting followed by a round-table conference on the first evening. According to Dr Dallas B Phemister of Chicago, president of the American College of Surgeons, several hundred persons are expected to attend each of the sectional meetings. Prominent local and visiting medical and hospital authorities will address the sessions.

## SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, DECEMBER 30

- FRIDAY DECEMBER 31
- \*9-00 a m-12-00 m Combined Medical and Surgical Staff Rounds Peter Bent Brigham Hospital
- MONDAY JANUARY 3
- \*12 15-1 15 p m Clinico-pathological Conference Main Amphitheater Peter Bent Brigham Hospital.
- TUESDAY JANUARY 4
- \*12 15-1 15 p m Clinico-roentgenological Conference Peter Bent Brigham Hospital
  - \*1 30-2 30 p m Pediatric Rounds Burnham Memorial Hospital for Children Massachusetts General Hospital
- WEDNESDAY JANUARY 5
- \*11-00 a m-12-00 m Medical Rounds Amphitheater Children's Hospital.
  - \*12-00 m-1-00 p m Clinico-pathological Conference (Children's Hospital) Amphitheater Peter Bent Brigham Hospital
  - \*2-00-3-00 p m Combined Clinic by the Medical Surgical and Orthopedic Services Amphitheater Children's Hospital

\*Open to the medical profession

OCTOBER 1-MAY 20 Metropolitan State Hospital Page 418 issue of September 9  
NOVEMBER 17-JANUARY 26 Boston State Hospital Psychiatric Seminar Schedule Page 762 issue of November 11

JANUARY 7-APRIL 13 1949 American College of Surgeons. Sectional Meetings Notice above

JANUARY 13 1949 The Present Status of the Peptic Ulcer Problem Dr S Allan Wilkinson Pentucket Association of Physicians 8 30 p m Haverhill

JANUARY 27-29 1949 American Association of Schools of Social Work Page 984 issue of December 16

MARCH 7-9 1949 American Academy of General Practice Page 728 issue of November 4

MARCH 28-APRIL 1 1949 American College of Physicians Page 158 issue of July 22

MAY 16-19, 1949 American Urological Association Biltmore Hotel Los Angeles California

MAY 24-26 1949 Massachusetts Medical Society Annual Meeting Worcester Memorial Auditorium Worcester

MAY 26-28 1949 American Gout Association Hotel Loraine Madison Wisconsin

MAY 30-JUNE 3 1949 International Congress on Rheumatic Diseases Page 800 issue of November 18

NOVEMBER 11-17 1949 Third Inter American Congress of Radiology Page 158 issue of July 22

## DISTRICT MEDICAL SOCIETIES

### HAMPDEN

JANUARY 23 8 30 p m Academy of Medicine Springfield A Review of the Sterility Problem Dr John Rock

APRIL 26 6-00 p m Hotel Highland Springfield (Dinner Meeting) Convulsive Disorders Dr Douglas T Davidson

### HAMPSHIRE

JANUARY 5 4 30 p m Experiences on a Medical Mission in Europe Dr Alexander M Burgess

MARCH 2 4 30 p m The Present Status of Treatment of Coronary Disease Dr Clarence E de la Chapelle

MAY 4 Annual Meeting and Election of Officers

### MIDDLESEX EAST

JANUARY 19

MARCH 23

MAY 11

### WORCESTER NORTH

FEBRUARY 23 Burbank Hospital Fitchburg

APRIL 27 Annual Meeting

## \* NORFOLK \* COUNTY TRUST COMPANY

*A Strong Neighborhood Bank at Your Service!*

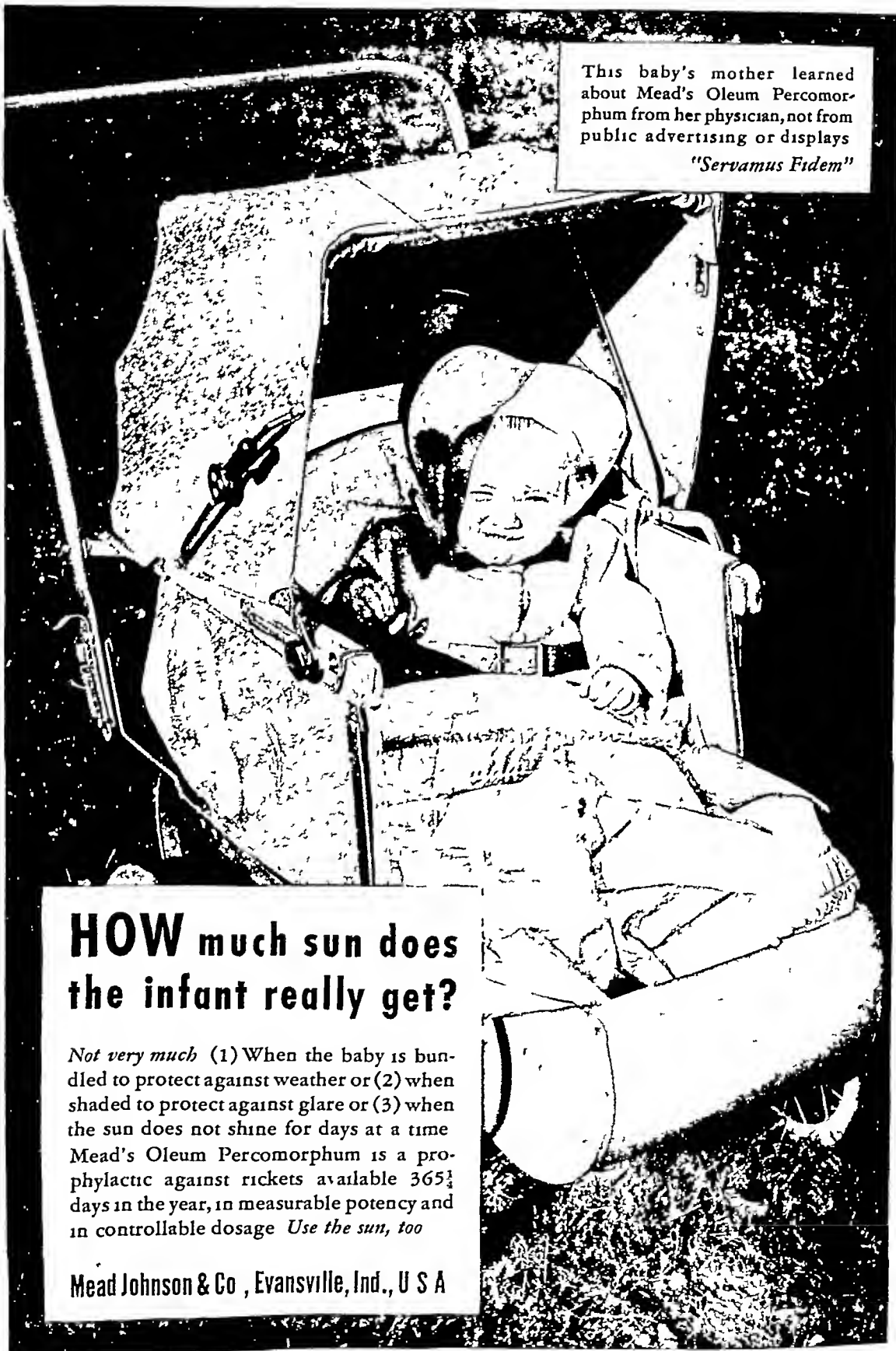
*Eleven Convenient Offices*

Brookline, Canton, Dedham, Franklin  
Needham, Needham Heights, Norwood, Quincy  
Stoughton, Walpole and East Walpole

*Member Federal Deposit Insurance Corporation*



*Dr Wise, as a holiday measure  
That his neighbors and relatives  
treasure,  
Puts his Journal away  
For some part of the day  
And devotes himself wholly to  
pleasure*



This baby's mother learned  
about Mead's Oleum Percomorphum from her physician, not from  
public advertising or displays

*"Servamus Fidem"*

## HOW much sun does the infant really get?

*Not very much* (1) When the baby is bundled to protect against weather or (2) when shaded to protect against glare or (3) when the sun does not shine for days at a time Mead's Oleum Percomorphum is a prophylactic against rickets available 365 $\frac{1}{2}$  days in the year, in measurable potency and in controllable dosage *Use the sun, too*

Mead Johnson & Co , Evansville, Ind., U S A

# The New England Journal of Medicine

Copyright 1948 by the Massachusetts Medical Society

Volume 239

DECEMBER 30, 1948

Number 27

## EARLY NEUROSYPHILIS

ISRAEL KOPP, M.D.\*

BOSTON

**I**NVASION of the central nervous system occurs in nearly all patients during the early stages of syphilis, usually during the first year of the infection. Early neurosyphilis is essentially a leptomeningitis. It is most often asymptomatic. The knowledge of its presence is of great importance since more intensive therapy and careful observation are necessary for these patients.

Early asymptomatic neurosyphilis can be detected only by spinal-fluid examination. The percentage of abnormal spinal fluids depends upon the time and frequency of the examination, ranging

neurosyphilis (tabes, paresis, optic atrophy and so forth).

The finding of a normal spinal fluid in early syphilis, of less than two years' duration, does not always indicate that neurosyphilis will not occur in the future. Neurosyphilis may develop despite what is commonly accepted as intensive and adequate therapy with mapharsen, bismuth or penicillin. For this reason it is essential that spinal-fluid examinations be repeated over a period of years before the patient can be given complete assurance that neurosyphilis will not develop. A

TABLE 1 *Spinal-Fluid Findings in Case 1*

DATE	WASSERMANN REACTION	CELL COUNT <i>per cc mm</i>	GLOBULIN	TOTAL PROTEIN <i>mg per 100 cc</i>	GOLD-SOL CURVE	COMMENT
1/10/44	Negative	5	Negative	—	Negative	Before treatment
3/ 2/44	± (0.5 cc.)	—	Negative	—	Negative	Before treatment
9/16/44	Negative	0	Negative	25	—	After mapharsen and bismuth therapy
7/12/45	— (0.1 cc.)	218 lymphocytes 5 polymorphonuclears	Positive	—	Negative	Neurorelapse
9/ 8/45	— (0.1 cc.)	197 lymphocytes	Trace	59	4444:21000	—
10/12/45	— (0.25 cc.)	5 lymphocytes	Negative	28	0023:00000	After malaria and penicillin therapy

from 9 per cent in primary syphilis to 16 and 48 per cent in early and late secondary syphilis.<sup>1</sup> The degree of spinal-fluid abnormality is also of importance, since Moore<sup>2</sup> has shown that with inadequate treatment parenchymatous neurosyphilis will develop in 70 to 80 per cent of patients in whom early examination revealed severe or so-called Group III changes.

Despite these facts, syphilis of the central nervous system has been looked upon by some as a late development of the disease. This attitude has been fostered by the failure to do spinal-fluid examinations in early syphilis, by the rather infrequent appearance of early symptomatic neurosyphilis (meningitis and thromboses) and by the late development of symptomatic parenchymatous

neurosyphilis. The following case reports bring out some important facts regarding the development, treatment and course of early neurosyphilis.

The following case reports bring out some important facts regarding the development, treatment and course of early neurosyphilis.

### CASE REPORTS

In the following case of early asymptomatic neurosyphilis with mild spinal-fluid abnormality the spinal fluid became normal after intensive mapharsen and bismuth therapy. A severe neurorelapse occurred ten months later.

**Case 1.** H. J. A., a 31-year-old man, developed a penile lesion in October, 1943. The blood Kahn reaction was positive on November 27 and December 6. He was given forty intravenous injections of mapharsen (0.060 gm each) and

\*Research fellow, Department of Psychiatry, Harvard Medical School; research associate, Department of Mental Health, Boston Psychopathic Hospital; assistant physician, Beth Israel Hospital; attending physician, Neuropsychiatric Service, Veterans Administration Hospital, West Roxbury, Massachusetts; formerly, chief, Neurosyphilis Section, Schick General Hospital, Clinton, Iowa.

sixteen intramuscular injections of bismuth subsalicylate (0.200 gm each) from March 10 to September 16, 1944. The results of spinal-fluid examinations are presented in Table 1.

Neurologic examination on August 30, 1945, was negative. The blood Kahn and Wassermann reactions were positive.

The patient was inoculated with tertian malaria on September 12 and was allowed ten paroxysms until October 6, 1945. He was also given one hundred and twenty doses of 30,000 units of penicillin intramuscularly at 3-hour intervals from September 30 to October 16, 1945.

This case provides an excellent example of the importance of repeated spinal-fluid examinations in early syphilis. The spinal fluid three months after the primary lesion and prior to any chemo-

The findings after combined penicillin and malaria therapy revealed the usual marked reduction in cell count and protein. Spinal fluid and clinical re-evaluations were recommended at six-month intervals until the spinal fluid becomes normal and then yearly for three years. Additional therapy, preferably penicillin, will be necessary if clinical or spinal-fluid relapse occurs.

In the following case of asymptomatic neurosyphilis with Group III spinal fluid and marked meningeal reaction nine months after seropositive primary syphilis and immediately after completion

TABLE 2 Spinal-Fluid Findings in Case 2

DATE	WASSERMANN REACTION	CELL COUNT per cu mm	GLOBULIN	TOTAL PROTEIN mg per 100 cc	GOLD SOL CURVE	COMMENT
10/5/44	+		Negative	—	Negative	After bismuth and mapharsen therapy
11/28/44	+(0.1 cc.)	795 lymphocytes 309 polymorphonuclears	Negative	40	0022210000	—
2/26/45	+(0.1 cc.)	17 lymphocytes 1 polymorphonuclear	Negative	10	0132200000	After additional chemotherapy

therapy was completely normal. Two months thereafter and again before therapy, nervous-system involvement had already occurred, as revealed by a positive spinal-fluid Wassermann reaction in 0.5 cc. The spinal fluid was again completely normal immediately after intensive chemotherapy with mapharsen and bismuth, only to relapse and reveal marked abnormalities ten months later.

of an intensive course of mapharsen and bismuth therapy, spinal-fluid improvement followed additional chemotherapy with mapharsen, bismuth and penicillin.

CASE 2 H A A, a 22-year-old Negro, developed a penile lesion on February 9, 1944. *Treponema pallidum* was not found on three dark-field examinations. The blood Kahn reaction was positive. Forty intravenous injections of mapharsen (0.060 gm each) and fifteen intramuscular injections

TABLE 3 Spinal-Fluid Findings in Case 3

DATE	WASSERMANN REACTION	CELL COUNT	GLOBULIN	TOTAL PROTEIN mg per 100 cc	GOLD-SOL CURVE	COMMENT
7/18/45	—	0	Trace	52.5	3222110000	Xanthochromic fluid question able Kahn reaction
8/7/45	++++	—	Positive	—	5543210000	—
9/8/45	+(0.1 cc.)	2 lymphocytes	Trace	78.0	5554432100	—
11/13/45	+(0.25 cc.)	2 lymphocytes	Negative	43.0	5443210000	After malaria inoculation and penicillin
	?(0.1 cc.)	1 polymorphonuclear				

The high cell count—223 per cubic millimeter, with 98 per cent lymphocytes—is indicative of a fairly severe meningeal reaction. Since the patient was free of symptoms and neurologic examination was negative, the neurorelapse would have been overlooked had not the spinal-fluid examination been repeated. This type of abnormal fluid is of considerable prognostic significance in the development of future parenchymatous neurosyphilis. Intensive therapy, occasionally reinforced by fever, is necessary if such an event is to be prevented. The finding of even slight spinal-fluid abnormalities in early asymptomatic neurosyphilis is of considerable importance and necessitates frequent clinical and spinal-fluid re-evaluations.

tions of bismuth subsalicylate (0.200 gm each) were given from March 20 to September 22. The blood Kahn and Wassermann reactions were positive after treatment. The spinal-fluid findings are presented in Table 2.

The patient was given a second course of thirty-one injections of mapharsen (0.060 gm each) and eight injections of bismuth subsalicylate (0.200 gm each) from December 4, 1944, to February 28, 1945, and sixty doses of 40,000 units of penicillin intramuscularly at 3-hour intervals from January 27 to February 6, 1945.

Central-nervous-system syphilis was detected shortly after intensive mapharsen and bismuth therapy for primary syphilis. The spinal-fluid abnormalities were severe (Group III). The high cell count indicated a marked meningeal reaction, but there were no symptoms of meningitis. Additional mapharsen, bismuth and penicillin therapy

resulted in a marked reduction of the cell count, but the spinal fluid remained abnormal. Though continued chemotherapy with trivalent arsenicals or penicillin often results in a normal spinal fluid in early neurosyphilis, malarial therapy was recommended. Repeated clinical and spinal-fluid evaluations are necessary for this patient, as recommended in Case 1.

In the following asymptomatic neurosyphilis with Group III spinal fluid ten months after seropositive primary syphilis followed treatment with penicillin, mapharsen and bismuth. Combined malaria and penicillin was then administered.

CASE 3 F R, a 32-year-old Negro, developed a penile lesion in September, 1944. The blood Kahn reaction was positive on September 7.

He was given 60 doses of 40,000 units of penicillin intramuscularly at 3-hour intervals from September 11 to September 18. Because healing of the penile lesion was slow, he

some hoarseness, as well as patchy areas of alopecia involving the scalp and eyebrows. Dark-field examinations of scrapings of the perianal lesion on May 8 and 9 revealed *Treponema pallidum*. A serologic test on May 8 revealed 240 Kahn units.

The patient was given sixty doses of 40,000 units of penicillin intramuscularly at 3-hour intervals from May 9 to May 15. The blood titer had fallen to 40 Kahn units on November 3.

The spinal-fluid findings 6 months after the secondary lesions had appeared and penicillin treatment had been instituted are presented in Table 4.

Neurologic examination was negative on November 17. The patient was inoculated with tertian malaria on January 12, 1946, and allowed nine paroxysms to January 31. He was given one hundred and twenty injections of 30,000 units of penicillin intramuscularly at 3-hour intervals from January 17 to February 1. Spinal-fluid examination after therapy was refused.

Penicillin therapy for secondary syphilis did not prevent the development of asymptomatic neurosyphilis with a Group III spinal fluid. The per-

TABLE 4 Spinal-Fluid Findings in Case 4

DATE	WASSERMANN REACTION	CELL COUNT <i>per cu. mm.</i>	GLOBULIN	TOTAL PROTEIN <i>mg per 100 cc.</i>	GOLD-SOL CURVE
11/ 5/45	+ (0.1 cc.)	45	+	—	5544332100
11/20/45	+ (0.1 cc.)	156 lymphocytes	Slight trace	57	55543321000

was also given forty intravenous injections of mapharsen (0.060 gm. each) and 16 intramuscular injections of bismuth subsalicylate (0.200 gm. each) from November, 1944, to July, 1945. The spinal-fluid findings are shown in Table 3.

Neurologic examination on September 1 was normal. The patient was inoculated with quartan malaria on September 25 and allowed ten paroxysms to November 10. Fever was also induced on four occasions by means of mixed typhoid vaccine intravenously. He was given one hundred and twenty doses of 30,000 units of penicillin intramuscularly at 3-hour intervals from October 28 to November 12.

Intensive chemotherapy, consisting of penicillin, mapharsen, and bismuth for primary seropositive syphilis, did not prevent the development of asymptomatic neurosyphilis with strong spinal-fluid abnormalities. Involvement of the nervous system was first detected ten months after the primary lesion had appeared and immediately after chemotherapy had been completed. Because of the strong abnormalities in the spinal fluid, malarial therapy combined with penicillin was given. This case reveals the importance of a spinal-fluid examination before the patient is discharged from treatment. Frequent clinical and spinal fluid re-evaluations are necessary, as recommended in Case 1.

In the following case there were marked spinal-fluid abnormalities (Group III) six months after penicillin treatment of secondary syphilis. The patient was also treated with combined penicillin and malaria.

CASE 4 A S P, a 29-year-old man, admitted repeated exposures in February and March, 1945. Lesions of the anus, penis, gums and tongue were noted on May 8. There was

sistence of positive serologic tests should cause one to suspect involvement of the central nervous system. The incidence of neurosyphilis following penicillin therapy of early syphilis is estimated as less than 2 per cent. Repeated courses of penicillin with or without mapharsen and bismuth might well have resulted in a normal spinal fluid since this was a case of early asymptomatic neurosyphilis. However, as long-continued therapy and observation were not possible, combined malaria and penicillin therapy were recommended. If it is among this group that the future paresis or tabes is most apt to develop, early malarial therapy should be of great benefit.

In the following case of asymptomatic neurosyphilis with progressively severe abnormalities in the spinal fluid despite intensive chemotherapy for secondary syphilis, a reversal of Group III spinal fluid to normal occurred after penicillin, malaria and typhoid vaccine fever.

CASE 5 M E H, a 28-year-old Negro, developed a primary lesion in December, 1943. This was followed by a right inguinal adenitis and a maculopapular rash of the face and back. Dark-field examination of the penile lesion was negative. The blood Kahn and Wassermann reactions were positive in December, 1943, and January, 1944. Forty intravenous injections of mapharsen (0.060 gm. each) and fifteen intramuscular injections of bismuth subsalicylate (0.200 gm. each) were given from January 18 to August 31.

The blood Kahn reaction became negative after treatment, remaining so until February, 1945, and then relapsing to positive. The results of the spinal-fluid examinations are shown in Table 5.

The patient was given eighty doses of 50,000 units intramuscularly of penicillin at 3-hour intervals from March 21 to March 31. He was inoculated with quartan malaria on May 24, and allowed eight paroxysms until July 26. Fever was also induced on seven occasions by means of mixed typhoid vaccine intravenously.

One year after a primary lesion and about three months after completion of intensive chemotherapy, the spinal fluid revealed an increase in cells, which was indicative of central-nervous-system involvement. Two months thereafter the spinal-fluid

developed in February, 1944. A diagnosis of lymphogranuloma inguinale was made. He was given sulfonamide therapy. The lymph nodes became less tender but remained enlarged for 3 or 4 months. A serologic test was positive in January and February, 1945. The results of spinal-fluid examination are presented in Table 6.

He was given fifteen intravenous injections of mapharsen (0.060 gm each) and five intramuscular injections of bismuth subsalicylate (0.200 gm each) from February 26 to April 13. The spinal fluid reverted to normal in 5 months.

Neurologic examination on June 30 was negative, as was a Frei test on July 7. The blood Kahn and Wassermann reactions were positive.

TABLE 5 Spinal-Fluid Findings in Case 5

DATE	WASSERMANN REACTION	CELL COUNT per cu mm	GLOBULIN	TOTAL PROTEIN mg per 100 cc	GOLD SOL CURVE	COMMENT
12/4/44	Not determined	32	—	—	Negative	—
2/9/45	—	73	+	—	5555421000	Kahn reaction positive
2/18/45	+ (0.25 cc)	23 lymphocytes	+	120	5555321000	—
	? (0.1 cc)	9 polymorphonuclears				
5/1/45	? (1.0 cc)	15 lymphocytes	+	96	5543310000	After penicillin
8/27/45	Negative (1.0 cc)	5 lymphocytes	Trace	45	1100000000	After malaria inoculation

abnormalities were severe (Group III). The fluid showed some improvement after the administration of penicillin and became practically normal after fever therapy.

It is possible that the spinal fluid would eventually have become normal as a result of penicillin therapy alone. Moore<sup>3</sup> states that the speed and extent of disappearance of all spinal-fluid abnormalities following penicillin depends upon the degree of these abnormalities before treatment.

From July 12 to July 19 the patient was given sixty injections of 40,000 units of penicillin intramuscularly at 3-hour intervals.

The neurosyphilis in this case was asymptomatic and evidently early. The penile lesion in December, 1943, was probably a chancre and not lymphogranuloma inguinale, since a Frei test two and a half years later was negative. A moderate amount of mapharsen and bismuth therapy had rapidly reversed a Group III spinal fluid to normal. This

TABLE 6 Spinal-Fluid Findings in Case 6

DATE	WASSERMANN REACTION	CELL COUNT per cu mm	GLOBULIN	TOTAL PROTEIN mg per 100 cc	GOLD SOL CURVE	COMMENT
2/15/45	++++	106 lymphocytes	—	53.5	5554420000	—
		12 polymorphonuclears				
2/28/45	++++	102 lymphocytes	—	65.5	5554442000	—
		11 polymorphonuclears				
7/4/45	Negative (1.0 cc)	4 lymphocytes	Negative	36.0	1110000000	After bismuth and mapharsen

and the duration of the syphilitic infection. In a series of 91 patients with asymptomatic neurosyphilis, 48 of less than four years' duration, observed on an average for about nine months, spinal-fluid normality once obtained seemed to be sustained. Serologic relapse like that in Case 5, which should always alert one to the possible presence of early neurosyphilis, demands a spinal-fluid examination.

In the following case of early asymptomatic neurosyphilis with marked spinal-fluid abnormalities, the spinal fluid became normal after a moderate amount of mapharsen and bismuth therapy.

CASE 6. J. L. R., a 24-year-old man, had negative serologic tests in December, 1942. A penile lesion appeared 7 to 10 days after exposure in December, 1943. Dark-field examinations were negative. Left inguinal adenopathy

is not uncommon in early asymptomatic neurosyphilis. However, repeated spinal-fluid and clinical re-evaluation for four years at least is necessary since relapse is not uncommon with this degree of abnormality.

In the following case of early meningo-vascular neurosyphilis with right cerebral thrombosis spinal-fluid abnormalities persisted after two courses of penicillin, malaria therapy was instituted.

CASE 7. H. J. B., a 27-year-old man, had a negative serologic test on December 15, 1943. On May 23, 1945, a central weakness of the left facial muscles developed, accompanied by a left hemiparesis. The spinal-fluid findings are shown in Table 7.

The Wassermann and Kahn reactions of the blood were positive on June 8. From June 23 to July 3 eighty doses of

50,000 units of penicillin were administered intramuscularly at 3-hour intervals

On August 8 neurologic examination revealed brisk and equal reflexes and a left Babinski sign. The serologic tests were again positive. The subsequent spinal-fluid findings are presented in Table 7.

The patient was given a second course of penicillin, consisting of one hundred and twenty doses of 30,000 units intramuscularly at 3-hour intervals from September 7 to 22. Since the protein and cell count remained elevated after completion of penicillin therapy, he was inoculated with tertian malaria and allowed eleven paroxysms.

Early symptomatic neurosyphilis is not common. The patient gave no history of primary or secondary syphilis. The first sign of neurosyphilis was weakness of the left side of the face and left side

in July, 1945, he was given four doses of 50,000 units of penicillin intramuscularly. He was again given some penicillin therapy, the exact amount not known, in September because of tonsillitis.

On October 3, he experienced a grand mal seizure with involvement of the right side of the face and right upper extremity. On October 5, 8 and 9 similar episodes without loss of consciousness occurred. During this time he complained of left frontal headaches. Central weakness of the right facial muscles and slurring of speech were observed on October 13.

The quantitative titer of the blood on October 15 and 15 was 10 Kahn units. X-ray study of the skull was negative. The spinal-fluid pressure and dynamics were normal. A sugar tolerance test was normal. The spinal-fluid findings are presented in Table 8.

From October 15 to 22 sixty doses of 40,000 units of penicillin were administered intramuscularly at 3-hour intervals.

TABLE 7 Spinal-Fluid Findings in Case 7

DATE	WASSERMANN REACTION	CELL COUNT <i>per cu mm</i>	GLOBULIN	TOTAL PROTEIN <i>mg per 100 cc</i>	GOLD-SOL CURVE	COMMENT
5/23/45	—	284	Negative	—	—	—
6/ 8/45	Positive	99 lymphocytes	++ + +	25	4433200000	—
8/11/45	— (0.25 cc.)	25 lymphocytes	Trace	108	Negative	After penicillin
9/24/45	+ (0.5 cc.)	27 lymphocytes	Negative	83	0011221000	After additional penicillin
	+ (0.25 cc.)					
11/ 6/45	+ (0.5 cc.)	5 lymphocytes	Negative	90	1100000000	After malaria therapy
	+ (0.1 cc.)					

of the body. This was indicative of a vascular lesion, but pure syphilitic arteritis rarely occurs without an associated meningitis or meningo-encephalitis. Though syphilis had been suspected as the cause after the finding of 284 cells per cubic millimeter in the spinal fluid, the Wassermann reaction of the spinal fluid and blood had not been determined. Strong spinal-fluid abnormalities and

Neurologic examination on October 30 revealed central weakness of the right facial muscles, and the reflexes of the right upper extremity were more active than those on the left.

The serologic titer on November 2 was 40 Kahn units, the blood Wassermann reaction was positive.

From January 9 to 16, 1946, the patient was given a second course of penicillin consisting of sixty doses of 40,000 units intramuscularly at 3-hour intervals.

The serologic titer was 10 Kahn units and the blood Wassermann reaction was negative on January 17.

TABLE 8 Spinal-Fluid Findings in Case 8

DATE	WASSERMANN REACTION	CELL COUNT <i>per cu mm</i>	GLOBULIN	TOTAL PROTEIN <i>mg per 100 cc</i>	GOLD SOL CURVE	COMMENT
10/13/45	—	65 lymphocytes	—	45	—	Kahn test positive
10/27/45	—	1 polymorphonuclear	—	32	—	After penicillin
12/ 4/45	Negative (1.0 cc.)	22 lymphocytes	Negative	40	Negative	Initial spinal-fluid pressure was equivalent to 145 mm of water; dynamics normal
		5 lymphocytes				

a positive serologic test were found two weeks thereafter. Spinal-fluid abnormalities were still present after two courses of penicillin, and it was considered best to administer malaria therapy. Clinical and spinal-fluid re-evaluations, as in Case 1, were recommended.

In the following case of early meningovascular neurosyphilis with Jacksonian attacks moderately severe spinal-fluid abnormalities rapidly returned to normal after 2,400,000 units of penicillin had been administered.

CASE 8 R E R, a 27-year-old man, had a negative serologic test in August, 1942. Because of a gonorrheal infection

A convulsive episode may be the first indication of neurosyphilis, early or late. This is due to a thrombosis of a cortical vessel that occasionally occurs in the leptomeningitis of neurosyphilis. The moderately severe spinal-fluid abnormalities rapidly reverted to normal after 2,400,000 units of penicillin had been administered. The patient will require clinical and spinal-fluid re-evaluations for at least three years. The convulsive episodes disappear in most cases with adequate anti-syphilitic therapy. If they recur, anticonvulsants should be given.

In the following case of syphilitic meningitis with cerebral thrombosis in early syphilis the patient suffered a neurorelapse

CASE 9 W R C, a 21-year-old man, developed a penile lesion in December, 1942. He received three intravenous treatments. A serologic test on February 12 and March 26, 1943, was positive. The spinal-fluid findings are presented in Table 9.

He was given thirty-nine injections of mapharsen (0.060 gm each) and seventeen of bismuth subsalicylate (0.200 gm each) from May to December.

From December, 1944, on he experienced frontal headaches of 2 or 3 hours' duration. Dizzy spells occurred in May, 1945. Numbness of the right forearm and the fourth and fifth fingers over 1 week's time was present in August. He was aphasic from September 1 to 8. There was also weakness

## DISCUSSION

The cases reported above are examples of early asymptomatic and symptomatic neurosyphilis. Of 154 cases of asymptomatic neurosyphilis from November, 1944, to February, 1946, 25 (15 per cent) were of less than two years' duration when the patients were first seen. Spinal-fluid abnormalities of varying degree were found from the secondary stage of syphilis on. These abnormalities may clear with chemotherapy, mapharsen, bismuth or penicillin, but occasionally relapse occurs despite intensive therapy.

TABLE 9 Spinal-Fluid Findings in Case 9

DATE	WASSERMANN REACTION	CELL COUNT <i>per cu mm</i>	GLOBULIN	TOTAL PROTEIN <i>mg per 100 cc</i>	GOLD-SOL CURVE	COMMENT
5/8/43	Negative (0.5 cc)	110	Negative	—	—	—
12/6/43	Negative	2	Negative	—	Negative	After bismuth and mapharsen
10/27/45	+ (0.25 cc.) ? (0.1 cc.)	172 lymphocytes	Trace	76	4443331000	—
12/11/45	+ (0.25 cc.) ? (0.1 cc.)	9 lymphocytes	Trace	46	5443210000	After penicillin and malaria

of the right upper extremity and numbness of the ulnar portion of the forearm.

A serologic test on September 7 revealed 40 Kahn units. Physical examination showed dysarthria, loss of the finer movements of the right hand and absent right abdominal reflexes.

The serologic titer on October 18 was 40 Kahn units, the blood Wassermann reaction was positive.

He was inoculated with tertian malaria on November 17 and allowed eleven paroxysms until December 9. He was also given one hundred and twenty doses of 30,000 units of penicillin intramuscularly at 3-hour intervals from November 22 to December 7.

This patient's spinal fluid revealed an increase in cell count five months after the appearance of a primary lesion. The spinal fluid was normal immediately after the completion of seven months of intensive mapharsen and bismuth therapy. One year later, progressively severe symptoms referable to the central nervous system developed. Neurorelapse with spinal-fluid abnormalities, Group III in type, were found twenty-two months after a normal spinal-fluid had been obtained and three years after the primary lesion.

The sequence of events in this patient again emphasizes the fact that one cannot rely on a single normal spinal-fluid specimen in early neurosyphilis, especially an examination performed shortly after the completion of chemotherapy. In addition, the necessity of adequate therapy for syphilitic meningitis has been stressed by various observers, since two thirds of inadequately treated patients have developed parenchymatous and late meningo-vascular neurosyphilis.<sup>4</sup> Since the patient's syphilis was of three years' duration, malaria therapy was given without hesitation.

These cases support the advice that treatment for early syphilis cannot be considered satisfactory unless a spinal-fluid examination is done before the patient is discharged. If the spinal fluid is normal, adequate follow-up study requires that it should be normal again at least four years after the primary lesion. If spinal-fluid abnormalities are present during the first two years of the infection, additional chemotherapy (formerly trivalent arsenicals and bismuth, now penicillin) is necessary, since early neurosyphilis will respond most often to chemotherapy alone. If marked improvement or a normal spinal fluid does not result within a year, fever therapy is given. However, if the infection is of more than two years' duration when the patient is first seen and significant spinal-fluid abnormalities are present, fever therapy should be administered immediately, combined now with penicillin. Further experience will be necessary before it can be determined whether penicillin alone will be adequate in these cases, as has been reported by some observers.<sup>5</sup>

The majority of the patients with early asymptomatic neurosyphilis included in this study had already received chemotherapy consisting of trivalent arsenicals and bismuth. A few had received penicillin. In many cases the treatment was considered adequate according to present standards. With the introduction of penicillin, it is now necessary to determine new methods for the treatment of neurosyphilis. It is already apparent that the incidence of neurosyphilis has been reduced considerably as a result of the treatment of early

sphilis with penicillin. Used alone, the drug has proved very effective in the treatment of syphilitic meningitis, asymptomatic and meningo-vascular neurosyphilis and, in the opinion of some observers, in parenchymatous neurosyphilis.

It is also evident from the cases reported above that malaria therapy was administered quite early for the treatment of neurosyphilis. Undoubtedly the spinal-fluid abnormalities in some cases would have responded to additional chemotherapy alone. Since it is especially among the patients with severe spinal-fluid abnormalities that future parenchymatous neurosyphilis may develop, and since circumstances prevented long-continued chemotherapy and observation in this group, malaria therapy was given early. Clinical and spinal-fluid evaluations of these patients over the years should be of considerable interest in demonstrating the preventive effect of combined malaria and penicillin therapy of early neurosyphilis upon the development of late parenchymatous disorders.

Prior to the introduction of penicillin, Moore<sup>6</sup> had expressed the opinion that fever therapy in asymptomatic neurosyphilis is seldom necessary except in patients with Group III spinal fluids and those of other groups in whom at least eighteen months of other forms of treatment had failed to effect serologic reversal. Malaria was not recommended by him if the infection was recent until the patient had had at least six months' treatment with the arsphenamines and heavy metal given for the treponemicidal effect. The latter was advised because of the great probability of infectious mucocutaneous relapse. It is possible that this objection can now be overcome by the concurrent use of penicillin, with its pronounced treponemicidal effect, and malaria.

## SUMMARY

Invasion of the central nervous system in syphilis is early, occurring in nearly all patients, usually within the first year of the infection.

Early neurosyphilis is most often asymptomatic but occasionally is symptomatic. When asymptomatic, it can be detected only by spinal-fluid examination.

Neurosyphilis may develop despite the administration of what is commonly accepted as adequate chemotherapy for early syphilis.

Complete reliance cannot be placed on the finding of a single normal spinal-fluid specimen in early syphilis before or immediately after therapy.

A negative spinal-fluid examination four years or more after the primary lesion, regardless of whether therapy has been given, is good assurance against the future development of meningo-vascular or parenchymatous neurosyphilis.

The treatment of early syphilis with penicillin has reduced considerably the incidence of early neurosyphilis. Penicillin alone is of great benefit in the therapy of neurosyphilis of the asymptomatic, meningo-vascular and meningitic types. Further experience is necessary to determine its value as the sole treatment for parenchymatous (general paresis, tabes dorsalis, optic atrophy and so forth) neurosyphilis.

74 Fenwood Road

## REFERENCES

1. Mills, H., Zurbelle, E. and Kreechel, J. Cited by Merritt, H. H., Adams, R. D. and Solomon, H. C. *Neurosyphilis*. 443 pp. New York: Oxford University Press, 1946. P. 7.
2. Moore, J. E. *Modern Treatment of Syphilis*. Second edition. 712 pp. Springfield, Ill.: Charles C. Thomas, 1947. Pp. 364 and 365.
3. *Idem*. *Penicillin in Syphilis*. 319 pp. Springfield, Ill.: Charles C. Thomas, 1946. Pp. 259 and 240.
4. Moore, J. E. P. 365.
5. Dattner, B. Neurosyphilis and latest methods of treatment. *M. Clin. North America* 32: 707-719, 1948.
6. Moore, J. E. P. 418.

## HOSPITAL AND HEALTH-CENTER FACILITIES IN MASSACHUSETTS

### The Massachusetts State Plan for the Administration of Public Law 725 (Hospital Survey and Construction Act)

VLADO A. GETTING, M.D., DR. P.H.,\* A. DANIEL RUBENSTEIN, M.D.,† AND CLAIRE F. RYDER, M.D.‡

BOSTON

THE acute shortage of hospital beds experienced everywhere in the country during the past few years resulted in 1946 in the enactment of Public Law 725 by the Seventy-Ninth Congress. This act, the Hospital Survey and Construction Act, previously known as Senate Bill 191, or the Hill-Burton Bill, was the first and only bill to be endorsed in Congressional hearings by the American Public Health Association, the American Hospital Association and the American Medical Association. The purpose of the Act is to enable communities throughout the nation to construct hospitals and health-center facilities under a federal grants-in-aid program for a period of five years beginning July 1, 1947. Such facilities are to be provided on the basis of need according to plans developed by each state. The federal Government is contributing a third of the cost of constructing and equipping hospitals and health centers, and the remaining two thirds is derived from sources within the state.

Of the \$75,000,000 authorized by Congress for hospital construction during the first year of the program, approximately \$1,600,000 has been allotted to Massachusetts. The amount of the grant to Massachusetts for the five-year period of the program totals approximately \$8,000,000. Since each dollar of federal grants must be matched by two dollars from state or local sources, the total expenditure under this program in Massachusetts amounts to \$24,000,000. State, county, municipal and private nonprofit hospitals may be assisted if individual projects are approved by the state operating agency (usually the health department) and the United States Public Health Service, and provided that the project is in accord with the plan<sup>1</sup> formulated by the state agency to meet the needs for additional facilities. The Massachusetts State Plan was approved by the Surgeon General of the United States Public Health Service on December 2, 1947. The state agency in Massachusetts directly responsible for the administration of Public Law 725 is the Department of Public Health. For the administration of this Act, a bureau of hospital survey and construction has been created, and an advisory council to the state agency has been appointed.

In accordance with the regulations promulgated by the United States Public Health Service regarding Public Law 725, the Commonwealth of Massachusetts has been divided into three types of hospital service areas—namely, base, intermediate and rural.

A base area is defined as one that, irrespective of population, contains a teaching hospital of a medical school, or one that has a total population of at least 100,000 and contains or will contain a general hospital of 200 beds or more providing internships and at least two or more residencies. An intermediate area has at least 25,000 persons and contains or will contain a general hospital of 100 beds or more. A rural area has a population under 25,000.

For the purposes of the Act, the term "hospital" includes public-health centers, general, tuberculosis, mental-disease and chronic-disease hospitals, and related facilities such as laboratories, outpatient departments, nurses' homes and schools and all service facilities operated in connection with such institutions. Federal hospitals and institutions providing primarily domiciliary care are not included in the above definitions.

Bed allowance for general hospitals is based upon the state's population density. In Massachusetts, with more than 12 persons per square mile, the maximum state allowance for general hospital beds is 4.5 per thousand population. Standards for area ratios also depend on population density. In Massachusetts, area ratio standards are as follows: base areas, 4.5 beds per thousand population, intermediate areas, 4 beds per thousand population, and rural areas, 2.5 beds per thousand population.

The differences in the number of beds allowable under the state and area ratios may be totaled and thus constitute a pool of general-hospital beds. Pool beds may be distributed throughout the state at the discretion of the state agency according to the needs of various areas. The number of beds required to provide adequate hospital services for the care of tuberculosis patients amounts to two and a half times the average annual deaths from tuberculosis, for mental patients, 5 beds per thousand population, and for patients with chronic diseases, 2 beds per thousand population. The total number of public-health centers allowed shall not exceed 1 for 30,000 persons.

\*Commissioner, Massachusetts Department of Public Health.

†Director of Hospital Survey and Construction.

‡Epidemiologist, Hospital Survey and Construction.

In the development of the hospital-construction program, consideration must be given to each of the five categories of facilities: general, tuberculosis and mental and chronic-disease hospitals and public-health centers. New hospitals and additions to existing hospitals have priority over replacements, with the exception of hospitals that constitute a public hazard and should be replaced. It is the intent of the law to provide facilities in areas of greatest need. Special attention must be given to projects in rural areas or in communities of low economic resources.

### EXISTING FACILITIES

In the development of the state plan for the administration of the Act, a survey of existing hospital and health-center facilities in Massachusetts has been completed. There are in the Commonwealth a total of 219 hospitals with a normal bed capacity of 44,044 beds. Of these institutions, 147 are general hospitals with 16,968 beds, and 24 allied special hospitals with 2210 beds (Table 1).

It is noteworthy that of the 147 general hospitals, 92 have 100 beds or less, 44 have 100 to 249 beds, and only 11 have 250 beds or more (Table 2).

There are 20 tuberculosis institutions with a total bed capacity of 3299 (Table 1). Of these,

Existing facilities for the care of patients with long-term illness are entirely inadequate in the Commonwealth as they are everywhere else in the country. There are now only 1100 beds for patients with chronic diseases in Massachusetts hospitals. How this shortage is to be overcome is a matter of debate. In Springfield, one hospital has set aside a complete ward for such patients. Although this ward was set up more than ten years ago, certain patients admitted at the time of its inception are still occupying beds in this institution. The problem is even more acute for certain categories of patients, such as those with terminal cancer. Ordinarily, these patients are not accepted

TABLE 2 *Distribution of General Hospitals by Size*

SIZE	TOTAL NUMBER	
	HOSPITALS	BEDS*
Less than 25 beds	25	436
25-49 beds	32	1 115
50-99 beds	37	2,460
100-249 beds	44	7 178
250-499 beds	8	2,597
More than 500 beds	5	3 184
Totals	147	16 968

\*The figures referring to number of beds indicate the normal bed capacity—that is, number of beds for which the hospital was built. In many instances because of overcrowding this figure is smaller than the actual number of beds in use for inpatient care (complement).

TABLE 1 *Distribution of Hospitals by Type*

TYPE	TOTAL NUMBER	
	HOSPITALS	BEDS*
General	147	16,968
Maternity	6	579
Contagious	6	564
Other special	12	1 267
Subtotals of general and allied special	171	19 178
Tuberculosis	20	3 299
Nervous and mental	24	21 000
Chronic and convalescent	4	517
Grand totals	219	44 044

\*The figures referring to number of beds indicate the normal bed capacity—that is, the number of beds for which the hospital was built. In many instances because of overcrowding this figure is smaller than the actual number of beds in use for inpatient care (complement).

4 are nongovernmental, nonprofit associations, and the remaining 16 are governmental hospitals. Of the latter, 12 are owned by cities or counties and provide nearly 2000 beds, primarily for the care of the patients with local settlements, and 2 are state institutions having a bed capacity of about 600 beds. In addition, there are 2 state hospitals caring for patients with extrapulmonary tuberculosis and tuberculosis in children. If tuberculosis units in general or board of health hospitals are included, the total number of existing beds for the care of tuberculosis is 3611.

In Massachusetts there are 24 mental hospitals with a normal bed capacity of 21,050 (Table 1). Of these, 12 institutions with a total of 604 beds are nongovernmental, and the remaining 12 with 20,446 beds are state owned.

for admission into general hospitals for indefinite or prolonged periods of stay. Nursing homes and convalescent homes are often too inadequately staffed to care for them. In summary, there are practically no facilities for the patient requiring terminal care.

Although each of the 351 municipalities is required by law to carry out certain governmental functions in the field of public health, as defined by Public Law 725, there are but 11 health centers in the Commonwealth. Of these, 10 are in Boston proper. The other is the public-health center in Averb, maintained by the Nashoba Health Unit, a union of several towns in the north central section.

### HOSPITAL SERVICE AREAS

In keeping with requirements of Public Law 725, all cities and towns in Massachusetts, singly or in groups are designated as the service areas of existing or proposed general hospitals. Accordingly, the Commonwealth was divided into 70 general-hospital service areas. Each of these areas contains at least one general hospital, with the exception of one area (Athol) where a new hospital facility has been proposed. Determination of the service area was based primarily on available data regarding the flow of patients into the hospital. Other factors taken into consideration were location of trading centers and lines of communication. Subsequently, each hospital service area was clas-

sified as base, intermediate or rural (the prerequisites of these area types were described above) Of the 70 hospital service areas in Massachusetts, 4 are base, 43 intermediate, and 23 rural

In addition, the state plan provides a method whereby each hospital service area will be co-ordinated with all others so that a uniform pattern of hospital care shall be formulated for the entire Commonwealth Theoretically, the base areas should offer consultation and diagnostic services to the intermediate areas, which, in turn, offer simi-

which the number assigned by area ratio is insufficient for the needs of the jurisdiction Pool beds were assigned in proportion to high occupancy rates, excessive bed-death ratios and special problems such as seasonal increases in population Of the 1661 pool beds, the greatest number was allocated to base areas (1011 beds), intermediate areas being allotted 440 and rural areas 210 beds (Table 3)

The number of existing and needed beds according to the several categories is as follows there are 18,224 general-hospital beds, whereas 23,829 beds

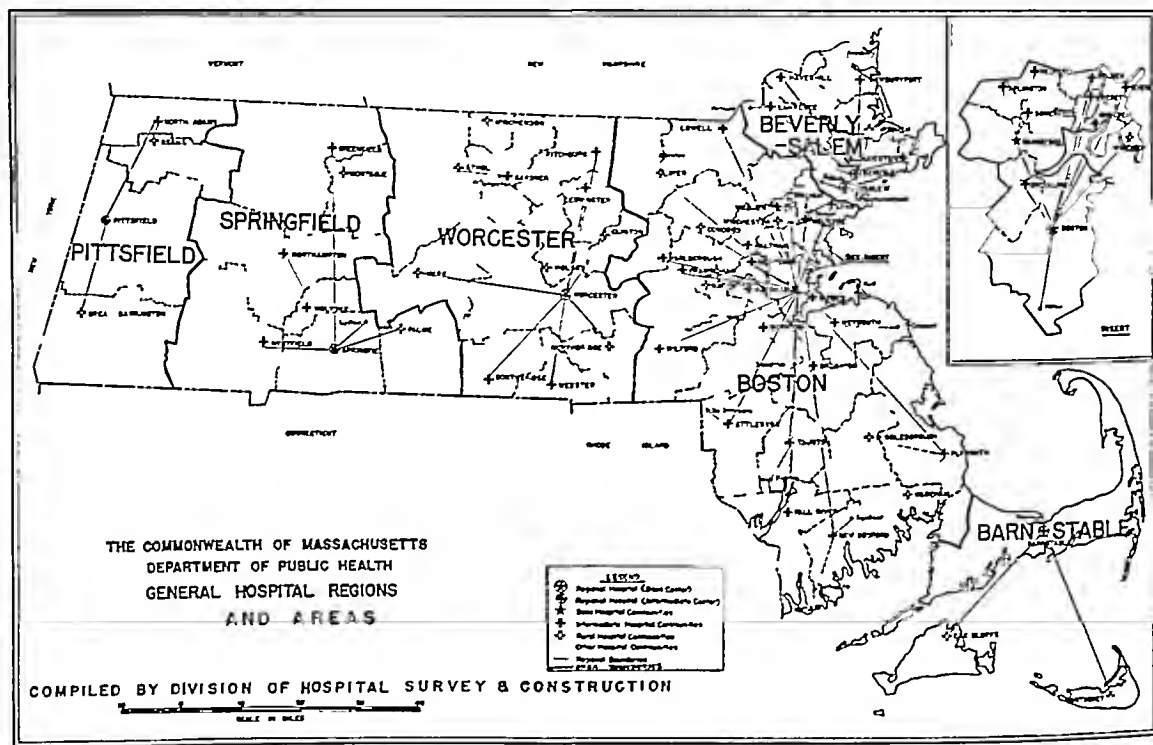


FIGURE 1 Hospital Service Areas in Massachusetts

lar service to rural areas To allow for this exchange of facilities, Massachusetts was divided into 6 regions of which 3 are composed of intermediate and rural areas, and the other 3 contain in addition base areas The former are the Beverly-Salem, Barnstable and Pittsfield regions, and the latter, the Boston, Worcester and Springfield regions (Fig 1)

#### DETERMINATION OF NEEDS FOR HOSPITALS AND HEALTH CENTERS

The number of beds apportioned to each general hospital service area is determined according to the formula established by law as mentioned above Of 3944 beds added by area ratio in Massachusetts, nearly all (3285 beds) went to intermediate areas and only 454 and 205 to base and rural areas respectively Pool beds may be allocated to areas in

are needed according to Public Law 725, making a deficit of 5605 beds For the care of tuberculosis, Massachusetts has in existence 3604 beds, 4408 beds are needed Therefore, 804 additional beds must be provided For patients with mental disease, there are 21,102 beds, 1738 additional beds are needed, since the total beds allowed are 22,840 Finally, for chronic-disease hospital facilities, there are only 1100 beds in existence, 9136 are needed, and therefore, a deficit of 8036 exists The figures of need met in these four categories of facilities are 76 per cent for general-hospital beds, 82 per cent for tuberculosis, 92 per cent for mental-disease and 12 per cent for chronic-disease beds (Fig 2)

The state plan must also give consideration to the need for health centers in Massachusetts For the Commonwealth as a whole, 31 public-health

centers are being proposed. For the most part, these centers have been allocated to the larger cities and towns with a population of 30,000 or more. It should be noted, in accordance with the ratio of 1 health center for each 30,000 persons, that many of the larger cities could plan for more than one health center provided that matching local funds were available. In addition, a health center has

greater financial resources than communities low in Dr Lambie's rating.

The primary consideration in developing the priority schedule was the percentage by which the existing acceptable hospital beds within an area met the total needs of that area. From the percentage of need met, additional deductions were made for rural areas and those of low financial

TABLE 3 *Relation of Population to Existing and Proposed General-Hospital Beds*

AREA TYPE	EXISTING BEDS		BEDS ADDED BY AREA RATIO	BEDS ADDED FROM POOL	TOTAL BEDS NEEDED		POPULATION	
	NO	PERCENTAGE			NO	PERCENTAGE	NO *	PERCENTAGE
Base	9 161	50.3	454	1 011	10 626	44.6	1 612	35.5
Intermediate	8 026	44.0	5 285	440	11 751	49.5	2 605	57.0
Rural	1 057	5.7	205	210	1 452	6.1	350	7.7
Totals	18 224		3 944	1 661	23 829		4,567	

\*In thousands

been proposed in Amherst for the Connecticut Valley State Health District and another for Barnstable County.

A recent report issued by the Special Commission to Study and Investigate Certain Public Health Matters<sup>2</sup> will suggest a plan to provide full-time health service for the entire Commonwealth. The findings of the Recess Commission will be given full consideration by the state agency and the advisory council in future planning of adequate health-center facilities, including physical plant and personnel.

#### PRIORITY SCHEDULES

To facilitate the equitable distribution of federal funds available for the construction of general hospitals, a system of priorities has been developed. This system gives full consideration to the provisions required in Public Law 725 and the federal regulations—namely, the relative need for beds in an area, rural character of the hospital service area and the financial rating.

Percentage of need met is determined by division of the total number of existing acceptable beds in each area by the total number of beds needed in the area, this figure being multiplied by 100 for the percentage. Rural character is established by the Act as any area with a population less than 25,000.

In 1941, Dr Morris B. Lambie<sup>3</sup> conducted a study of the municipal finances of the 351 cities and towns in the Commonwealth at the Harvard Graduate School of Public Administration. His comparative rating of these municipalities was based on three-year averages of three factors: tax rates, assessed per capita valuation, and direct tax per capita. According to these criteria, the municipalities were classified into eleven categories. Communities in the first grouping have relatively

rating. The final figure determined the standing in the priority scheme (Table 4).

The priority scheme for chronic-hospital projects has been computed in the same manner as for general hospitals, and is based primarily on the percentage of need met. Metropolitan areas of greatest population density will stand highest in

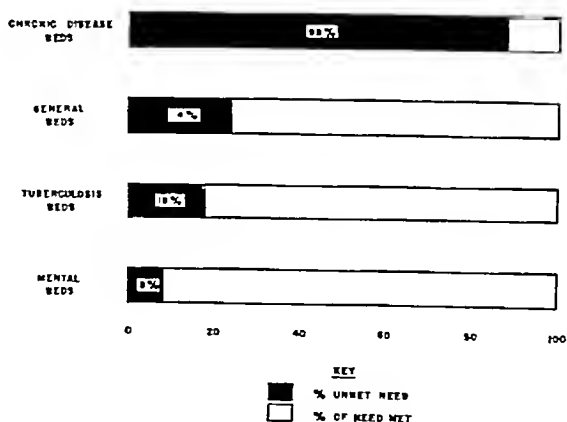


FIGURE 2 *Need for Additional Hospital Beds in Massachusetts*

the scheme. With respect to general hospitals it became apparent that strict application of the federal formula favored rural and intermediate areas rather than base areas. It was believed that construction of chronic-hospital units in metropolitan areas would compensate in part for the low standing in the priority schedule of the base areas. It will therefore be possible to allocate federal funds for chronic-hospital projects in such areas as Boston, Worcester, Springfield and Pittsfield.

The need for public-health centers in the Commonwealth is so great that no attempt has been made to establish a priority scheme for this cate-

sified as base, intermediate or rural (the prerequisites of these area types were described above) Of the 70 hospital service areas in Massachusetts, 4 are base, 43 intermediate, and 23 rural

In addition, the state plan provides a method whereby each hospital service area will be co-ordinated with all others so that a uniform pattern of hospital care shall be formulated for the entire Commonwealth Theoretically, the base areas should offer consultation and diagnostic services to the intermediate areas, which, in turn, offer simi-

which the number assigned by area ratio is insufficient for the needs of the jurisdiction Pool beds were assigned in proportion to high occupancy rates, excessive bed-death ratios and special problems such as seasonal increases in population Of the 1661 pool beds, the greatest number was allocated to base areas (1011 beds), intermediate areas being allotted 440 and rural areas 210 beds (Table 3)

The number of existing and needed beds according to the several categories is as follows there are 18,224 general-hospital beds, whereas 23,829 beds

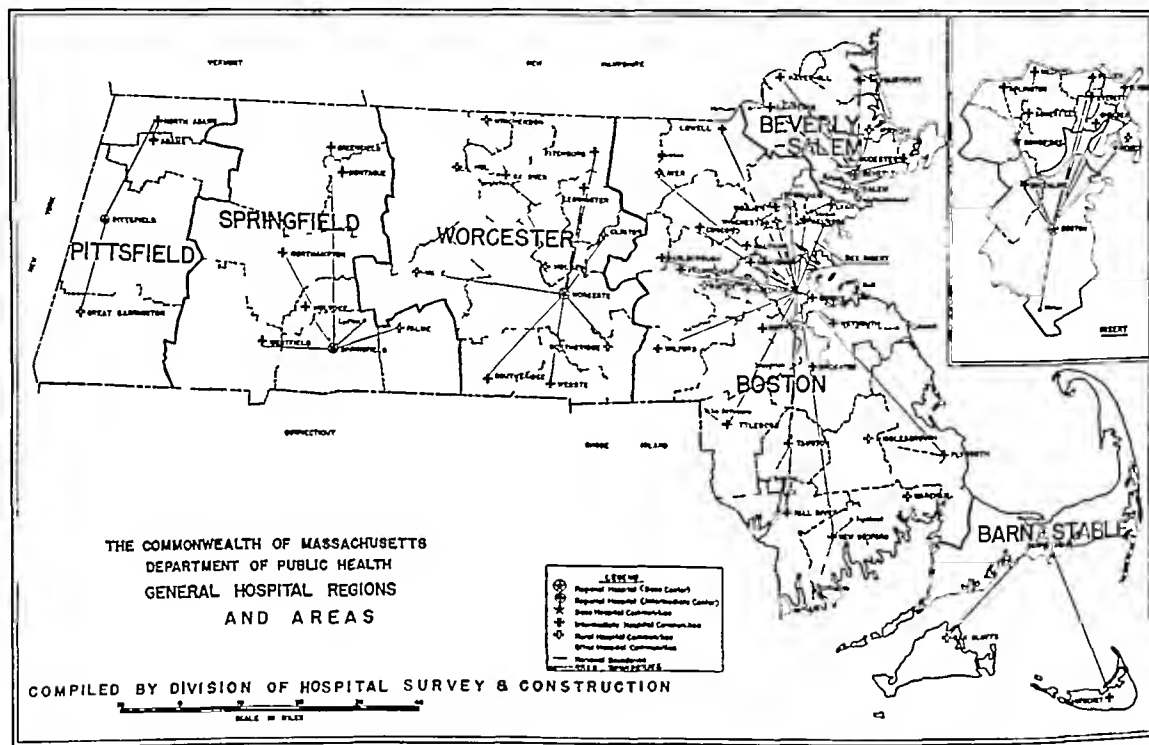


FIGURE 1 Hospital Service Areas in Massachusetts

lar service to rural areas To allow for this exchange of facilities, Massachusetts was divided into 6 regions of which 3 are composed of intermediate and rural areas, and the other 3 contain in addition base areas The former are the Beverly-Salem, Barnstable and Pittsfield regions, and the latter, the Boston, Worcester and Springfield regions (Fig 1)

#### DETERMINATION OF NEEDS FOR HOSPITALS AND HEALTH CENTERS

The number of beds apportioned to each general hospital service area is determined according to the formula established by law as mentioned above Of 3944 beds added by area ratio in Massachusetts, nearly all (3285 beds) went to intermediate areas and only 454 and 205 to base and rural areas respectively Pool beds may be allocated to areas in

are needed according to Public Law 725, making a deficit of 5605 beds For the care of tuberculosis, Massachusetts has in existence 3604 beds, 4408 beds are needed Therefore, 804 additional beds must be provided For patients with mental disease, there are 21,102 beds, 1738 additional beds are needed, since the total beds allowed are 22,840 Finally, for chronic-disease hospital facilities, there are only 1100 beds in existence, 9136 are needed, and therefore, a deficit of 8036 exists The figures of need met in these four categories of facilities are 76 per cent for general-hospital beds, 82 per cent for tuberculosis, 92 per cent for mental-disease and 12 per cent for chronic-disease beds (Fig 2)

The state plan must also give consideration to the need for health centers in Massachusetts For the Commonwealth as a whole, 31 public-health

centers are being proposed. For the most part, these centers have been allocated to the larger cities and towns with a population of 30,000 or more. It should be noted, in accordance with the ratio of 1 health center for each 30,000 persons, that many of the larger cities could plan for more than one health center provided that matching local funds were available. In addition, a health center has

greater financial resources than communities low in Dr Lambie's rating.

The primary consideration in developing the priority schedule was the percentage by which the existing acceptable hospital beds within an area met the total needs of that area. From the percentage of need met, additional deductions were made for rural areas and those of low financial

TABLE 3 *Relation of Population to Existing and Proposed General-Hospital Beds*

AREA TYPE	EXISTING BEDS		BEDS ADDED BY AREA RATIO	BEDS ADDED FROM POOL	TOTAL BEDS NEEDED		POPULATION	
	NO	PERCENTAGE			NO	PERCENTAGE	NO *	PERCENTAGE
Base	9 161	50.3	454	1 011	10 626	44.6	1 612	35.5
Intermediate	8 026	44.0	1 285	440	11 751	49.5	2 605	57.0
Rural	1 037	5.7	205	210	1 452	6.1	350	7.7
Totals	18 224		1 944	1 661	23 829		4 567	

\*In thousands

been proposed in Amherst for the Connecticut Valley State Health District and another for Barnstable County.

A recent report issued by the Special Commission to Study and Investigate Certain Public Health Matters<sup>2</sup> will suggest a plan to provide full-time health service for the entire Commonwealth. The findings of the Recess Commission will be given full consideration by the state agency and the advisory council in future planning of adequate health-center facilities, including physical plant and personnel.

#### PRIORITY SCHEDULES

To facilitate the equitable distribution of federal funds available for the construction of general hospitals, a system of priorities has been developed. This system gives full consideration to the provisions required in Public Law 725 and the federal regulations—namely, the relative need for beds in an area, rural character of the hospital service area and the financial rating.

Percentage of need met is determined by division of the total number of existing acceptable beds in each area by the total number of beds needed in the area, this figure being multiplied by 100 for the percentage. Rural character is established by the Act as any area with a population less than 25,000.

In 1941, Dr Morris B. Lambie<sup>3</sup> conducted a study of the municipal finances of the 351 cities and towns in the Commonwealth at the Harvard Graduate School of Public Administration. His comparative rating of these municipalities was based on three-year averages of three factors: tax rates, assessed per capita valuation, and direct tax per capita. According to these criteria, the municipalities were classified into eleven categories. Communities in the first grouping have relatively

rating. The final figure determined the standing in the priority scheme (Table 4).

The priority scheme for chronic-hospital projects has been computed in the same manner as for general hospitals, and is based primarily on the percentage of need met. Metropolitan areas of greatest population density will stand highest in

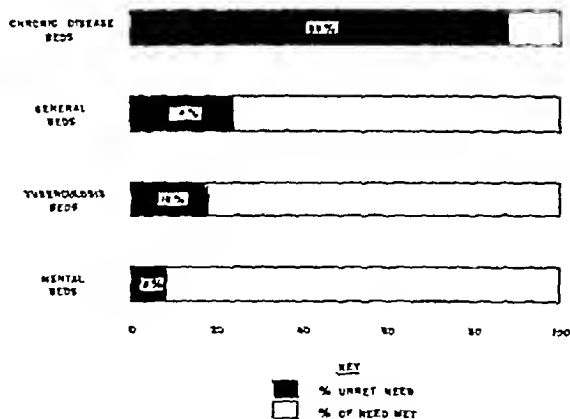


FIGURE 2 *Need for Additional Hospital Beds in Massachusetts*

the scheme. With respect to general hospitals it became apparent that strict application of the federal formula favored rural and intermediate areas rather than base areas. It was believed that construction of chronic-hospital units in metropolitan areas would compensate in part for the low standing in the priority schedule of the base areas. It will therefore be possible to allocate federal funds for chronic-hospital projects in such areas as Boston, Worcester, Springfield and Pittsfield.

The need for public-health centers in the Commonwealth is so great that no attempt has been made to establish a priority scheme for this cate-

gory Applications will be considered as they are submitted It is expected that at least some of the larger communities will take advantage of federal assistance for the construction of health centers

As indicated above, the need for tuberculosis and mental beds is relatively less than that for beds in chronic and general hospitals It has been determined that at least for the first two years of the program, federal assistance will be devoted to the construction of general and chronic hospitals and public-health centers

The federal funds provisionally allotted for these three categories during the fiscal years 1948

TABLE 4 Rank of General-Hospital Areas in First Two Priority Groups (1947-1948)

PRIORITY	AREA NO	AREA NAME
A-1	R-17	Athol
A-2	I-18	Needham
A-3	I-17	Medford
A-4	R-12	Northbridge
A-5	I-31	Woburn
A-6	I-32	Milford
A-7	R-9	Ipswich
B-1	R-16	Webster
B-2	R-6	Concord
B-3	I-20	Revere
B-4	I-43	Marlboro
B-5	I-21	Somerville
B-6	I-12	Arlington
B-7	I-11	Weymouth
B-8	I-15	Everett
B-9	R-13	Palmer
B-10	I-2	Barnstable
B-11	I-9	Norwood
B-12	I-7	Brockton
B-13	I-5	Plymouth
B-14	I-6	Taunton
B-15	I-28	Melrose

and 1949 are \$1,177,128 for general hospitals, \$1,119,707 for chronic-disease hospitals, and \$574,209 for public-health centers The total amount of federal funds is \$2,871,044, representing an allotment of \$3,190,050, less a 10 per cent contingency fund for rising prices

During the first year of the program (1947-1948) five applications for new construction were approved The total number of beds to be added by these projects is approximately 300, of which 225 are of the general-hospital and 75 of the chronic-hospital category.

### Discussion

From Table 3 it is apparent that 50 per cent of existing hospital beds are in base areas that have 35 per cent of the population, whereas 44 per cent of the beds are in intermediate areas with 57 per cent of the population The figures of the rural areas are more nearly equal—namely, 57 per cent of the beds and 77 per cent of the population

After application of the federal formulas developed under Public Law 725, the discrepancies between the percentage of population and the percentage of total beds needed in base and intermediate areas are diminished but not to a marked degree In other words, the general pattern of the distribution of general-hospital beds in suburban and rural areas

has not been altered to a marked extent It was believed that general hospitals in Massachusetts have grown in accordance with the need of the population for this type of medical facility It was the policy of the state agency in setting up the plan not to interfere with this natural development.

It is expected that the priority scheme for the general-hospital category will be altered for the second year of the program to take into account obsolescent and substandard facilities Several of the general hospitals in Massachusetts were built at the turn of the century and are obsolete according to modern specifications Many are frame buildings or of substandard construction in other respects It is apparent, therefore, that many beds will be declared noncomputable as far as this plan is concerned This will alter considerably the priority standing of many areas that are now low in the schedule to a much more favorable position

Funds allocated by the federal Government for this program are inadequate to fulfill the entire need within the Commonwealth The state plan indicates an over-all lack of 16,183 beds in all categories A conservative estimate for the cost of building these beds is roughly \$190,000,000, exclusive of public-health centers It is apparent, therefore, that the total of \$24,000,000 that would be spent under this program is by no means adequate to construct all necessary facilities The cost of construction has risen to such a degree that without federal assistance many projects that have been planned will not be undertaken All of this may be taken as evidence that Public Law 725 is meeting a great need in the Commonwealth

### SUMMARY

A survey of existing hospital facilities revealed that there are 219 hospitals in Massachusetts with a normal bed capacity of 44,044

In accordance with the provisions of Public Law 725, the Commonwealth was divided into 70 general hospital service areas of which 4 are base, 43 intermediate and 23 rural In addition, to provide an integrated hospital system, 6 regions were formed, composed of the service areas mentioned above

By application of the formulas contained in the Act, it was found that there is a deficit of 16,183 beds, of which 5605 are general, 804 tuberculosis, 1738 mental-disease and 8036 chronic-disease beds

A priority schedule based primarily upon need for additional beds has been established for general and chronic hospitals

### REFERENCES

- 1 Massachusetts State Plan for the Administration of Public Law 725 (Hospital Survey and Construction Act)
- 2 Report of the Special Commission to Study and Investigate Certain Public Health Matters (Chapter 73 of the Resolves of 1947) December 3, 1947 Commonwealth of Massachusetts.
- 3 Lambie, M. B. *Experiments in Methods of Municipal Analysis* 305 pp Cambridge, Mass. Bureau for Research in Municipal Government Harvard School of Public Administration, 1941 Pp 101 104

PNEUMOCOCCAL PNEUMONIA TREATED WITH AQUEOUS PENICILLIN AT  
TWELVE-HOUR INTERVALS\*

PHILIP A. TUMULTY, M.D.,† AND GORDON ZUBROD, M.D.‡

BALTIMORE

THE efficacy of penicillin in the treatment of patients with pneumococcal lobar pneumonia is well established.<sup>1,2</sup> However, the manner in which it may be employed to yield the best therapeutic results and with the least discomfort to the patient is still debated. It has been considered that to achieve maximum therapeutic response the blood concentration of penicillin must be maintained constantly at a level greater than the penicillin sensitivity of the particular organism.<sup>3</sup> Because of this assumption penicillin has generally been administered either in aqueous solution at frequent intervals or in some repository form. On the other hand, it has not been demonstrated either experimentally or clinically that this is necessary or desirable.<sup>4</sup> The relation of dosage frequency to therapeutic effectiveness has been examined in a streptococcal infection in mice treated with aqueous penicillin G.<sup>5</sup> The drug was just as effective when given once a day as when given more frequently. Similar results have been reported by others in the treatment of experimental infections in mice.<sup>6-10</sup> A few investigators have successfully employed aqueous penicillin given at infrequent intervals in pneumococcal lobar pneumonia,<sup>11</sup> subacute bacterial endocarditis<sup>12</sup> and pharyngitis due to the beta-hemolytic streptococcus.<sup>13</sup> It seemed worth while, therefore, to extend these observations to the treatment of patients.

## PLAN OF STUDY

Pneumococcal lobar pneumonia was chosen for this study because of the relatively sharp clinical end-point obtainable. A consecutive series of patients was treated with aqueous penicillin G given intramuscularly at twelve-hour intervals. The patients were admitted to the public wards of the Johns Hopkins Hospital between October, 1947, and May, 1948. Only cases of clear-cut pneumococcal lobar pneumonia were included, selection being based upon a characteristic history, physical and x-ray evidence of pulmonary consolidation, fever, leukocytosis and the presence of typable pneumococci in the sputum, nasopharynx or blood. There were 82 such cases. All were not seen by us, the care of the patients being primarily the

responsibility of the resident staff. An effort was made to retain in the study all patients admitted with pneumococcal lobar pneumonia. However, because of misunderstandings, 3 patients were omitted from the series. They were only moderately ill and recovered uneventfully. Five patients were placed on intermittent intramuscular therapy after a short trial on the twelve-hour schedule. In 2 of these cases the regimen was altered because of the development of complications discussed below. In the remaining 3, discontinuance of the experimental dosage was considered in review to have been arbitrary, and the administration of 100,000 units of penicillin every two hours produced no dramatic alteration of the clinical course. All patients recovered. The total number receiving the trial dosage was therefore 79.

Cultures of the sputum, nasopharynx and blood were obtained before penicillin treatment was started. Most of the patients received a potassium salt of crystalline penicillin G of a single lot number, provided for these studies in 300,000-unit vials. The remainder were given the usual ward supply of penicillin, which varied somewhat as to degree of purity. The penicillin was given intramuscularly in distilled water. The initial dose was 300,000 units repeated at twelve-hour intervals until the temperature had remained normal for forty-eight hours, when 300,000 units was given at twenty-four-hour intervals for an additional forty-eight hours, unless there was some indication for more prolonged therapy. In 2 cases 600,000 units was given initially to severely ill patients.

No control series was established, the number of patients treated at this hospital each year making this impractical. However, there are available for comparison data on the patients with lobar pneumonia treated at this hospital with penicillin during the same period of 1945-1946 and 1946-1947. There were 69 patients in the 1945-1946 series. These were divided almost equally into three groups, receiving respectively 20,000, 40,000 and 80,000 units of aqueous penicillin intramuscularly at three-hour intervals. Fifty-eight patients were treated in 1946-1947 with penicillin in oil and beeswax. The majority of this group were given 300,000 units intramuscularly every twenty-four hours. A few initially received 300,000 units every twelve hours.

Comparative data for the three series regarding population sample, pneumococcal types and severity of disease are shown in Table 1. In general

\*From the Department of Medicine and the Department of Pharmacology and Experimental Therapeutics, Johns Hopkins University School of Medicine and Johns Hopkins Hospital.

†Instructor in medicine, Johns Hopkins University School of Medicine; physician-in-charge, Medical-Surgical Group Clinic; assistant director of medical clinics and physician, Johns Hopkins Hospital.

‡Roche Fellow in Experimental Medicine and Therapeutics and instructor in medicine, Johns Hopkins University School of Medicine.

the pneumonia was considered to be of average and equal severity in the three groups studied. No deaths or serious complications occurred in the 1945-1946 or 1946-1947 series. However, neither of these groups comprised all the patients admitted because of pneumonia during the years concerned, since a few of the most severely ill patients were given massive amounts of penicillin or a sulfonamide in addition. Death and complications

no superiority in the response of patients receiving frequent dosages of aqueous penicillin or repository penicillin as contrasted with the response of those receiving aqueous penicillin G at twelve-hour intervals. What minor differences there were favored the latter schedule.

Two deaths occurred in the 82 patients treated during 1947-1948. One happened three hours after admission in a patient with severe hyperthyroidism,

TABLE 1 *Summary of Data*

DATA	PATIENTS GIVEN AQUEOUS PENICILLIN (1945-1946)				PATIENTS GIVEN PENICILLIN IN OIL AND BEESWAX (1946-1947)	PATIENTS GIVEN AQUEOUS PENICILLIN (1947-1948)
	20 000 UNITS*	40 000 UNITS*	80 000 UNITS*	TOTAL*	300 000 UNITS†	300 000 UNITS‡
Total patients	23	25	21	69	58	82
Male	14	16	14	44	45	53
Female	9	9	7	25	13	29
Negro	20	19	18	57	52	70
White	3	6	3	12	6	12
Age of patients						
Under forty years	19	12	13	44	31	52
Forty to fifty-nine years	3	10	7	20	24	27
Sixty years and over	1	3	1	5	3	3
Severity of disease						
Mild	4	0	1	5	14	14
Moderate	16	16	11	43	37	45
Severe	3	7	4	14	6	19
Critical	0	2	5	7	1	4
Duration of illness						
Less than two days	7	3	4	14	8	11
Two to three days	11	13	9	33	26	36
Four to six days	5	5	6	16	18	29
Seven days or more	0	4	2	6	6	6
Indications of severity						
Dehydration	3	4	3	10	18	28
Cyanosis	5	9	3	17	11	9
Jaundice	2	2	4	8	7	7
Disorientation	0	3	3	6	7	11
Shock	0	1	1	2	1	1
Leukopenia (white-cell count below 8000)	1	3	2	6	6	7
Bacteremia	1	5	5	11	8	10
Multilobar	3	8	8	19	12	17
Alcoholism	2	2	2	6	16	18
Cardiac failure	1	1	3	5	2	3
Cardiac disease	2	8	2	12	3	8
Diabetes	0	1	0	1	2	2
Hepatic insufficiency	1	1	0	2	1	3
Pregnancy	1	0	0	1	2	1
Pneumococcal types						
1-8	7	13	9	29	31	45
Higher types	5	9	6	20	19	27
Untyped	4	6	4	14	8	7
None found	2	2	2	6	0	3
Patients receiving sulfonamides prior to admission	1	1	2	4	3	1

\*Every three hours

†Every twenty four hours

‡Every twelve hours

occurred in a few of these excluded patients. Therefore, the mortality and occurrence of complications in these two groups cannot be compared to those of the relatively consecutive 1947-1948 series. But it is valid to use these earlier groups as a basis of comparison of the rapidity of response to penicillin therapy.

### RESULTS

The response of the patients to the several regimens of penicillin is shown in Table 2 and expressed in terms of total febrile days, total days in bed and period of hospitalization. Within the limitations of this type of clinical study there was

auricular fibrillation and cardiac failure after a single injection of 900,000 units of aqueous penicillin. The other occurred seven hours after admission in a patient with a severe head injury who was given 100,000 units of aqueous penicillin intramuscularly at three-hour intervals. Two patients in this group developed complications of their infection. Pneumococcal meningitis appeared in one patient sixteen hours after admission. He had a pneumonia due to a pneumococcus Type 2 with bacteremia. The other complication appeared in a fifty-nine-year-old Negro known to have had chronic pulmonary disease for twelve years. He was admitted with pneumonia of the right upper and

middle lobes due to a Type 7 pneumococcus with bacteremia. Thirteen days after admission cavitation was noted in the right middle lobe. There is a reasonable possibility that both these complications had their inception before the institution of therapy. With the appearance of these complications, the patients were given massive doses of penicillin and sulfonamides. Recovery occurred in both cases.

Only a single patient in the 1947-1948 series developed a penicillin reaction. This followed the use of the highly purified penicillin G and consisted of fever and exfoliative dermatitis on the twelfth

circulating penicillin. Since therapeutic response was so satisfactory it appears questionable whether a constant blood level of penicillin is necessary in the treatment of pneumococcal pneumonia. The employment of repository forms such as penicillin in oil and beeswax or procaine penicillin, or the administration of aqueous penicillin at short intervals, is unnecessary in the therapy of lobar pneumonia. Whether infrequent dosage of penicillin in aqueous solution will be effective in the treatment of other infections has not been determined. The experimental work suggests that it would be effective. However, only careful clinical observation

TABLE 2 Duration of Fever, Bed Care and Hospitalization after Start of Penicillin in Recovered Patients

DATA	PATIENTS GIVEN AQUEOUS PENICILLIN (1945-1946)				PATIENTS GIVEN PENICILLIN IN OIL AND BEESWAX (1946-1947)	PATIENTS GIVEN AQUEOUS PENICILLIN (1947-1948)
	20 000 UNITS*	40 000 UNITS*	80 000 UNITS*	TOTAL*	300 000 UNITS†	300 000 UNITS‡
Total cases	—	—	—	69	58	75§
Duration of fever						
One day or less	8	1	6	15	10	29
Two days	8	3	6	19	6	18
Three days	2	6	3	11	5	8
More than three days	5	13	6	24	37	20
Days in bed						
Six or less	10	4	7	21	14	27
Seven to twelve	13	13	5	31	33	41
Thirteen or more	0	5	9	17	11	7
Days in hospital						
Eight or less	6	1	1	8	6	15
Nine to sixteen	16	14	12	42	33	40
Seventeen or more	1	10	8	19	19	20

\*Every three hours.

†Every twenty-four hours.

‡Every twelve hours.

§Excludes 2 deaths, 2 complications and 3 patients who did not start on experimental regimen.

day of therapy. No severe local reactions occurred. With aqueous "ward-stock" penicillin at three-hour intervals, the systemic reaction rate was 10 per cent, and with penicillin in oil and beeswax it was 19 per cent. An additional 25 per cent of patients had a local reaction to penicillin in oil and beeswax, characterized by pain, redness and edema at the site of injection.

## DISCUSSION

Penicillin G in aqueous solution given at twelve-hour intervals was found to be a highly effective means of treating pneumococcal lobar pneumonia. Death and complications each occurred in but 2.4 per cent of the 82 cases. In terms of the number of febrile days, the number of days in bed and the period of hospitalization, the administration of penicillin at twelve-hour intervals was at least as effective as the schedules designed to maintain a constant penicillin blood concentration.

A single dose of 300,000 units of aqueous penicillin G given intramuscularly maintains the concentration in the blood above 0.1 unit per cubic centimeter for only five or six hours,<sup>14</sup> so that for about half the time these patients had little if any

will demonstrate how universally this method of therapy may be safely applied.

It is quite likely that the amounts of penicillin G employed in this study were in excess of what is needed for adequate therapy of pneumococcal lobar pneumonia. A total dose of 90,000 to 300,000 units of aqueous penicillin will cure some patients with lobar pneumonia.<sup>1</sup> However, there seems to be little justification for determining the minimal effective dosage of penicillin in a disease with a potential mortality of 30 per cent. This position is supported by the infrequency of complications accompanying the use of fairly brisk dosage and by the lack of toxicity of pure penicillin G. It has been shown in streptococcal infections in mice that a large initial dose of penicillin G keeps the mice alive much longer than the same dose split into smaller fractions, even though the dose is too small to save any of the mice ultimately.<sup>5</sup> It seems wise to use similar large initial priming doses of penicillin G in the treatment of pneumococcal pneumonia and other infections. Such priming doses are an essential part of the successful use of the sulfonamides, and it is a curious circumstance that a similar loading device has not been carried over to the penicil-

lin treatment of infections In the use of slowly absorbed penicillin preparations such as penicillin in oil and beeswax and procaine penicillin or indeed when penicillin in aqueous solution is given in equal fractions at three-hour intervals, the advantage of a priming dose is lost

### SUMMARY AND CONCLUSION

Two hundred and six cases of pneumococcal lobar pneumonia treated with penicillin are reported In these cases 79 patients were treated with aqueous penicillin G given intramuscularly every twelve hours, 69 received aqueous penicillin intramuscularly every three hours, and 58 were given penicillin in oil and beeswax

The patients who were treated with 300,000 units of aqueous penicillin G intramuscularly every twelve hours fared as well as those on the usual schedules of administration

The intramuscular administration of 300,000 units of aqueous penicillin G every twelve hours is the treatment of choice for pneumococcal lobar pneumonia

We are indebted to Dr K K Chen, of Eli Lilly and Company, Indianapolis, Indiana, for a generous supply of the potassium salt of pure penicillin G

### REFERENCES

- 1 Tillett, W S Cambier M J and McCormack, J E. Treatment of lobar pneumonia and pneumococcal empyema with penicillin. *Bull New York Acad Med* 20 142 178 1944
- 2 Meads M Harris H W, and Finland, M. Treatment of pneumococcal pneumonia with penicillin *New Eng J Med* 232 747 755 1945
- 3 Eagle H. Speculations as to therapeutic significance of penicillin blood level *Ann Int Med* 28 260 278 1948
- 4 Marshall E K Jr Dosage schedule of penicillin in bacterial infections *Bull Johns Hopkins Hosp* 82 403-407 1948
- 5 Zabrud C G Comparative efficiency of single and multiple dosage regimens of penicillins *Bull Johns Hopkins Hosp* 81 400-410 1947
- 6 Jawetz, E Dynamics of action of penicillin in experimental animals: observations on mice *Arch Int Med* 77 1-15 1946
- 7 White H J Lee, M E, and Alverson C Therapeutic effectiveness of single oral doses of penicillin *Proc Soc Exper Biol & Med* 62 35 1946
- 8 White H J Baker, M J, and Jackson E R. Therapeutic effectiveness of single and divided doses of penicillin in streptococcal infection in mice *Proc Soc Exper Biol & Med* 67 199 203 1948
- 9 McLeod, C M, and Stone E R. Differences in nature of antibacterial action of sulfonamides and penicillin and their relation to therapy *Bull New York Acad Med* 21,375-388 1945
- 10 Gibson C D Jr Comparative effectiveness of two penicillin treatment schedules in pneumococcal infections in mice. *Proc Soc Exper Biol & Med* 67 278 280 1948
- 11 Conference on therapy treatment of pneumonia *Am J Med* 4, 423-435 1948
- 12 Bloomfield A L and Halpern R M. Penicillin treatment of subacute bacterial endocarditis some problems *J A M A* 129 1135 1141 1945
- 13 Jawetz, E Dynamics of action of penicillin time-dose relationship in human streptococcal disease *Arch Int Med* 81,203 208 1948
- 14 McDermott W Bann P A Benoit, M DuBois R, and Reynolds, M E Absorption, excretion and destruction of orally administered penicillin *J Clin Investigation* 25 190 210 1946

## THE USE OF TESTOSTERONE IN THE TREATMENT OF DEPRESSIONS\*

MARK D ALTSCHULE, M D,† AND KENNETH J TILLOTSON, M D.‡

BOSTON AND WAVERLEY, MASSACHUSETTS

SEX hormones and related substances have been used in the treatment of depressions for a number of years Although the use of estrogenic substances of various types has yielded disappointing results in deeply depressed women, the injection of testosterone has been known for a decade or more to cause remission in male patients with depressions, provided large doses are used Danziger and Blank<sup>1</sup> reviewed the earlier clinical literature bearing on this point, a more recent review by Danziger et al<sup>2</sup> is also available The rationale for the use of testosterone in the past has been that of replacement therapy in men past middle life However, the fact that small doses are ineffective should have suggested the inadequacy of this concept

Recent studies have shown that electroconvulsive therapy gives rise to effects resembling those caused by the action of some steroid hormones<sup>3-8</sup> The effects of electroshock therapy that resemble those occurring after the injection of steroid hor-

mones consist, briefly, in fall in plasma protein level, decrease in lymphocytes in the peripheral blood and reduction in eosinophil count, increased diuretic response to water and evidence of extracellular retention of water and sodium The administration of desoxycorticosterone and of progesterone in large doses having failed here to cause remission of mental symptoms, it was decided to use testosterone, all three of the hormones mentioned have the effect of causing salt and water retention, but only the last has an additional marked anabolic action The present report summarizes experience here to date

### MATERIAL AND METHODS

Thirty-one patients, ranging in age from thirty-one to seventy-four years, were given testosterone by injection They included patients with depressed phase of the manic-depressive psychosis, with involutional psychoses with depression, with reactive depressions and, in 1 case, schizophrenia with a strong depressive component Only 3 were women, 2 of them having involutional psychoses and the third a manic-depressive psychosis in the depressed phase

\*From the Clinical Services and the Laboratories of Clinical Physiology, McLean Hospital Waverley Massachusetts, and the Departments of Medicine and Psychiatry Harvard Medical School

†Assistant professor of medicine, Harvard Medical School director of research in clinical physiology McLean Hospital

‡Formerly, associate in psychiatry Harvard Medical School formerly, psychiatrist-in-chief McLean Hospital

Testosterone was given intramuscularly in doses of 50 mg daily for two or three weeks, in most cases it was given in two doses of 25 mg each day. In 1 case the material was given for six weeks, discontinued for a month and given again for a month. After discharge some of the patients were given methyl-testosterone orally, 30 mg per day. Seven of the patients received electroshock therapy at approximately the same time as the injection of the hormone, 7 had had shock therapy previously, and 6 were given it subsequently.

## OBSERVATIONS

### Clinical Results

Of the 7 patients, all men, given testosterone at approximately the same time as shock therapy, all improved and were discharged.

In the 17 patients who had not had shock therapy before receiving testosterone, the following effects were noted: improved (discharged), 11 (10 men, 1 woman), discontinued, 2 men, and not improved, 4 men.

Of the 4 men not improved by injection of testosterone, 3 subsequently were given electroshock therapy. All 3 improved, 1 after six treatments in the course of a month, 1 after four treatments a week apart, and 1 after thirty-two shocks given over a period of several months.

Seven patients were given testosterone during relapse after improvement with electroconvulsive therapy, with the following results: 3 men given testosterone one month after relapse were improved (discharged), neither of 2 women given testosterone one month after relapse improved, 1 man given testosterone five months after relapse improved (discharged), and 1 man given testosterone twelve months after relapse showed no improvement.

In 2 patients in this group who recovered after getting testosterone, relapse occurred after the hormone had been discontinued. Brief abstracts of these cases are as follows:

**CASE 1.** A 39-year-old man with a reactive depression was first seen in August, 1946. After five treatments of electroshock, given between December 10 and 20, he improved and gained 8 pounds. Later in that month he suffered a relapse. Eight additional electroshock treatments were given from January 1 to 17, 1947, with improvement and another gain of 8 pounds in weight. Another relapse occurred, and the patient was therefore given 25 mg of testosterone twice a day from February 8 to 21. He improved, gained 6 pounds and was discharged. A third relapse occurred in May.

**CASE 2.** A 54-year-old man with a manic-depressive (depressed) psychosis was seen in May, 1946. After six electroshock treatments in July he was improved, but during that month he relapsed. From January 17 to 31, 1947, seven electroshock treatments were given, with improvement and a gain of 14 pounds in weight. Another relapse occurred in February, and 25 mg of testosterone was given twice a day from March 4 to 26. The patient improved and gained 15 pounds, but suffered a further relapse during the following month. In May, improvement and a gain of 9 pounds in weight followed fourteen electroshock treatments.

All 3 patients in this group who did not respond to testosterone were subsequently given shock therapy. The 2 women improved after twelve shocks given over a period of five weeks, they soon relapsed, however. Still another course of shock therapy was then given to 1 of these patients, who died during the treatment, with massive hemorrhage of an adrenal gland. The man in this group improved after six shocks and maintained his improvement for two months before relapsing.

### Side Reactions

Two patients could not receive the full course of treatment with testosterone because of the development of edema, tachycardia and severe dyspnea, both were known to have had mild congestive failure previously. Digitalis and ammonium chloride did not influence these symptoms, which remained markedly discomforting for approximately a week. Two other patients exhibited mild edema and shortness of breath, they had no evidence of heart disease.

Two patients exhibited gynecomastia during the course of treatment, one was a man of forty-four who many years previously had had a testicle removed for tumor, and the other was a man of sixty-three with no unusual previous findings in history or physical examination.

The women showed heavy overgrowth of facial hair.

## Discussion

The earlier work with testosterone<sup>1, 2</sup> involved the use of the hormone as a form of replacement therapy in men with involutional melancholia. Some authors<sup>1, 2</sup> gave as many as six injections, each of 25 mg of the hormone, each week for more than twelve weeks. In the present study the rationale of treatment was different in that the hormone was used as a substance with marked anabolic effects and not as a specific sex hormone.

The effect of testosterone is largely or entirely on the affective disorder, paranoid or other serious disturbances in thinking were not changed, and neurotic manifestations were influenced but little. The disappearance of depression, confusion and retardation, however, was definite.

Analysis of the clinical results is difficult. The 7 patients who received electroconvulsive therapy at approximately the same time as the injections of testosterone afford no data for judging the value of the latter. These patients were given testosterone when the course of shock therapy was interrupted by fractures or because the clinical staff believed that the patients' histories raised the possibility of early relapse after shock. In the 11 patients in whom improvement occurred when they were given testosterone not in relation to shock therapy, it is likewise difficult to evaluate the role of the hormone.

The natural history of depressions includes high rates of remission irrespective of therapy, the patients treated here were all receiving psychotherapy during the period of administration of testosterone, and all but 1 were hospitalized. Accordingly, the role of testosterone in relation to clinical improvement cannot be stated with certainty in spite of the fact that individual patients appeared to show no evidence of improvement until after the drug was started. The failures in this group are, however, of interest. They include 2 patients who could not receive the full course of therapy because of aggravation of the manifestations of congestive failure, 4 others who received the full course of injections did not respond, and 3 were then given shock therapy. One improved after thirty-two shocks given over a period of several months, and the other 2 improved after short courses of shock therapy. The last 2 of these patients must be regarded as definite cases of failure of testosterone therapy, but the first patient who received testosterone for only two weeks and then shock therapy for several months need not be.

The results in the patients who received testosterone after relapse following improvement due to electroshock therapy show that the effects of testosterone and of electroshock are interchangeable, at least in some cases. The only failure in the men was a patient who received testosterone a year after receiving shock therapy, he subsequently improved again with shock therapy. Possibly a longer course of testosterone should have been given in his case if one can judge by the results in the man who was given testosterone five months after shock, this patient required six weeks of testosterone for striking benefit to be obtained, although he showed some improvement after two weeks. The 2 women who failed to respond to testosterone given a month after relapse following improvement with shock therapy received the drug for three weeks, both required five weeks of shock therapy for temporary remission of their depressions.

It is possible, judging from the earlier work cited above,<sup>1,2</sup> that longer courses of treatment with testosterone would have helped some of the patients who showed no improvement in the present study. Long courses have not been employed here as a rule because of the untoward cosmetic effects in women, and because of the more rapid improvement caused by electroshock therapy in patients who might be suicidal, the expense of unnecessary prolongation of hospitalization was also taken into account.

The untoward effects of testosterone therapy—that is, hirsutism in women and excessive salt re-

tention in patients with myocardial insufficiency—were expected. The occasional occurrence of gynecomastia resembles that reported by McCullagh and Rossmiller<sup>9</sup> in patients receiving androgen therapy.

The fact that the effects of testosterone and of electroshock therapy are interchangeable supports the concept that the physiologic changes indicative of increased production of some steroid hormones seen during shock therapy are causally related to remission of mental disease caused by the latter. Since the steroid hormone effects involved are not those of salt and water retention but seem to be an anabolic reaction, it is possible that the effects of electroshock therapy are primarily reparative and, if at all destructive, only incidentally so. This concept may explain the fact that affective disorders occurring during the course of such destructive processes as general paresis and multiple sclerosis are benefited by shock therapy.

#### SUMMARY AND CONCLUSIONS

The administration of testosterone in large doses is followed by remission of mental symptoms in some patients with all types of depression. The hormone acts apparently not as a specific sex hormone but as a substance with strong anabolic effects. In some patients it can be shown that the effects of electroshock and of testosterone are interchangeable, a phenomenon that suggests that the beneficial effects of convulsant therapy are the results of increased production of some steroid hormones. It is not unlikely that the favorable effects of electroshock therapy are reparative and not destructive.

#### REFERENCES

1. Danziger L. and Blank H. R. Androgen therapy of agitated depressions in the male. *M. Ann. District of Columbia* 11:181-183, 1942.
2. Danziger L., Schroeder H. T. and Unger A. A. Androgen therapy for involutional melancholia. *Arch. Neurol. & Psychiat.* 51:457-461, 1944.
3. Altschule M. D., Cram J. E. and Tillotson K. J. Fall in plasma protein level associated with rapid gain in weight during course of electroshock therapy. *Arch. Neurol. & Psychiat.* (in press).
4. Altschule M. D. and Tillotson K. J. Effects of electroconvulsive therapy on diuretic response to water in psychotic patients. *Arch. Neurol. & Psychiat.* (in press).
5. Altschule M. D., Ascoli I. and Tillotson K. J. Changes in extracellular fluid and plasma volumes during course of electroshock therapy. *Arch. Neurol. & Psychiat.* (in press).
6. Altschule M. D. and Tillotson K. J. Effect of electroconvulsive therapy on water metabolism in psychotic patients. *Am. J. Psychiat.* (in press).
7. Altschule M. D., Altschule L. H. and Tillotson K. J. Unpublished data.
8. Altschule M. D., Parkhurst B. H. and Tillotson K. J. Decrease in blood eosinophilic leukocytes after electrically induced convulsions. *J. Clin. Endocrinol.* (in press).
9. McCullagh E. P. and Rossmiller, H. R. Methyl testosterone. I. Androgenic effects and production of gynecomastia and oligospermia. *J. Clin. Endocrinol.* 1:496-502, 1941.

## POLLEN SENSITIVITY IN 100 ASTHMATIC CHILDREN

LEWIS WEBB HILL, M D \*

BOSTON

IT IS well known that pollen sensitivity is common in asthmatic children. The full importance of this, however, is not generally appreciated and in most textbooks and other discussions of asthma in childhood more emphasis is given to such allergens as house dust, animal danders and foods than to pollens. In my experience pollen sensitization and the common infectious cold are the two most frequent causes of asthmatic attacks in children and the number of cases that are helped by removal of a cat, a mattress or some food is small indeed when compared with those in which the attacks are precipitated by pollen or infectious colds.

In an allergy practice or clinic devoted to adults, patients with uncomplicated hay fever predominate. With children this is not so, and of 100 consecutive cases of respiratory allergy from my office files there were 80 cases of asthma and only 20 of hay fever. A high proportion of children who begin with hay fever have pollen asthma after a few seasons.

The pollen season in New England lasts about six months (from April 15 to October 10), and in children the majority of attacks of asthma occurring during this period are due to pollen.

Of 100 asthmatic patients between the ages of three and twelve years tabulated in alphabetic order from my office records, 70 gave positive scratch tests to one or more pollens. In contrast to positive tests with foods (about 20 per cent etiologic), a positive test with pollen as a rule indicates clinical sensitivity. Among the 70 children who gave positive reactions to pollen there were 225† positive tests. Of these, approximately 90 per cent were thought to be of clinical significance (Table 1).

## INTRACUTANEOUS TESTS

As a rule, skin sensitivity to pollen in children is not of such high degree as that in adults. The younger the child and the shorter time he has had symptoms the more likely is this to be so. The more delicate intracutaneous test often reveals sensitization when the scratch test will not. It is my practice first to do scratch tests with pollens as a routine on all asthmatic patients, which are followed by intracutaneous tests if the child has symptoms during the season of any pollen and fails to react to it by scratch test. In children the scratch test can by no means be relied upon to demonstrate pollen sensitization.

Intracutaneous tests were done on 20 of the 30 children who failed to give a positive scratch test to any pollen. There were positive reactions to one or more pollens in 14. Of the 100 children under discussion, therefore, 84 gave positive tests, either scratch or intracutaneous, to pollen. All the positive intracutaneous tests were presumably of clinical significance, since they were done only on a

TABLE 1 Positive Scratch Tests to Pollens in 100 Asthmatic Children

POLLEN	No of Positive Tests
Birch	26
Maple	18
Ash	3
Elm	5
Oak	10
English plantain	4
Grass pollen	40
Ragweed	45

selected group, whose histories suggested clinical sensitivity.

## TREE POLLEN

In New England birch and oak are the most important trees as far as asthma is concerned. Maple pollen gives a good many positive reactions, but is relatively unimportant as a cause of asthma, for it is heavy and sticky and is therefore not disseminated as readily as birch and oak pollen.

## GRASS POLLEN

Twenty-two patients reacted to all the four grass pollens employed in scratch tests, 18 reacted to one or more, but not to all. There were 28 patients who gave positive intracutaneous but negative scratch tests to grass pollen. There were therefore 68 out of 100 who reacted to grass pollen. Positive scratch tests were about equally divided between the four grasses, as follows: timothy, 30, red top, 27, June grass, 28, and orchard grass 29.

## RAGWEED

In 28 patients there was a positive intracutaneous test to ragweed with a negative scratch test. There were therefore 73 out of the 100 children who reacted to this pollen.

## ASSOCIATED SENSITIZATIONS

There was no child who reacted to pollen who did not also react to other environmental allergens. House dust, cat hair and mold (alternaria or hor-mo-dendrum) were the most common, with 65 positive reactions to dust, 39 to cat hair, and 38 to

\*Associate in pediatrics, Harvard Medical School, visiting physician, Child in a Hospital.

†The discrepancy between this figure and the sum total of the figures given in the table is because tests were done with four different grass pollens and usually more than one gave positive tests.

The natural history of depressions includes high rates of remission irrespective of therapy, the patients treated here were all receiving psychotherapy during the period of administration of testosterone, and all but 1 were hospitalized. Accordingly, the role of testosterone in relation to clinical improvement cannot be stated with certainty in spite of the fact that individual patients appeared to show no evidence of improvement until after the drug was started. The failures in this group are, however, of interest. They include 2 patients who could not receive the full course of therapy because of aggravation of the manifestations of congestive failure, 4 others who received the full course of injections did not respond, and 3 were then given shock therapy. One improved after thirty-two shocks given over a period of several months, and the other 2 improved after short courses of shock therapy. The last 2 of these patients must be regarded as definite cases of failure of testosterone therapy, but the first patient who received testosterone for only two weeks and then shock therapy for several months need not be.

The results in the patients who received testosterone after relapse following improvement due to electroshock therapy show that the effects of testosterone and of electroshock are interchangeable, at least in some cases. The only failure in the men was a patient who received testosterone a year after receiving shock therapy, he subsequently improved again with shock therapy. Possibly a longer course of testosterone should have been given in his case if one can judge by the results in the man who was given testosterone five months after shock, this patient required six weeks of testosterone for striking benefit to be obtained, although he showed some improvement after two weeks. The 2 women who failed to respond to testosterone given a month after relapse following improvement with shock therapy received the drug for three weeks, both required five weeks of shock therapy for temporary remission of their depressions.

It is possible, judging from the earlier work cited above,<sup>1,2</sup> that longer courses of treatment with testosterone would have helped some of the patients who showed no improvement in the present study. Long courses have not been employed here as a rule because of the untoward cosmetic effects in women, and because of the more rapid improvement caused by electroshock therapy in patients who might be suicidal, the expense of unnecessary prolongation of hospitalization was also taken into account.

The untoward effects of testosterone therapy—that is, hirsutism in women and excessive salt re-

tention in patients with myocardial insufficiency—were expected. The occasional occurrence of gynecomastia resembles that reported by McCullagh and Rossmiller<sup>9</sup> in patients receiving androgen therapy.

The fact that the effects of testosterone and of electroshock therapy are interchangeable supports the concept that the physiologic changes indicative of increased production of some steroid hormones seen during shock therapy are causally related to remission of mental disease caused by the latter. Since the steroid hormone effects involved are not those of salt and water retention but seem to be an anabolic reaction, it is possible that the effects of electroshock therapy are primarily reparative and, if at all destructive, only incidentally so. This concept may explain the fact that affective disorders occurring during the course of such destructive processes as general paresis and multiple sclerosis are benefited by shock therapy.

#### SUMMARY AND CONCLUSIONS

The administration of testosterone in large doses is followed by remission of mental symptoms in some patients with all types of depression. The hormone acts apparently not as a specific sex hormone but as a substance with strong anabolic effects. In some patients it can be shown that the effects of electroshock and of testosterone are interchangeable, a phenomenon that suggests that the beneficial effects of convulsant therapy are the results of increased production of some steroid hormones. It is not unlikely that the favorable effects of electroshock therapy are reparative and not destructive.

#### REFERENCES

1. Danziger L. and Blank, H. R. Androgen therapy of agitated depressions in the male. *M. Ann. District of Columbia* 11:181-183, 1942.
2. Danziger L., Schroeder H. T. and Unger A. A. Androgen therapy for involuntional melancholia. *Arch. Neurol. & Psychiat.* 51:457-461, 1944.
3. Altschule M. D., Cram J. E. and Tillotson K. J. Fall in plasma protein level associated with rapid gain in weight during course of electroshock therapy. *Arch. Neurol. & Psychiat.* (in press).
4. Altschule M. D. and Tillotson K. J. Effects of electroconvulsive therapy on diuretic response to water in psychotic patients. *Arch. Neurol. & Psychiat.* (in press).
5. Altschule M. D., Ascoli I., and Tillotson K. J. Changes in extracellular fluid and plasma volumes during course of electroshock therapy. *Arch. Neurol. & Psychiat.* (in press).
6. Altschule M. D. and Tillotson K. J. Effect of electroconvulsive therapy on water metabolism in psychotic patients. *Am. J. Psychiat.* (in press).
7. Altschule M. D., Altschule L. H. and Tillotson K. J. Unpublished data.
8. Altschule M. D., Parkhurst B. H. and Tillotson K. J. Decrease in blood eosinophilic leukocytes after electrically induced convulsions. *J. Clin. Endocrinol.* (in press).
9. McCullagh E. P. and Rossmiller, H. R. Methyl testosterone. I. Androgenic effects and production of gynecomastia and oligospermia. *J. Clin. Endocrinol.* 1:496-502, 1941.

BAL was ineffective in preventing *in vitro* hemolysis of red blood cells by arsine, whereas a related compound, BAL ethyl ether (2, 3-dimercaptopropylether), worked very well. These findings were borne out in arsine inhalation poisoning in rabbits and cats, in which BAL ethyl ether given immediately after exposure was found to be an effective agent, whereas BAL was useless.<sup>46, 47</sup> Because of its great toxicity, it seems unlikely that BAL ethyl ether will be of value in the treatment of arsine poisoning among human beings. Leivy<sup>48</sup> found that another compound, ethane-1,2-dithiol, given intraperitoneally decreased the toxicity of arsine for mice. This compound was effective when given as long as three to four hours after exposure to arsine.

Hughes,<sup>49</sup> studying the effects of lewisite on the rabbit eye, found that it produced rapid necrosis of the cornea and conjunctiva, and that arsenic liberated from the lewisite rapidly penetrated into the chambers of the eye. BAL, in a 5 per cent ointment, proved to be a satisfactory antidote because it not only detoxified the lewisite at the surface of the eye but also rapidly penetrated the tissues of the eye to unite with the arsenic there. Because of the rapid action of lewisite, the ointment had to be applied within two minutes of the lewisite to protect the eye completely; if applied after thirty minutes, permanent damage from the lewisite always occurred. BAL itself in ointment concentrations greater than 5 per cent was found to produce a transient opacification of the superficial layers of the cornea.

#### *Clinical Uses*

After it became apparent that BAL was effective against arsenic poisoning in animals, it was tried in various clinics in the treatment of accidental arsenic poisoning and the undesirable side effects occurring in arsenotherapy.

BAL has been used extensively in the treatment of arsenical dermatitis with good results.<sup>30, 50, 51</sup> In severe cases, edema, fever and pruritus disappear or greatly decrease in twenty-four hours, and complete recovery may occur within two weeks. However, some patients respond only partially, or may relapse and require another course of BAL, whereas others may show no improvement at all. Occasionally, as has been noted, abscesses, which are probably due to secondary infection, occur at the sites of intramuscular injection. Although injections of BAL are beneficial in dermatitis, they are not so effective as intramuscular injections and may cause skin sensitization to BAL.

Eagle and Magnuson<sup>30</sup> have reported the results of BAL therapy in 55 cases of arsenical encephalitis, usually a lethal complication of arsenotherapy. Only 11 patients died, and in 5 of these BAL therapy was not started until nine to seventy-two hours after the onset of encephalitis. These workers

likewise studied the value of BAL in the treatment of 16 patients with so-called post-arsenical jaundice. Only 5 of the 16 patients recovered within ten days of initiation of therapy. The results in this small series of cases suggest that BAL is not very effective in postarsenical hepatitis, but it must be remembered that some authorities consider this condition to be an infection rather than a toxic manifestation of arsenic.

BAL has been of value in some blood dyscrasias associated with arsenotherapy. Eagle and Magnuson<sup>30</sup> reported the failure of BAL to affect the course of 3 cases of aplastic anemia and 1 case of agranulocytosis with thrombocytopenia occurring in persons undergoing arsenotherapy. On the other hand, 10 cases of agranulocytosis responded promptly to BAL—all showing an increase in granulocytes by the second day and a normal count by the seventh day. Holley<sup>52</sup> reported equally good results in 12 cases of arsenical agranulocytosis treated with BAL. Schrumph<sup>53</sup> reported a favorable result following BAL in a patient with thrombocytopenic hemorrhages associated with neoarsphenamine therapy. In 11 days there was an increase in the platelet count from 2500 to 280,000.

BAL has been used in 4 patients who had received massive doses of mapharsen by error.<sup>30</sup> Three patients had received doses of between 400 and 600 mg of mapharsen each and made uneventful recoveries after the administration of BAL. The fourth patient was given 1200 mg of mapharsen and died after inadequate BAL treatment in spite of an initially favorable response.

Several cases of optic complications following arsenotherapy have been treated by BAL. Eagle and Magnuson<sup>30</sup> reported a good response in 3 of 6 patients with visual impairment associated with triparsamide therapy. Friedenber<sup>54</sup> observed that a tabetic patient in whom a decrease in visual fields followed triparsamide therapy had a return of vision after the administration of BAL.

Woody and Kometani<sup>55</sup> have reported on the use of BAL in a large group of infants and children. They treated 42 infants and children who had ingested arsenic-containing substances. Of these, 22 had taken potentially lethal amounts of arsenic. There were no deaths in this series, and in all cases signs and symptoms of arsenic poisoning disappeared within twelve hours of the initiation of BAL therapy.

#### MERCURY

It has been shown that BAL can both prevent the inhibitory effect of mercuric chloride on a brain brei preparation, and reactivate the enzyme succinoxidase after mercury inactivation.<sup>55, 56</sup>

Studies with BAL, BAL glucoside and the monothiol thiosorbitol<sup>44</sup> demonstrated that all three could protect rabbits against acute mercury poisoning if therapy was begun properly. Quantitative evalu-

mold I doubt whether uncomplicated pollen allergy exists in asthmatic children, and it is uncommon in children with hay fever. This is a very different situation from that in adults, among whom uncomplicated pollen allergy in hay fever is common.

#### SUMMARY AND CONCLUSIONS

In a series of 100 asthmatic children between the ages of three and twelve years, there were positive skin reactions to one or more pollens in 84.

Approximately 90 per cent of these reactions were of clinical significance.

The scratch test, particularly in children, is frequently not delicate enough to demonstrate pollen sensitization.

Asthmatic children who are sensitized to pollen are always sensitized to other environmental allergens as well.

The importance of pollen sensitization in the asthma of children is not sufficiently appreciated. In New England, pollen is the most important factor contributing to asthma in children during the spring, summer and early fall—approximately six months of the year.

319 Longwood Avenue

## MEDICAL PROGRESS

### BAL (Concluded)\*

RAYMOND V. RANDALL, M.D., AND ALBERT O. SEELER, M.D.†

BOSTON

#### ARSENIC

Stocken and Thompson<sup>39</sup> found that the topical application of BAL to lewisite burns was followed by an increase in the urinary excretion of arsenic. These authors then demonstrated that parenteral administration of BAL saved rats poisoned by the application of lethal amounts of lewisite to the body surface. Harrison and his co-workers<sup>40</sup> concluded from their experiments on dogs that the most effective way to treat extensive lewisite burns was to use BAL ointment to combat the local skin effects of lewisite, and, at the same time, to use the compound parenterally to combat the effects of the absorbed arsenic.

Eagle et al.<sup>4</sup> have shown that BAL applied to the skin or given parenterally was effective in the treatment of acute and subacute arsenic poisoning in various animals. In animals so treated, there was a striking increase in the rate of urinary arsenic excretion with the peak of excretion coming two to four hours after the administration of BAL. In conjunction with these findings, Riker and Rosenfield,<sup>41</sup> in studies on the effect of BAL on mapharsen-poisoned cats, found that it increased the concentration of arsenic in the plasma. After the injection of BAL, a high level of plasma arsenic was reached within one hour and a peak at two hours. These results were considered to be in accord with the concept that BAL effects a withdrawal of arsenic from the tissues.

Peters and Stocken<sup>42</sup> prepared a complex from mapharsen and BAL and found it to be more toxic than either BAL or arsenic alone. However, when this complex was injected together with one mole excess of BAL, it was only one fifth as toxic as arsenic alone. The authors suggested that this phenomenon could be explained by the dissociation of the mapharsen-BAL complex to release arsenic in areas where it could cause the maximum toxic effects. However, when excess BAL was present, the extent of dissociation and, consequently, the toxicity of the complex were decreased. Another explanation may be that one mole of arsenic can unite with one or two moles of BAL to form complexes of greatly different properties, as cadmium and mercury do.<sup>43-44</sup> Even more paradoxical are the findings of Koppanyi and Sperling,<sup>45</sup> who gave BAL to rabbits that had received nonlethal doses of sodium arsenite, and found that the animals developed intense central-nervous-system stimulation. The same amounts of arsenite or BAL alone did not produce symptoms, and massive doses of a preformed arsenite-BAL complex were likewise nontoxic. Similar effects were not noted with arsenates or organic arsenicals. On the basis of these experiments, the authors warned that persons poisoned by arsenites (such as Fowler's solution) might conceivably develop undesirable side effects if treated with BAL.

Several investigators have studied the effect of BAL and related compounds on arsine poisoning. Inhalation of this extremely toxic gas may cause intense hemolysis of the red blood cells, with subsequent hemoglobin nephrosis. It is also an inhibitor of tissue respiration. Kensler et al.<sup>46</sup> found that

\*From the Department of Industrial Hygiene, Harvard School of Public Health.

This study was aided by a grant from the Medical Advisory Committee of the American Petroleum Institute.

†Assistant professor of industrial medicine, Harvard School of Public Health.

matitis, of possible benefit in 2 cases of dermatitis and of no value in a case of dermatitis of moderately short duration

Lockie and his co-workers<sup>72</sup> found BAL to be strikingly effective in the treatment of 2 patients with blood dyscrasias following chemotherapy. A patient with thrombocytopenia, bleeding gums and coma from a possible subarachnoid hemorrhage responded to BAL within several days and had a concurrent increase in platelets from 15,000 to 120,000. The other patient had agranulocytosis, and within seventy-two hours after initiation of BAL therapy the granulocytes increased from zero to 17 per cent, and by the seventh day they had increased to 45 per cent.

### LEAD

Although BAL can reverse the lead inhibition of the sulfhydryl-containing enzyme, succinoxidase,<sup>56</sup> and can increase the urinary output of lead, there is no satisfactory evidence that it is of value in the treatment of lead poisoning.

### Animal Studies

Braun et al.<sup>73</sup> concluded that BAL was ineffective in both acute and chronic experimental lead poisoning. They gave BAL to rabbits poisoned by a single large dose of lead nitrate and to others poisoned by multiple small doses of lead nitrate, and in each case the mortality in animals treated with BAL was greater than that in animals receiving lead nitrate alone. This suggested that BAL had an additive effect. Germuth and Eagle<sup>74</sup> likewise found that BAL failed to protect rabbits against acute or chronic lead poisoning, and in one group of animals found that BAL hastened the onset of death. BAL did cause a marked increase in the urinary excretion of lead, but this response decreased with each subsequent injection. The period of increased urinary excretion of lead began immediately after the injection of BAL, reached a peak in about two hours and then returned to the preinjection level in three or four hours. A preformed lead-BAL complex was injected into rabbits and found to be almost as toxic as lead acetate, despite the fact that it had a low dissociation constant. These authors concluded that BAL can release some lead from its combination with the tissues and force it to be excreted in the urine, but that the amount of lead thus eliminated is too small to effect the eventual outcome of the poisoning. In addition, they pointed out the possibility that a toxic lead-BAL complex could be formed *in vivo*, and postulated that this could account for the additive effects of BAL in experimental lead poisoning.

Chiodi and Sammartino<sup>75</sup> were able to increase the weight of rat kidneys by the daily administration of lead acetate. This increase in kidney weight did not appear when BAL was given concurrently with the lead acetate.

### Human Poisoning

Telfer<sup>76</sup> studied the effect of BAL on a patient suspected of having lead poisoning. Although prior to BAL therapy the patient's urinary output of lead was within normal limits, the urinary lead excretion increased after therapy.

Ryder and his co-workers<sup>77</sup> studied the effects of a single intramuscular dose of BAL on the lead concentration in the blood and urine of men who had been exposed to lead. After BAL the concentration of lead in the whole blood started to fall within seven and a half minutes, reached a minimum in eight hours and returned to the original level in twenty-four hours. Simultaneously, there was an increase in the urinary output of lead. This effect could be produced repeatedly by subsequent injections of BAL. In spite of the reduction in the whole-blood lead concentration by BAL, the plasma levels were unaffected, indicating that large amounts of lead were released from the erythrocytes and rapidly removed from the blood stream. Although BAL produced these findings, which are of interest, it failed to shorten the clinical course of lead intoxication.

### CADMIUM

Cadmium is a sulfhydryl enzyme inhibitor, and its inhibitory effect can be reversed by BAL and other dithiols. The monothiol glutathione can bring about reactivation also, but only when given in large amounts.<sup>56</sup>

Lethal doses of cadmium given parenterally cause intense gastrointestinal activity, muscular weakness, prostration, severe dyspnea and death within twenty-four hours. Gilman and his co-workers<sup>78</sup> found that BAL could prevent this acute death from taking place in rabbits, if it were given just prior to the cadmium, but a delayed death from renal damage invariably occurred. Paradoxically, when BAL was given thirty minutes after a lethal dose of cadmium, only 50 per cent of the animals died, although, again, all deaths were the result of renal failure. More effective than BAL was BAL glucoside, which protected the majority of animals from the lethal effects of cadmium. Thiosorbitol and thioxylate, both monothiols, saved only a limited number of animals from cadmium deaths. Strangely enough, all the fatal results in the monothiol-treated animals were from typical acute cadmium poisoning rather than from renal damage as in animals dying after BAL and BAL glucoside therapy. The authors postulated that the renal deaths following BAL therapy could be explained by the assumption that BAL and cadmium form a relatively unstable complex. Hence, although BAL diverts the cadmium away from tissues usually affected by this metal, it carries it to the kidney, where enough cadmium dissociates to cause severe renal damage. The decrease in renal damage seen

ation of the protective activity of these compounds showed that the dithiols were far superior to thiosorbitol. BAL glucoside proved to be more active than BAL itself. Rabbits receiving inadequate doses of the thiol compounds died of renal failure. It is interesting to note that although BAL and BAL glucoside can also prevent the development of fatal renal damage in dogs after large intravenous doses of mercuric chloride, some of the animals succumbed to acute pulmonary edema. When mercuric chloride was given orally, BAL and BAL glucoside were also effective in preventing renal deaths, but some of the animals died of a hemorrhagic gastroenteritis.

Because of the extensive use of sodium formaldehyde sulfoxylate as an antidote for mercury poisoning, Stocken<sup>67</sup> compared the effectiveness of this compound with that of BAL. He found that BAL fully protected rats from lethal doses of mercuric chloride, whereas sodium formaldehyde sulfoxylate proved ineffective under similar conditions.

### *Human Poisoning*

Longcope and Luetscher<sup>68</sup> have used BAL extensively in the treatment of acute poisoning in man after the ingestion of mercury bichloride. They reported that of 42 patients suffering from acute mercury poisoning in whom BAL was used, only 2 died. These 2 patients were in a group of 5 cases in which BAL was not started until six to forty-two hours after the ingestion of mercury. Not one of 37 patients receiving BAL within four hours died, regardless of the severity of symptoms or the amount of mercury taken. This stresses the importance of instituting BAL therapy at the earliest possible moment. However, one should not overlook the value of general supportive measures such as intravenous fluids and transfusions. The schedule of BAL treatment for mercury poisoning recommended by the Council on Pharmacy and Chemistry of the American Medical Association (as listed below under dosage schedules) is based on the experience of these authors.

### *Effects on Mercurial Diuretics*

BAL can prevent the occurrence of convulsions and cardiac arrhythmias produced in experimental animals by the administration of mercurial diuretics. It can also prevent the characteristic diuresis produced by these drugs<sup>69-71</sup>. In contrast to BAL, which inhibits both the toxic and the diuretic effects, the monothiols cysteine and glutathione can protect the hearts of animals against toxic effects of the mercurial diuretic mersalyl without abolishing its diuretic effect<sup>65</sup>. Further evidence that monothiols reduce the toxicity of mercurials is supplied by the work of Lehman,<sup>66</sup> who synthesized a diuretic containing thioglycolic acid that proved to be only one-fourth as toxic as one-sixth as toxic as comparably effective mer-

curial diuretics. These findings suggest the possibility of using certain monothiols either in chemical combination or by simultaneous administration to abolish the undesirable effects of mercurials without impairing their diuretic action. However, each mercurial compound must be thoroughly investigated before clinical use in such a manner, because Cohen<sup>67</sup> has reported that a number of alkyl mercuric thioglycollates can produce severe central-nervous-system effects.

### *Acrodynia*

Because mercury has recently been suspected of having a causal relation to acrodynia, Bivings and Lewis<sup>68</sup> gave a twelve-day course of BAL to an infant in whom the diagnosis of acrodynia had been made. It is of interest that this infant had been given twelve doses of calomel and rhubarb a number of weeks before the onset of the signs and symptoms that led to the diagnosis of acrodynia. The urine showed a mercury concentration of 100 microgm per 100 cc before the initiation of BAL therapy. Eight days after the last dose of BAL, the urine was found to be free of mercury, and a week or two later all signs and symptoms of acrodynia had disappeared.

### *GOLD*

Thompson and Whittaker<sup>65</sup> found that BAL can protect the brain pyruvate oxidase system from the toxic effects of gold. However, the striking difference in effectiveness between dithiols and monothiols noted in arsenic poisoning was not found; glutathione gave the same degree of protection against gold inhibition as BAL did.

Gold therapy is used extensively in rheumatoid arthritis although it is a potentially toxic agent capable of causing pruritus, dermatitis, stomatitis, agranulocytosis, thrombocytopenia and other disorders. BAL has been used in several clinics to treat these complications of gold therapy. Ragan and Boots<sup>69</sup> reported a series of 5 patients with gold dermatitis who were treated with BAL. In 4 patients there was prompt subsidence of pruritus, and the rash disappeared within one month of BAL treatment. No change took place in the fifth patient's condition. All patients showed an increase in excretion of urinary gold, concurrent with the administration of BAL. Four of the patients had a recurrence of arthritic symptoms shortly after the BAL treatment, offering some support to the contention that chrysotherapy has only a temporary effect on rheumatoid arthritis. Cohen et al<sup>70</sup> found that BAL caused prompt recovery in 5 cases of gold dermatitis of short duration. The authors attribute these excellent results, in part, to the fact that BAL therapy was instituted early in each case. Margolis and Caplan<sup>71</sup> state that in their experience BAL was of marked benefit in a case of severe stomatitis and a case of dermatitis and sto-

matitis, of possible benefit in 2 cases of dermatitis and of no value in a case of dermatitis of moderately short duration

Lockie and his co-workers<sup>22</sup> found BAL to be strikingly effective in the treatment of 2 patients with blood dyscrasias following chrysotherapy. A patient with thrombocytopenia, bleeding gums and coma from a possible subarachnoid hemorrhage responded to BAL within several days and had a concurrent increase in platelets from 15 000 to 120 000. The other patient had agranulocytosis and within seventy-two hours after initiation of BAL therapy the granulocytes increased from zero to 17 per cent, and by the seventh day they had increased to 45 per cent.

### LEAD

Although BAL can reverse the lead inhibition of the sulfhydryl-containing enzyme, succinoxidase<sup>23</sup> and can increase the urinary output of lead, there is no satisfactory evidence that it is of value in the treatment of lead poisoning.

### Animal Studies

Braun et al.<sup>24</sup> concluded that BAL was ineffective in both acute and chronic experimental lead poisoning. They gave BAL to rabbits poisoned by a single large dose of lead nitrate and to others poisoned by multiple small doses of lead nitrate, and in each case the mortality in animals treated with BAL was greater than that in animals receiving lead nitrate alone. This suggested that BAL had an additive effect. Germuth and Eagle<sup>25</sup> likewise found that BAL failed to protect rabbits against acute or chronic lead poisoning and in one group of animals found that BAL hastened the onset of death. BAL did cause a marked increase in the urinary excretion of lead but this response decreased with each subsequent injection. The period of increased urinary excretion of lead began immediately after the injection of BAL, reached a peak in about two hours and then returned to the preinjection level in three or four hours. A preformed lead-BAL complex was injected into rabbits and found to be almost as toxic as lead acetate despite the fact that it had a low dissociation constant. These authors concluded that BAL can release some lead from its combination with the tissues and force it to be excreted in the urine but that the amount of lead thus eliminated is too small to effect the eventual outcome of the poisoning. In addition they pointed out the possibility that a toxic lead-BAL complex could be formed *in vivo* and postulated that this could account for the additive effects of BAL in experimental lead poisoning.

Chiodi and Sammartino<sup>26</sup> were able to increase the weight of rat kidneys by the daily administration of lead acetate. This increase in kidney weight did not appear when BAL was given concurrently with the lead acetate.

### Human Poisoning

Telfer<sup>27</sup> studied the effect of BAL on a patient suspected of having lead poisoning. Although prior to BAL therapy the patient's urinary output of lead was within normal limits, the urinary lead excretion increased after therapy.

Ryder and his co-workers<sup>28</sup> studied the effects of a single intramuscular dose of BAL on the lead concentration in the blood and urine of men who had been exposed to lead. After BAL the concentration of lead in the whole blood started to fall within seven and a half minutes, reached a minimum in eight hours and returned to the original level in twenty-four hours. Simultaneously, there was an increase in the urinary output of lead. This effect could be produced repeatedly by subsequent injections of BAL. In spite of the reduction in the whole-blood lead concentration by BAL, the plasma levels were unaffected, indicating that large amounts of lead were released from the erythrocytes and rapidly removed from the blood stream. Although BAL produced these findings, which are of interest, it failed to shorten the clinical course of lead intoxication.

### CADMIUM

Cadmium is a sulfhydryl enzyme inhibitor, and its inhibitory effect can be reversed by BAL and other dithiols. The monothiol glutathione can bring about reactivation also but only when given in large amounts.<sup>29</sup>

Lethal doses of cadmium given parenterally cause intense gastrointestinal activity, muscular weakness, prostration, severe dyspnea and death within twenty-four hours. Gilman and his co-workers<sup>30</sup> found that BAL could prevent this acute death from taking place in rabbits if it were given just prior to the cadmium but a delayed death from renal damage invariably occurred. Paradoxically, when BAL was given thirty minutes after a lethal dose of cadmium, only 50 per cent of the animals died, although again, all deaths were the result of renal failure. More effective than BAL was BAL glucoside, which protected the majority of animals from the lethal effects of cadmium. Thiosorbitol and thioxylate, both monothiols, saved only a limited number of animals from cadmium deaths. Strangely enough, all the fatal results in the monothiol-treated animals were from typical acute cadmium poisoning rather than from renal damage as in animals dying after BAL and BAL glucoside therapy. The authors postulated that the renal deaths following BAL therapy could be explained by the assumption that BAL and cadmium form a relatively unstable complex. Hence, although BAL diverts the cadmium away from tissues usually affected by this metal, it carries it to the kidney, where enough cadmium dissociates to cause severe renal damage. The decrease in renal damage seen

when BAL is given thirty minutes after the administration of cadmium is explained by the supposition that some of the cadmium becomes irreversibly fixed in the tissues, and thus a smaller amount eventually reaches the kidneys

The same authors found that, depending upon the pH of the solution, cadmium united with one or two moles of BAL to form two different complexes Cd-BAL and Cd (BAL). Cadmium also formed similar complexes with BAL glucoside, thiosorbitol, and thioxyolate. Although the Cd-(BAL)<sub>2</sub> complex had a low dissociation constant in vitro, a readily available supply of cadmium ions seemed to be available when this complex was preformed and then injected into rabbits. Depending upon the amount given, the animals died either acutely from typical cadmium poisoning or several days later from renal impairment. Preformed Cd (BAL glucoside)<sub>2</sub> proved to be relatively non-toxic, probably because the complex is too large to be absorbed readily by the renal cells.

Both BAL and BAL glucoside were found to increase the excretion of cadmium from cadmium-poisoned animals. The BAL-treated animals showed an increase in both urinary and fecal cadmium, whereas those treated with BAL glucoside showed an increase in urinary cadmium only.<sup>78</sup>

In an extensive inhalation study in dogs and mice, it has been shown that cadmium mists can cause acute death from massive pulmonary edema, or delayed death from diffuse pneumonitis often associated with lung abscesses, anorexia, bloody diarrhea and generalized wasting. BAL prevented death in a number of animals when it was given one to three hours after the cadmium exposure. However, when BAL was given prior to the exposure to cadmium, it actually hastened death, presumably by fixing the cadmium in the lungs, where it could do the most damage.<sup>79</sup>

### SILVER

In a limited study, Olcott and Riker<sup>80</sup> found BAL ineffective against experimental argyria. They gave small daily doses of silver nitrate to 2 white rats for four hundred and fifty-six days. One animal was then given nine injections of BAL over a period of eighteen days. Autopsy and histologic examination showed no essential differences in the amounts of silver deposited in the two animals. The authors concluded that BAL would probably be of no value in the treatment of argyria in man.

### MISCELLANEOUS METALS

#### Antimony

Barron and Kalnitsky<sup>86</sup> reported that attempts to reactivate the succinoxidase enzyme system inhibited by antimony were unsuccessful with BAL, whereas glutathione was effective in reversing this inhibition. On the other hand, Thompson and

Whittaker<sup>85</sup> found that BAL not only protected the brain pyruvate oxidase system from inhibition by antimony but also protected rats poisoned with this metal. Eagle and his co-workers<sup>81</sup> observed that BAL protected rabbits poisoned with various antimony compounds. An increase in antimony excretion in the urine persisting for two to four hours occurred after each injection of BAL. Similar results were obtained by Braun et al.<sup>73</sup>

#### Tellurium

Amdur<sup>82</sup> used BAL to treat 3 men who had inhaled tellurium-containing fumes and developed a characteristic garliclike odor of the breath. Although BAL failed to cause an increased urinary excretion of tellurium, the author believed that it was instrumental in decreasing the duration of halitosis from a possible period of weeks or months to a period of eleven to fourteen days in each case.

#### Copper, Bismuth, Chromium, Nickel, Zinc, Thallium, Selenium and Vanadium

McDonald<sup>83</sup> has reported that BAL glucoside in small doses caused an increased urinary copper excretion in normal sheep. The excretion reached a maximum of thirty times normal within an hour and then fell rapidly to a normal rate.

In enzyme-inhibition studies, Barron and Kalnitsky<sup>86</sup> found that BAL was effective against zinc, only partly effective against bismuth and totally ineffective against vanadium and selenium. Braun et al.,<sup>73</sup> in animal experiments, found BAL to be an effective antidote in poisoning from bismuth, chromium and nickel, but of no value against thallium and selenium. The administration of BAL actually hastened the death of animals poisoned with the latter metal.

### ALLOXAN

Lazarow<sup>84</sup> reported that large doses of monothiois such as cysteine, glutathione and thioglycolic acid completely protected rats against a diabetogenic dose of alloxan. The dithiol BAL in smaller amounts was found to be equally effective in protecting the animals from alloxan. However, neither the dithiol nor the monothiois protected the animals unless given before or immediately after the administration of alloxan. It has been postulated that alloxan causes an immediate, irreversible change, which can be prevented only by the early use of sulfhydryl groups, and, in contrast to heavy-metal poisonings, this change cannot be reversed by dithiois.

### PHENYLTHIOUREA

After the introduction of phenylthiourea and ANTU (alpha-naphthyl-thiourea) as powerful rodenticidal agents, a search has been made for suitable antidotes to be used in cases of accidental

poisonings Harvey and his co-workers,<sup>55</sup> on the basis of the findings of Du Bois<sup>56</sup> that ANTU inhibits sulfhydryl-containing enzymes, investigated the value of BAL and 1-thiosorbitol in phenylthiourea poisoning. ANTU and phenylthiourea are similar in action, and the latter was used in this experiment because of its greater solubility in water. The authors found that 1-thiosorbitol given to rats immediately after the administration of phenylthiourea protected these animals from the toxic and lethal effects of phenylthiourea. On the other hand, BAL increased rather than decreased the toxic effects of phenylthiourea. This paradox of a monothiol affording protection from a substance while a dithiol increases the toxic effects of that substance is similar to a situation seen in cadmium poisoning in which thiosorbitol is effective but BAL fails and even potentiates the action of cadmium.

### DOSAGE SCHEDULES

Sufficient experience in the use of BAL has been accumulated to permit tentative recommendations concerning proper dosage schedules for the treatment of arsenic and mercury poisonings. However, too little clinical information is available, as yet, to justify the formation of specific dosage regimens for the use of BAL in other metal poisonings.

The Council on Pharmacy and Chemistry of the American Medical Association<sup>57</sup> suggests that BAL be given by intramuscular injection according to the following schedules:

*For severe arsenic reactions*, each injection to contain 3 mg of BAL per kilogram of body weight

First day } 6 injections per day, at the rate  
Second day } of one injection every four hours

Third day 4 injections

Following ten }  
days or until } 2 injections per day  
recovery

*For mild arsenic reactions*, each injection to contain 2.5 mg per kilogram

First day } 4 injections per day  
Second day }

Third day 2 injections

Following ten }  
days or until } one injection per day  
recovery

*For mercury poisoning*, larger doses of BAL are suggested. An initial dose of 5 mg per kilogram of body weight should be given, to be followed in one to two hours by a dose of 2.5 mg per kilogram. After two to four hours a second dose of 2.5 mg should be administered, and in

severe cases a third dose of 2.5 mg should be given within the first twelve hours. On the second day, two doses of 2.5 mg per kilogram should be used, and on the third day one dose of 2.5 mg per kilogram is to be given.

Woodr and Kometani<sup>52</sup> successfully treated 42 infants and children with BAL for arsenic poisoning. Children suspected of arsenic ingestion but without symptoms of arsenic poisoning were given three to six doses of 2.5 mg per kilogram of body weight each at intervals of four to eight hours. Children with mild symptoms of arsenic poisoning were given six to twelve doses of 2.5 to 3.5 mg per kilogram each at intervals of four to eight hours. Those with severe symptoms were given six to twelve doses of 3.5 to 5.0 mg per kilogram each at intervals of four to eight hours.

### SUMMARY

BAL (2,3-dimercaptopropanol) was developed as an antidote against poisoning from the arsenic-containing war gas, lewisite. Since it is easily oxidized and unstable in aqueous solutions, BAL is commercially available only in a preparation containing peanut oil and benzyl benzoate, which is suitable for intramuscular administration alone. BAL is of value in the treatment of certain metal poisonings because it displaces the metal from its combination with the sulfhydryl groups of enzyme proteins with the formation of a metal-BAL complex, which is excreted. Although BAL in therapeutic doses may produce unpleasant side effects these are transient. BAL has been shown to be of clinical value in the treatment of arsenic, mercury and gold poisonings. Further clinical studies are necessary before the efficacy of BAL in other metal poisonings can be evaluated. Studies on animals suggest that BAL actually enhances the toxicity of certain metals. Therefore, BAL should not be used indiscriminately in the treatment of metal poisonings.

55 Shattuck Street

### REFERENCES

39. Stocken L. A., and Thompson R. H. S. British anti lewisite: arsenic and thiol excretion in animals after treatment of lewisite burns. *Biochem. J.* 40:548-554 1946.
40. Harrison H. E. et al. Treatment by 2,3-dimercaptopropanol (BAL) of systemic toxic effects of skin contamination with lewisite and phenyldichlorarsine. *J. Pharmacol. & Exper. Therap.* (Supp.) 87:81-84 1946.
41. Riker W. F. Jr. and Rosenfield, G. Effect of 2,3-dimercaptopropanol on whole blood and plasma concentration of arsenic after mapharsen in cats. *J. Pharmacol. & Exper. Therap.* (Supp.) 87:72-75 1946.
42. Peters R. A. and Stocken L. A. Preparation and pharmacological properties of 4-hydroxy methyl-2 (3-amino-4-hydroxyphenyl)-1,3-dithia-2-arsa-cyclopentane (mapharside BAL compound). *Biochem. J.* 41:53-56 1947.
43. Gilman A., Philips F. S., Allen R. P., and Koelle E. S. Treatment of acute cadmium intoxication in rabbits with 2,3-dimercaptopropanol (BAL) and other mercaptans. *J. Pharmacol. & Exper. Therap.* (Supp.) 87:55-101 1946.
44. Gilman A., Allen R. P., Philips F. S. and St. John E. Clinical uses of 2,3-dimercaptopropanol (BAL). V. Treatment of acute systemic mercury poisoning in experimental animals with BAL, thiosorbitol and BAL glucoside. *J. Clin. Investigation* 25:549-556 1946.

when BAL is given thirty minutes after the administration of cadmium is explained by the supposition that some of the cadmium becomes irreversibly fixed in the tissues, and thus a smaller amount eventually reaches the kidneys

The same authors found that, depending upon the pH of the solution, cadmium united with one or two moles of BAL to form two different complexes Cd-BAL and Cd (BAL)<sub>2</sub>. Cadmium also formed similar complexes with BAL glucoside, thiosorbitol, and thioxylate. Although the Cd-(BAL)<sub>2</sub> complex had a low dissociation constant in vitro, a readily available supply of cadmium ions seemed to be available when this complex was preformed and then injected into rabbits. Depending upon the amount given, the animals died either acutely from typical cadmium poisoning or several days later from renal impairment. Preformed Cd (BAL glucoside)<sub>2</sub> proved to be relatively non-toxic, probably because the complex is too large to be absorbed readily by the renal cells.

Both BAL and BAL glucoside were found to increase the excretion of cadmium from cadmium-poisoned animals. The BAL-treated animals showed an increase in both urinary and fecal cadmium, whereas those treated with BAL glucoside showed an increase in urinary cadmium only.<sup>78</sup>

In an extensive inhalation study in dogs and mice, it has been shown that cadmium mists can cause acute death from massive pulmonary edema, or delayed death from diffuse pneumonitis often associated with lung abscesses, anorexia, bloody diarrhea and generalized wasting. BAL prevented death in a number of animals when it was given one to three hours after the cadmium exposure. However, when BAL was given prior to the exposure to cadmium, it actually hastened death, presumably by fixing the cadmium in the lungs, where it could do the most damage.<sup>79</sup>

### SILVER

In a limited study, Olcott and Riker<sup>80</sup> found BAL ineffective against experimental argyria. They gave small daily doses of silver nitrate to 2 white rats for four hundred and fifty-six days. One animal was then given nine injections of BAL over a period of eighteen days. Autopsy and histologic examination showed no essential differences in the amounts of silver deposited in the two animals. The authors concluded that BAL would probably be of no value in the treatment of argyria in man.

### MISCELLANEOUS METALS

#### *Antimony*

Barron and Kalnitsky<sup>56</sup> reported that attempts to reactivate the succinoxidase enzyme system inhibited by antimony were unsuccessful with BAL, whereas glutathione was effective in reversing this inhibition. On the other hand, Thompson and

Whittaker<sup>55</sup> found that BAL not only protected the brain pyruvate oxidase system from inhibition by antimony but also protected rats poisoned with this metal. Eagle and his co-workers<sup>81</sup> observed that BAL protected rabbits poisoned with various antimony compounds. An increase in antimony excretion in the urine persisting for two to four hours occurred after each injection of BAL. Similar results were obtained by Braun et al.<sup>73</sup>

#### *Tellurium*

Amdur<sup>82</sup> used BAL to treat 3 men who had inhaled tellurium-containing fumes and developed a characteristic garliclike odor of the breath. Although BAL failed to cause an increased urinary excretion of tellurium, the author believed that it was instrumental in decreasing the duration of halitosis from a possible period of weeks or months to a period of eleven to fourteen days in each case.

#### *Copper, Bismuth, Chromium, Nickel, Zinc, Thallium, Selenium and Vanadium*

McDonald<sup>83</sup> has reported that BAL glucoside in small doses caused an increased urinary copper excretion in normal sheep. The excretion reached a maximum of thirty times normal within an hour and then fell rapidly to a normal rate.

In enzyme-inhibition studies, Barron and Kalnitsky<sup>56</sup> found that BAL was effective against zinc, only partly effective against bismuth and totally ineffective against vanadium and selenium. Braun et al.,<sup>73</sup> in animal experiments, found BAL to be an effective antidote in poisoning from bismuth, chromium and nickel, but of no value against thallium and selenium. The administration of BAL actually hastened the death of animals poisoned with the latter metal.

### ALLOXAN

Lazarow<sup>84</sup> reported that large doses of monothiols such as cysteine, glutathione and thioglycolic acid completely protected rats against a diabetogenic dose of alloxan. The dithiol BAL in smaller amounts was found to be equally effective in protecting the animals from alloxan. However, neither the dithiol nor the monothiols protected the animals unless given before or immediately after the administration of alloxan. It has been postulated that alloxan causes an immediate, irreversible change, which can be prevented only by the early use of sulfhydryl groups, and, in contrast to heavy-metal poisonings, this change cannot be reversed by dithiols.

### PHENYLTHIOUREA

After the introduction of phenylthiourea and ANTU (alpha-naphthyl-thiourea) as powerful rodenticidal agents, a search has been made for suitable antidotes to be used in cases of accidental

poisonings Harvey and his co-workers<sup>55</sup> on the basis of the findings of Du Bois<sup>56</sup> that ANTU inhibits sulfhydryl-containing enzymes, investigated the value of BAL and l-thiosorbitol in phenylthiourea poisoning. ANTU and phenylthiourea are similar in action, and the latter was used in this experiment because of its greater solubility in water. The authors found that l-thiosorbitol given to rats immediately after the administration of phenylthiourea protected these animals from the toxic and lethal effects of phenylthiourea. On the other hand, BAL increased rather than decreased the toxic effects of phenylthiourea. This paradox of a monothiol affording protection from a substance while a dithiol increases the toxic effects of that substance is similar to a situation seen in cadmium poisoning in which thiosorbitol is effective but BAL fails and even potentiates the action of cadmium.

### DOSAGE SCHEDULES

Sufficient experience in the use of BAL has been accumulated to permit tentative recommendations concerning proper dosage schedules for the treatment of arsenic and mercury poisonings. However, too little clinical information is available, as yet, to justify the formation of specific dosage regimens for the use of BAL in other metal poisonings.

The Council on Pharmacy and Chemistry of the American Medical Association<sup>57</sup> suggests that BAL be given by intramuscular injection according to the following schedules:

*For severe arsenic reactions*, each injection to contain 3 mg of BAL per kilogram of body weight

First day } 6 injections per day, at the rate  
Second day } of one injection every four hours

Third day 4 injections

Following ten }  
days or until } 2 injections per day  
recovery

*For mild arsenic reactions*, each injection to contain 2.5 mg per kilogram

First day } 4 injections per day  
Second day }

Third day 2 injections

Following ten }  
days or until } one injection per day  
recovery

*For mercury poisoning*, larger doses of BAL are suggested. An initial dose of 5 mg per kilogram of body weight should be given, to be followed in one to two hours by a dose of 2.5 mg per kilogram. After two to four hours a second dose of 2.5 mg should be administered, and in

severe cases a third dose of 2.5 mg should be given within the first twelve hours. On the second day, two doses of 2.5 mg per kilogram should be used and on the third day one dose of 2.5 mg per kilogram is to be given.

Woodv and Kometani<sup>52</sup> successfully treated 42 infants and children with BAL for arsenic poisoning. Children suspected of arsenic ingestion but without symptoms of arsenic poisoning were given three to six doses of 2.5 mg per kilogram of body weight each at intervals of four to eight hours. Children with mild symptoms of arsenic poisoning were given six to twelve doses of 2.5 to 3.5 mg per kilogram each at intervals of four to eight hours. Those with severe symptoms were given six to twelve doses of 3.5 to 5.0 mg per kilogram each at intervals of four to eight hours.

### SUMMARY

BAL (2,3-dimercaptopropanol) was developed as an antidote against poisoning from the arsenic-containing war gas, lewisite. Since it is easily oxidized and unstable in aqueous solutions, BAL is commercially available only in a preparation containing peanut oil and benzyl benzoate, which is suitable for intramuscular administration alone. BAL is of value in the treatment of certain metal poisonings because it displaces the metal from its combination with the sulfhydryl groups of enzyme proteins with the formation of a metal-BAL complex, which is excreted. Although BAL in therapeutic doses may produce unpleasant side effects, these are transient. BAL has been shown to be of clinical value in the treatment of arsenic, mercury and gold poisonings. Further clinical studies are necessary before the efficacy of BAL in other metal poisonings can be evaluated. Studies on animals suggest that BAL actually enhances the toxicity of certain metals. Therefore, BAL should not be used indiscriminately in the treatment of metal poisonings.

55 Shattuck Street

### REFERENCES

39. Stoeken L. A. and Thompson R. H. S. British anti-lewisite: arsenic and thiol excretion in animals after treatment of lewisite burns. *Biochem. J.* 40:548-554 1946.
40. Harrison H. E. et al. Treatment by 2,3-dimercaptopropanol (BAL) of systemic toxic effects of skin contamination with lewisite and phenyldichlorarsine. *J. Pharmacol. & Exper. Therap.* (Supp.) 87:81-84 1946.
41. Riker W. F. Jr. and Rosenfield G. Effect of 2,3-dimercaptopropanol on whole blood and plasma concentration of arsenic after mapharsen in cats. *J. Pharmacol. & Exper. Therap.* (Supp.) 87:72-75 1946.
42. Peters R. A. and Stoeken L. A. Preparation and pharmacological properties of 4-hydroxymethyl 2 (3'-amino-4'-hydroxyphenyl) 1,3-dithia-2-arsacyclopentane (mapharside BAL compound). *Biochem. J.* 41:53-56 1947.
43. Gilman A., Philips F. S., Allen R. P. and Koelle E. S. Treatment of acute cadmium intoxication in rabbits with 2,3-dimercaptopropanol (BAL) and other mercaptans. *J. Pharmacol. & Exper. Therap.* (Supp.) 87:95-101 1946.
44. Gilman A., Allen R. P., Philips F. S. and St. John E. Clinical uses of 2,3-dimercaptopropanol (BAL). \ Treatment of acute systemic mercury poisoning in experimental animals with BAL, thiosorbitol and BAL gluconate. *J. Clin. Investigation* 25:549-556 1946.

- 45 Koppanyi T, and Sperling F Central and antonomic effects following combined administration of sodium arsenite and 2,3-dimercaptopropanol (BAL) *J Pharmacol & Exper Therap* 89:350-355 1947
- 46 Kensler C J, Ahels J C and Rhoads C P Arsenic poisoning mode of action and treatment. *J Pharmacol & Exper Therap* 88:99-108 1946
- 47 Riker W F Jr Treatment of experimental arsenic poisoning with dithiols *J Pharmacol & Exper Therap* (Supp) 87:66-71 1946
- 48 Levy G A Study of arsenic poisoning *Quart J Exper Physiol* 34:47-67 1947
- 49 Hughes W F Jr Clinical uses of 2,3-dimercaptopropanol (BAL) IX. Treatment of lewisite burns of eye with BAL. *J Clin Investigation* 25:541-548 1946
- 50 Carleton A B et al Clinical uses of 2,3-dimercaptopropanol (BAL) VI. Treatment of complications of arseno-therapy with BAL (British anti lewisite) with appendix upon excretion of arsenic. *J Clin Investigation* 25:497-527 1946
- 51 Longcope W T, Lentscher J A Jr, Wintrobe M M and Jäger V Clinical uses of 2,3-dimercaptopropanol (BAL) VII. Treatment of arsenical dermatitis with preparations of BAL. *J Clin Investigation* 25:528-533 1946
- 52 Holley H L Use of BAL (2,3-dimercaptopropanol) in treatment of agranulocytosis following intensive arsenotherapy for syphilis. *Ann. Int Med* 27:231-238 1947
- 53 Schrumph A BAL therapy of thrombopenic purpura after arsenophane mine treatment *J A M A* 135:1152 1947
- 54 Friedenberg S Trypanamide optic neuritis treated by 2,3-dimercaptopropanol (BAL) *J A M A* 135:1072 1947
- 55 Thompson R H S and Whittaker V P Antidotal activity of British anti lewisite against compounds of antimony gold and mercury *Biochem J* 41:342-346 1947
- 56 Barron E S G and Kalnitsky G Inhibition of succinoxidase by heavy metals and its reactivation with dithiols *Biochem J* 41:346-351 1947
- 57 Stocken L A British anti-lewisite as antidote for acute mercury poisoning *Biochem J* 41:358-360 1947
- 58 Longcope W T and Luetscher J A Jr Clinical uses of 2,3-dimercaptopropanol (BAL) XI. Treatment of acute mercury poisoning by BAL. *J Clin Investigation* 25:557-567 1946
- 59 Long W K and Farah A Influence of certain sulfhydryl compounds on toxicity of organic mercurial diuretic. *J Pharmacol & Exper Therap* 88:388-399 1946
- 60 Long W K and Farah A Effect of some sulfhydryl-containing substances on toxicity of organic mercurial compound *Science* 104:220 1946
- 61 Sussman R M and Schack J A BAL inhibition of mercurial diuresis in congestive heart failure *Proc Soc Exper Biol & Med* 66:247 1947
- 62 Mareah G Jr and Farah A Effect of 2,3-dimercaptopropanol upon diuretic action of mersalyl. *Federation Proc* 6 (Part II) 354 1947
- 63 Earle D P, and Berliner R W Effect of 2,3-dimercaptopropanol on diuresis *Am J Physiol* 151:215-220 1947
- 64 Handley C A and LaForge M Effect of thiols on mercurial diuresis *Proc Soc Exper Biol & Med* 65:74 1947
- 65 Farah A and Mareah G Influence of sulfhydryl compounds on diuresis and renal and cardiac circulatory changes caused by mersalyl *J Pharmacol & Exper Therap* 92:73-82 1948
- 66 Lehman R A Further studies on acute toxicity of mercurial diuretics *Proc Soc Exper Biol & Med* 64:428-433 1947
- 67 Cohen S J Pharmacology and toxicology of some new organomercury compounds *J Pharmacol & Exper Therap* 35:343-350 1929
- 68 Bivings L and Lewis G Acrodynia new treatment with BAL. *J Pediatr* 32:63-65 1948
- 69 Ragan C and Boots R H Treatment of gold dermatitis use of BAL (2,3-dimercaptopropanol) *J A M A* 133:752-754 1947
- 70 Cohen A, Goldman J and Duhhs A W Treatment of acute gold and arsenic poisoning use of BAL (2,3-dimercaptopropanol (British anti lewisite)) *J A M A* 133:749-752 1947
- 71 Margolis H M and Caplan P S BAL in treatment of toxicity from gold. *Ann. Int. Med.* 27:353-360 1947
- 72 Lockie L M, Norcross B M and George C W Treatment of two reactions due to gold response of thrombopenic purpura and granulocytopenia to BAL therapy *J A M A* 133:754 1947
- 73 Brann H A, Linsky L M and Calvery H O Efficacy of 2,3-dimercaptopropanol (BAL) in therapy of poisoning by compounds of antimony bismuth, chromium mercury and nickel *J Pharmacol & Exper Therap* (Supp) 87:119-125 1946
- 74 Germuth F G Jr and Eagle H Efficacy of BAL (2,3-dimercaptopropanol) in treatment of experimental lead poisoning in rabbits *J Pharmacol & Exper Therap* 92:397-410 1948
- 75 Chiodi H and Sammartino R A Nephrotoxic and renoprotective effects of lead on white rats and its prevention by BAL. *Nature, London* 160:680 1947
- 76 Teller J G Use of BAL in lead poisoning preliminary report on one case *J A M A* 135:835-837, 1947
- 77 Ryder H W, Chohal, J and Kehoe R A Influence of dithiopropanol (BAL) on human lead metabolism *Science* 106:63 1947
- 78 Tepperman H M Effect of BAL and BAL-glucoside therapy on excretion and tissue distribution of injected cadmium. *J Pharmacol & Exper Therap* 89:343-349 1947
- 79 Tobias J M, et al Pathology and therapy with 2,3-dimercaptopropanol (BAL) of experimental Cd poisoning *J Pharmacol & Exper Therap* (Supp) 87:102-118 1946
- 80 Olcott C T, and Riker W F Jr Experimental argyria. II. Treatment of rats receiving silver with 2,3-dimercaptopropanol (BAL) *Science* 105:67 1947
- 81 Eagle H, Germuth F G, Magnusson H J, and Fleischman R Protective action of BAL in experimental antimony poisoning *J Pharmacol & Exper Therap* 89:196-204 1947
- 82 Amdur M L Tellerium accidental exposure and treatment with BAL in oil *Occup Med* 3:386-391 1947
- 83 McDonald I W Effect of BAL-intrav on excretion of copper by sheep *Nature London* 157:837 1946
- 84 Lazarow, A Further studies of effect of sulphur compounds on production of diabetes with alloxan *Proc Soc Exper Biol. & Med.* 66:47 1947
- 85 Harvey T S, Tatum H J and Himmelfarb S L thiosorbitol and BAL as antidotes in phenylthiourea poisoning *J Pharmacol & Exper Therap* 90:348-350 1947
- 86 Du Bois K P Cited by Harvey Tatum and Himmelfarb
- 87 Report of the Council on Pharmacy and Chemistry of the American Medical Association "BAL (British anti lewisite) in treatment of arsenic and mercury poisoning *J A M A* 131:824 1946

## ADDITIONAL REFERENCES

- Barron E S G et al Reactivation by dithiols of enzymes inhibited by lewisite *Biochem J* 41:69-74 1947
- Chance A C and Levy G A Effects of BAL on excretion of arsenoxides *Quart J Exper Physiol* 34:79-82 1947
- Eagle H Systemic treatment of arsenic poisoning with BAL (2,3-dimercaptopropanol) *J Ven Dis Inform* 27:114-121 1946
- Eagle H Recent studies in arsenical chemotherapy *Tr & Stud., Coll Physicians Philadelphia* 14:49-54 1946
- Editorial Substance called BAL. *Brit M J* 1:240 1946
- Editorial BAL in oil for treatment of severe mapharsen reactions. *Bull U S Army Med Dept* 4:327 1945
- Gilman A Therapeutic applications of chemical warfare agents. *Federation Proc* 5:285-292, 1946.
- Harrison H E et al Poisoning from inhalation of vapors of lewisite and phenyldichlorarsine its pathology in dog and treatment with 2,3-dimercaptopropanol (BAL) *J Pharmacol & Exper Therap* (Supp) 87:76-80 1946
- Krop S Action of 2,3-dimercaptopropanol (BAL) and related dithiols on isolated skeletal muscle of frog *J Pharmacol & Exper Therap* (Supp) 87:60-65 1946
- Luetscher J A, Eagle H and Longcope W T Clinical uses of 2,3-dimercaptopropanol. VIII. Effect of BAL on excretion of arsenic in arsenical intoxication *J Clin Investigation* 25:534-540 1946
- Report from the BAL Conference Medical Research Council British anti lewisite its use and therapeutic value in arsenical intoxications. *Lancet* 2:497 1947
- Stocken L A, Thompson R H S and Whittaker V P British anti-lewisite antidotal effects against therapeutic arsenicals *Biochem J* 41:47-52 1947
- Sulzberger M B and Baer R L Development and use of BAL review with particular reference to arsenical dermatitis *J A M A* 133:293-296 1947
- Thompson J F, Savit J and Goldwasser E Tests of 2,3-dimercaptopropanol (BAL) and related dithiols for decontamination of lewisite on human skin *J Pharmacol & Exper Therap* 89:113 1947
- Whittaker, V P Experimental investigation of "ring hypothesis" of arsenical toxicity *Biochem J* 41:56-62 1947

## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

TRACY B MALLORY, M D, *Editor*

BENJAMIN CASTLEMAN, M D, *Associate Editor*

EDITH E PARRIS, *Assistant Editor*

### CASE 34531

#### PRESENTATION OF CASE

A sixty-one-year-old man was admitted to the hospital because of vomiting and diarrhea of one year's duration.

The diarrhea, which was described as occurring five or six times daily, was watery, brownish and without gross evidence of blood. The vomiting occurred once or twice a week, usually at night after retiring. It was accompanied by moderate epigastric fullness and dull substernal discomfort, which were not apparently related to food ingestion. In the six months before admission frequency of the attacks of vomiting increased to almost every night. At this time the patient noted the onset of burning and rolling sensations in the pit of the stomach. These symptoms were relieved somewhat by the emesis, which was liquid and mucoid in character. Anorexia was very marked. There was no postprandial distress, pain between meals, tarry stools or jaundice. He had lost 70 pounds since the onset of illness.

The past history revealed rheumatoid arthritis since the age of thirty years, when he had a severe attack with involvement of almost every joint. A bilateral knee-joint reconstruction was done after the acute stage. At this time he experienced the onset of mild exertional dyspnea and dependent edema. In spite of this he was alleged to have been in good general health but was unable to work because of the arthritis.

Physical examination revealed an extremely cachectic man in no acute distress. The chest was emphysematous, with limited expansion. There were moist, sibilant rales in the left axilla and at both bases. The heart was not enlarged. The liver edge was palpated four fingerbreadths below the costal margin. The spleen was not felt. A large reducible, supraumbilical, ventral hernia was present. Marked arthritic changes involving almost every joint, with limitation of movements, were observed. These appeared to be in a quiescent stage.

The temperature was 99°F, the pulse 80, and the respirations 20. The blood pressure was 120 systolic, 80 diastolic.

Examination of the blood showed a red-cell count of 5,300,000, with a hemoglobin of 12 gm, and a white-cell count of 21,300, with 70 per cent neutrophils. The urine had a specific gravity of 1.014 and contained no albumin. Subsequent specimens gave +++ to ++++ tests for albumin. There were a few white cells in the sediment. The nonprotein nitrogen was 50 mg, and the total protein 7.75 gm per 100 cc, with an albumin of 3 gm and a globulin of 4.75 gm. The chloride was 108 milliequiv per liter, and the alkaline phosphatase 6.6 units. The prothrombin time was 17 seconds (normal, 16 seconds); the cephalin flocculation test was ++ at twenty-four hours and +++ at forty-eight hours, and the bromsulfalein test showed 10 per cent retention of the dye. A Congo-red test revealed a 52 per cent retention of dye in the serum.

X-ray studies of the gastrointestinal tract gave findings suggestive of pyloric obstruction, with marked pylorospasm. A barium enema was negative. A chest film showed extensive fibrotic emphysematous and bronchiectatic changes in both lungs. An electrocardiographic record was within normal limits. The gastric fluid on analysis revealed high acidity and was guaiac negative. Cytologic study of smears was reported negative. The stools were guaiac negative. After admission repeated gastric aspirations of 150 to 300 cc resulted in some decrease of the vomiting, but the patient continued complaining of gastric fullness.

On the eighth hospital day a partial gastrectomy and repair of the ventral hernia were performed. Following operation he noted no relief of the gastric fullness and complained of increasing pain and stiffness of joints. The nonprotein nitrogen began to rise, from 50 mg to 72 to 170 mg, finally reaching 225 mg per 100 cc, with a fall of the chloride to 78 milliequiv per liter and of the total protein to 5.4 gm per 100 cc. The watery diarrhea recurred, and marked dyspnea and cyanosis developed. Moist rales were heard almost to the top of both lungs. On the twenty-second hospital day he became unresponsive and died.

#### DIFFERENTIAL DIAGNOSIS

DR BERNARD M JACOBSON: Can you tell us the figures on the acidity of the gastric fluid?

DR TRACY B MALLORY: A fasting specimen was reported as 50 units of free and 80 units of combined acid.

DR JACOBSON: A considerable degree of acidity.

As I read over this patient's history and before I got to the report of the x-ray examination, a number of thoughts occurred to me about the fundamental diagnosis. Apparently for a considerable period of time there was a watery, brownish diarrhea without gross evidence of blood but with associated cramps in the lower abdomen. The diarrhea seemed more prominent than the vomiting, which occurred only once or twice a week, usually after retiring. The

possibilities that ran through my mind as causes of long-continued diarrhea without pus or blood or tenesmus include a few common conditions and a few unusual conditions that might be mentioned. Against such a condition as ulcerative colitis or regional ileitis was the lack of blood, pus or tenesmus. The presence of a carcinomatous lesion anywhere in the gastrointestinal tract from the stomach downward should certainly be considered. The question of a fistula between various segments of the gastrointestinal tract must be considered, and that could account for this type of diarrhea. The possibilities outside the gastrointestinal tract — general and systemic disease that can cause this type of diarrhea — come to mind. Chronic uremia is one of the commonest. Chronic nitrogen retention can be associated with this type of diarrhea and last many months. One thinks of such diseases as Addison's disease as causing diarrhea and vomiting and also of pernicious anemia and sprue, but the subsequent physical and laboratory findings give no evidence for either Addison's disease, pernicious anemia or sprue, nor is there any evidence later on that suggests hyperthyroidism as the cause of that type of diarrhea. As one goes along a little bit in the history, one finds that when the vomiting became more pronounced, beginning to occur almost daily, the material vomited was liquid and mucoid. I presume we would know from the patient whether the liquid was heavily stained with bile because that is usually mentioned at some time in a patient's history. In the absence of small-bowel content of the vomitus I think we must assume that there was obstruction at the pylorus. This was not low intestinal obstruction. The amount of vomiting, it seems to me, is out of proportion to what we may expect as secondary to some of the systemic diseases I have mentioned.

On physical examination the liver edge was four fingerbreadths below the costal margin. In view of the obvious emphysema I assume the upper border was quite low and the liver was not large but merely ptotic. I am rather surprised we were not told about the examiner's feeling a mass in the abdomen, especially in the presence of the hernia. Perhaps I should not expect to feel a mass, but I think I do.

As far as the laboratory work goes, there are a few items of interest. A mild hypochromic anemia was present. We are told that one urine on admission had a specific gravity of 1.014, probably the patient did not have a specific-gravity concentration test, but it would be of some interest to know if he could concentrate. Most of the urine apparently contained a huge amount of albumin and a few pus cells. I would be interested to know if the patient had an intravenous phenolsulfonephthalein test, since we see later that kidney failure played an important part in the patient's terminal career.

DR MALLORY There was a phenolsulfonephthalein excretion of 0 in fifteen minutes, 5 per cent in sixty and 5 per cent in twelve

DR JACOBSON What volume?

DR MALLORY No volume was recorded.

DR JACOBSON Assuming that the urinary volume was fairly good, this obviously indicates impairment in renal function — no excretion in fifteen minutes.

DR MALLORY No concentration test is recorded but subsequent specific gravities are 1.005, 1.003, 1.010 and 1.006.

DR JACOBSON Reversal of the albumin-globulin ratio is of some interest, suggesting systemic disease with increasing serum globulin. There is no good evidence of any one disease. Some degenerative disease of the liver might have caused this high serum globulin. Rheumatoid arthritis can sometimes cause high serum globulin. I doubt if that would be suggestive of multiple myeloma or sarcoid or some of the other conditions. I suspect that the globulin may be elevated due to rheumatoid arthritis. The amount of liver-function defect, as measured by the cephalin flocculation and bromsulfalein test, is of no great significance in a person as malnourished as this. Later we note the low serum chloride, which was initially rather high, perhaps because of dehydration. The phosphatase of 6.6 units is against biliary obstruction. The normal prothrombin time is also against marked derangement of liver function.

DR STANLEY M. WYMAN The films of the chest show a diffuse linear process throughout both lung fields extending from the hilum. There are suggestions of dilated bronchi in the periphery of the right-upper-lung field. The hilar shadows are prominent, but I can see no definite lymph nodes or other masses. The heart shadow is not remarkable for a man of this age. The chest is increased in the anteroposterior diameter, and I think the whole picture is quite consistent with fibrosis and emphysema, although of course lymphatic metastases cannot be entirely excluded. The films of one barium-enema examination show an intrinsically normal-appearing colon, with a loop of barium-filled bowel, I think probably ileum, extending out into the hernial sac and other gas-filled loops of bowel, which are probably ileum in the sac. The hepatic flexure is displaced downward, and the upper margin of the liver extends reasonably high, which makes me wonder about increase in the size of the liver from this examination.

The next films are of the gastrointestinal examination done on at least two occasions. I am sure the examiner had a great deal of difficulty with this patient because of the arthritis. I think the important thing on these films is that there is a large, soft-tissue shadow in the right upper quadrant that I believe displaced the duodenum and stomach to the left, and, as one can see in this projection, this lies somewhat anteriorly. Apparently, the examiner had a great deal of difficulty in obtaining good visualization of the pylorus and the distal duodenum, and we have no film with good filling of the distal duodenum. The few traces that we have of barium in the duodenum show a suggestion of some irregularity

in the mucosal pattern. There is a suggestion of some radiolucency overlying the liver. This, again, is not a definite finding. The film that might have shown it best is of unsatisfactory quality. There is one, and only one, spot film that shows an unusual accumulation of barium at this point, which makes one wonder about barium in the common duct. I would say that the liver was enlarged and displaced the stomach. It may be that the second portion of the duodenum is narrowed. I cannot comment intelligently on the pylorus. The changes may be due to extrinsic pressure.

DR JACOBSON: Dr Wyman has pointed out that the upper portion of the liver was not low as I suspected and that the stomach was apparently pushed to the left. In that case we must believe the liver was large and was the seat of disease.

The Congo-red test, which showed 52 per cent retention, apparently a doubtful borderline finding, gave no definite evidence of systemic amyloid disease. There are certain forms of amyloid disease — the atypical type that might infiltrate the walls of the small bowel — that will not take up Congo-red dye. We cannot see any visualization of the small bowel — no leakage of barium directly into the colon.

DR WYMAN: I should not say so.

DR JACOBSON: If we could have a picture of the upper small bowel, it would be helpful.

DR WYMAN: This is the closest we came to it. I would consider these jejunal folds to be within normal limits.

DR JACOBSON: Was an intravenous pyelogram done?

DR WYMAN: No.

DR JACOBSON: I rather suspect that the correct diagnosis was not well understood preoperatively and that some of the reasoning that I have gone through was also discussed by the clinicians on the service before operation. This patient obviously had pyloric obstruction. We must assume vomiting secondary to pyloric obstruction and not systemic disease.

What of the diarrhea? We have no evidence of intrinsic small-bowel or large-bowel disease. Can we tie up the vomiting and the diarrhea into one diagnosis? It is possible if we assume that the patient had carcinoma of the pylorus. Many patients with carcinoma of the stomach have diarrhea, the exact mechanism of which we do not know. The evidence for carcinoma of the stomach in this patient is the progressive downhill course. The history of the type of discomfort he had in the stomach is perfectly consistent with it. For the diagnosis of pyloric obstruction due to ulcer there may be more evidence from the laboratory point of view — high gastric acidity and the negative cytologic smear. The lack, however, of a good, clear history of postprandial pain typical of ulcer stands out, and the combination of pyloric obstruction and diarrhea inclines me a little more to the diagnosis of carcinoma rather than ulcer. Some

few cases of carcinoma do have high gastric acidity. I cannot visualize any other specific cause for diarrhea.

What happened after operation is certainly an interesting phenomenon. The kidney failure, which may have been very minimal before operation, set in quite promptly. The patient obviously died in uremia. Terminally he had left-sided heart failure and pulmonary edema.

I believe that in recent years major surgery in patients with cardiac disease has become less and less of a risk and that the experience of many surgeons and physicians is that renal failure is probably a most important postoperative condition.

What was the renal failure due to? We have no good evidence that this patient had chronic glomerulonephritis or chronic vascular nephritis, although it may well be that the initial blood pressure of 120 systolic, 80 diastolic, reflected a man with some degree of heart failure, with lowered blood pressure. Against increased hypertension is the fact that the heart shadow was normal.

Could this have been pyelonephritis? It certainly could. At these sessions Dr Mallory has pointed out to many of us how often we miss the diagnosis of chronic pyelonephritis. The diagnosis is not too easy to make. The findings in the urinary sediment when the patient comes to the hospital may be minimal, and the blood pressure elevated or normal, all forms of kidney-function tests, of course, are markedly abnormal.

Could this have been an acute renal failure due to lower-nephron defect? We have no history of the patient's having received sulfonamides or incompatible transfusion. I shall assume that they were not given, and the possibility can be discarded.

I should like to conclude with a diagnosis of carcinoma of the pylorus, diarrhea secondary to the carcinoma, chronic pyelonephritis, terminal uremia, rheumatoid arthritis, bronchiectasis and terminal heart failure.

DR F DENNETTE ADAMS: I am worried about Dr Jacobson's statement that he attributed the lower border of the liver and low diaphragm to emphysema. I doubt if it could happen. I do not believe I have seen it due to that, but I may be wrong. It seems to me that a low diaphragm due to emphysema would not have enough pressure to push the liver down.

I would like to ask if perhaps amyloid disease would explain the terminal picture, especially in a man with arthritis for so many years.

DR JACOBSON: I think I have seen a low liver — that is, a ptotic liver — pushed down by the diaphragm, even without pulmonary emphysema. In view of the demonstration of the soft-tissue mass by Dr Wyman, I am more suspicious that the liver was the seat of carcinomatous metastases.

Against amyloid disease, I do not believe the rheumatoid arthritis was active enough to produce that

much amyloid disease. The Congo-red test was not conclusive, nor was there enough bronchiectasis in the history to suggest amyloid disease secondary to that.

DR JOHN B STANBURY I was much impressed by one interesting physical finding. You could pass your hand through the ventral hernia and outline a firm, smooth liver as I have never been able to do before — just as well as Dr Mallory could examine it at post-mortem examination.

The thing that puzzled us was why after operation the patient suddenly went into renal failure. He had borderline failure before operation. He had pyloric obstruction preceding operation. We took the risk. It did not work. He went quickly into renal failure, developed uremia, pulmonary edema and low chloride, went into pulmonary edema and heart failure and died. We gave him no sulfonamide.

DR JACOBSON No mass was felt in the abdomen through the hernia?

DR STANBURY No, just the liver.

#### CLINICAL DIAGNOSIS

Amyloid nephropathy, with uremia

#### DR JACOBSON'S DIAGNOSES

Carcinoma of pylorus  
Chronic pyelonephritis  
Terminal uremia  
Rheumatoid arthritis  
Bronchiectasis  
Terminal heart failure

#### ANATOMICAL DIAGNOSES

*Rheumatoid arthritis, chronic*  
*Amyloidosis of liver, spleen, kidneys and adrenal glands*  
Bronchiectasis  
Bronchopneumonia  
Hypertrophy of heart  
*Pericarditis, acute fibrinous, probably uremic*  
Operative wound resection of pylorus for obstruction

#### PATHOLOGICAL DISCUSSION

DR MALLORY Autopsy showed that several of the organs were larger than the x-ray examinations indicated. The heart weighed over 500 gm, and the liver 3500 gm — double the normal size. The spleen weighed 500 gm, and both kidneys 450 gm. We found that the liver, spleen and kidneys showed very extensive amyloid disease and there was also some involvement of the adrenal glands. There was extensive bronchiectasis, a terminal bronchopneumonia and an acute pericarditis. The stomach, which had been resected, was a great disappointment to the pathologists. We could find nothing wrong with it.

At the time of operation a biopsy on which a frozen section was done showed only normal, smooth muscle, and the resected specimen only questionable hypertrophy of the muscle of the pyloric ring and perfectly normal mucosa — neither tumor nor ulcer. Localized amyloid tumors of the gastrointestinal tract do occur, and in the face of extensive amyloid disease we thought we might find amyloid in the pyloric ring, but there was none whatever.

DR EDWARD B D NEUHAUSER Why was a gastrectomy done?

DR STANBURY There seemed to be no question that the patient had functional pyloric obstruction. Perhaps a surgeon can answer that.

DR W R RICHARDSON I am sorry that Dr John McKittrick is not here. I assisted at the operation and shall try to explain our findings and the choice of procedure.

A gastrotomy was done, and the pylorus and pyloric antrum visualized. There was a definite organic obstruction at the pylorus, an annular thickening that was submucosal with no ulceration. It narrowed the lumen to a diameter of less than 1 cm and did not permit the passage of more than the distal portion of a hemostat. This band was broken down during the digital examination, with several linear mucosal tears resulting. Much of the band was removed submucosally and sent for frozen-section diagnosis, which revealed no evidence of a malignant lesion and was eventually noted as "hypertrophy of the pylorus."

Subtotal gastrectomy was performed because it was considered inadvisable to leave traumatized areas. That this was probably an unfortunate choice is now clear, and we would have felt much better had a gastroenterostomy or even a pyloroplasty been carried out, accepting whatever hazard there might have been in leaving the traumatized pylorus and pyloric antrum.

DR MALLORY One cause of pyloric obstruction seen from time to time in adults is ectopic pancreatic tissue in the pyloric sphincter. We looked carefully for that but were unable to find it. I think we must assume that the pyloric obstruction was functional. I have no doubt it was real.

DR JACOBSON Would Dr Ropes comment on the significance of the Congo-red test?

DR MARIAN ROPES I think we have now seen enough cases corroborated at autopsy to say that this figure may mean amyloid disease. We still do not know what the percentages mean, but half our patients with rheumatoid arthritis show levels between 50 and 65 per cent and several have shown amyloid disease at autopsy. In addition, 15 per cent have positive levels — less than 50 per cent left in the serum. It is interesting also that the Congo-red retention does not seem to correspond with the severity of the arthritis or with the duration. We

have seen it in varying degrees of severity of arthritis.

DR MALLORY The amyloid deposits stained beautifully with Congo red at autopsy. It was the type that should have absorbed dye, I should think.

## CASE 34532

### PRESENTATION OF CASE

A forty-nine-year-old photographer entered the hospital complaining of dyspnea relieved by belching.

Five months before admission he experienced an episode of nausea, weakness and pain in the left arm which was relieved by induced vomiting. He remained in bed for three days, and at this time a chest x-ray film showed an enlarged heart. He continued his usual activities but three months later awoke one night with sudden dyspnea, relieved by sitting on the edge of the bed for a few minutes. Since that time he had noticed gradually increasing dyspnea on exertion and frequent episodes of epigastric distress following meals, often associated with dyspnea.

Ten days prior to admission he noticed swelling of the ankles, which increased subsequently. During the past few months he had lost about 15 pounds.

Physical examination revealed a well developed, quiet man in no distress. The cardiac border was percussed 11 cm to the left of the midline. There was a questionable diastolic gallop. The liver edge was palpated four fingerbreadths below the costal margin and was slightly tender. There was ++ edema of the ankles, extending up to the sacrum.

The temperature was 99.4°F, the pulse 90 and the respirations 24. The blood pressure was 115 systolic, 90 diastolic.

Examination of the blood revealed a hemoglobin of 14 gm, and a white-cell count of 12,000, with 77 per cent neutrophils, 19 per cent lymphocytes and 4 per cent monocytes. The urine had a specific gravity of 1.026 and gave a +++ test for albumin. Microscopical examination of the sediment showed rare red cells and 5 to 8 white cells per high-power field.

On the day following admission he experienced sudden pain in the right upper chest with a little sputum. Later a friction rub was heard on the right side, and a few rales at the right back. An x-ray film disclosed an area of somewhat mottled density lying in the anterior segment of the right upper lobe with its base against the pleura. There was a moderate quantity of fluid in the right pleural space. The lung fields otherwise appeared essentially clear except for some atelectasis in the right-lower-lung field medially. The heart shadow was enlarged to the right and left with a cardiothoracic ratio of 18/31.5, it was without characteristic configuration, and the pulsations were diminished in amplitude. Plain films of the abdomen showed the tip of the liver to lie unusually low, suggesting some enlargement of the

liver. There was a hazy density obscuring some of the visceral shadows and raising the question of fluid in the abdomen. An electrocardiogram showed a normal rhythm, with a rate of 100, and a PR interval of 0.14, the T waves were inverted in Lead I and low in Leads 2 and 3, and there was a well marked left-axis deviation and an inverted T wave in Lead AVL with a small Q wave. The chest leads showed an upright T wave in Leads V-2 and V-4 and a flat T wave in V-5.

On the day following the episode of chest pain a bilateral superficial femoral-vein ligation was performed and dicumarol and digitoxin were started. Tenderness of the right calf was noted on the next day. The patient continued to experience some dyspnea and occasionally raised some blood-streaked sputum. He began to run a temperature of about 100°F, and the rales at the right base persisted. The prothrombin activity became as low as 24 per cent, and digitoxin was stopped because he complained of nausea. An x-ray film on the seventh day again demonstrated the area of increased density within the anterior portion of the right upper lobe. This had increased in size since the previous examination. The right leaf of the diaphragm was considerably elevated. Very little, if any, fluid was made out. The left lung was clear. The heart was again observed to be markedly enlarged.

He continued to be nauseated and occasionally raised more bloody sputum. He developed a prominent gallop rhythm with occasional extrasystoles and dropped beats. He continued to fail slowly and developed pleural pain over the left chest posteriorly, with a loud friction rub. On the tenth hospital day he had a sudden episode of dyspnea and became increasingly cyanotic, with increase in pulse rate and lowering of blood pressure. Following this he was described as in a "chronic shock state" and died on the following day.

### DIFFERENTIAL DIAGNOSIS

DR GORDON S. MYERS May we see the x-ray films?

DR STANLEY M. WYMAN Unfortunately, we were unable to find any but these two portable films of the chest. They show the area of rather homogeneous density in the right-lung field, which appears to lie against the pleura of the anterior chest wall. There is some fluid in the fissure between the middle and lower lobes and the upper and lower lobes. The right lower lobe is decreased in size, and there is some density posteriorly, suggesting possibly another infarct. However, this film is of insufficient quality to warrant a definite conclusion. The heart shadow cannot be delineated, but it is a large heart, I believe, and is prominent in the region of the left ventricle. The left lung on these films appears clear.

DR MYERS Do you think the density here in the lower portion of the lobe as seen posteriorly can be consistent with pulmonary infarction?

DR WYMAN Yes, with some pleural fluid

DR BENJAMIN CASTLEMAN This last set of films was taken on the tenth day, six days before the patient died

DR MYERS I would like to begin by saying what I think the diagnosis may be and then try to explain my reasoning I believe this man most likely had coronary-artery disease and the onset of the acute illness began with myocardial infarction, although we have no proof of that I believe also that he had congestive failure and recurrent pulmonary emboli, both prior to and probably following treatment by superficial vein ligation and dicumarol

The chief complaint was that of dyspnea, relieved by belching That is an unusual chief complaint, but I suppose it is a valid one If he had congestive failure with limitation of vital capacity and gaseous distention of the abdomen, the elevation of the diaphragm may have been responsible for some additional dyspnea, since we believe that dyspnea is proportional to ventilation divided by vital capacity

Five months before admission this man had a curious episode of nausea, weakness and pain in the left arm, relieved by induced vomiting That in itself is a nonspecific history One would think, first of all, that he had something going on in the gastrointestinal tract In view of the fact that later on we find that he had lost weight despite the fact that he was becoming edematous, one might consider the possibility of carcinoma or some other serious lesion in the gastrointestinal tract This history does not suggest pulmonary infarction or embolus at that time The fact that he had pain in the left arm, even without chest pain, and that he had symptoms of indigestion certainly is consistent with the occurrence of myocardial infarction We know that myocardial infarcts sometime occur without any symptoms He remained in bed three days at this time He had chest x-ray films, which showed an enlarged heart If he had a myocardial infarct at this time, it might explain the fact that the heart appeared to be large on x-ray study and that he went on to symptoms suggesting left-sided heart failure Thus, we can justifiably suspect myocardial infarct, but we cannot make a definite diagnosis of it from the facts at hand

I think that the diagnosis of coronary-artery disease in a man forty-nine years old who showed congestive failure but no heart murmurs is the best bet It is very unlikely that he had one of the rarer kinds of heart disease such as those following sulfonamide therapy and virus infection We know that he had an episode of orthopnea He woke up short of breath and was relieved by sitting on the edge of the bed He had clear-cut dyspnea on exertion and also epigastric distress following meals, associated with dyspnea If he had coronary-artery disease the symptoms of indigestion were not unusual since we know various functional gastrointestinal diseases are commonly associated with coronary disease —

for example, cardiospasm, which gives symptoms of indigestion apart from the heart trouble He may have had dyspnea after meals, partly because of abdominal distention and also because the work of the heart is increased after a full meal

Ten days prior to admission he noted swelling of the ankles, which had increased Despite this, he had a 15-pound weight loss, and one wonders if he had some kind of cachectic disease I do not believe we can skip over that weight loss too lightly However, he may have been afraid to eat, simply because eating aggravated his symptoms Later on there is no clear-cut evidence of wasting disease such as thyrotoxicosis, cancer, diabetes or the like

The physical examination, as stated, is consistent with congestive heart failure there was a large heart, rapid pulse, a questionable diastolic gallop and so forth The protocol states that the blood pressure was 115 systolic, 90 diastolic It would be helpful to know if he had had any previous hypertension, whether or not there was venous distention, and also about the loudness of the pulmonic second sound, to get some idea whether there was pulmonary hypertension associated with left-sided heart failure

DR CASTLEMAN The record states that there was distention and pulsation of the neck veins for 5 cm above the clavicle

DR MYERS That is additional evidence in favor of congestive failure It certainly fits in with the rest of the picture

Examination of the blood showed no definite anemia, a little increase in white-cell count and no real increase in neutrophils or lymphocytes The urinary findings are consistent with the presence of congestive failure

On the day following admission the patient experienced sudden pain in the right upper chest, with cough productive of a little sputum, and later a friction rub and a few rales were noted This episode and the x-ray findings seem to be consistent with the presence of pulmonary infarction, although the small amount of fluid in the right pleural space could have been due either to congestive failure or to a pulmonary infarct that happened to be on the right side The x-ray report states that there was atelectasis in the right-lower-lung field, but I believe that is a not uncommon statement in cases of small pulmonary infarcts There may or may not have been additional atelectasis The heart was large, without any special configuration, perhaps prominent in the region of the left ventricle The cardiac pulsations were diminished I do not believe that fact to be too helpful Diminished pulsations may be due to the presence of pericardial fluid or simply to an enlarged, failing heart. There is certainly no evidence of constrictive pericarditis in the x-ray films or in the rest of the data that we have The plain films of the abdomen, which we do not have here, were consistent with the presence of fluid and an enlarged liver, which were probably due to congestive heart failure

We then come to the electrocardiograms. I am glad to have been able to see the tracings myself just now because they look a little more markedly deformed than one gathers from the description in the protocol. I am struck with the fact that there is a tendency to low voltage in the QRS complexes in the limb leads, and small R waves all across the chest with an M-shaped QRS wave in V-5. The rest of the tracing is as stated in the protocol. The electrocardiogram is certainly not diagnostic. If one takes electrocardiograms of a large number of patients with pulmonary emboli, only about 10 per cent show characteristic findings of acute cor pulmonale. Thus, we need not be surprised when the electrocardiogram does not give us the diagnosis even if the patient had, as I assume he did, pulmonary infarcts.

How about the question of myocardial infarction? Certainly this electrocardiogram per se is not diagnostic of either old or recent myocardial infarction, however, it is consistent with coronary-artery disease as well as with other diseases which I do not believe we need go into because there is no other evidence in favor of them. How can the electrocardiogram be so nonspecific in acute myocardial infarction? In the first place, electrocardiograms may occasionally actually revert to normal a few months after the occurrence of a myocardial infarct. The initial episode here was five months before admission. In the second place, the localization of the myocardial infarct may be such that the standard procedure for placing the electrodes in a routine electrocardiogram fails to show the infarction even though present. The electrocardiogram may thus be normal unless special efforts are made to explore the chest thoroughly or unless an esophageal lead is taken. Third, and most important, is that serial electrocardiograms very frequently help to make the diagnosis of myocardial infarction by showing specific changes in pattern where a single tracing is of no help. Apparently, only one electrocardiogram was taken in this case. We can summarize the electrocardiographic findings by saying that although they are not diagnostic they certainly do not rule out an old anterior infarction. They are, in any case, consistent with the presence of coronary-artery disease. They do not show the typical changes of acute cor pulmonale, but we cannot be surprised at this, even in the presence of multiple pulmonary infarcts.

Following the initial episode in the hospital a superficial femoral-vein ligation was done and dicumarol given. We know that superficial femoral-vein ligations are occasionally followed by repeated pulmonary emboli, which also occur after treatment with dicumarol. It is true that superficial femoral-vein ligation is rarely followed by fatal pulmonary emboli, the same reservation holds for adequate treatment with dicumarol. The statement is made that the prothrombin level went as low as 24 per cent. That is not the important point. The point is

whether over the period of treatment it had regularly been kept at a low level, somewhere between 10 and 30 per cent. If the prothrombin percentage gets down to 24 and a few days later it is up to 100, obviously we have inadequate protection for the patient. I think that the remainder of the story here is consistent with pulmonary infarcts despite the therapy that was carried out. The patient developed some cardiac arrhythmia. That may have been stimulated by the pulmonary emboli added to the presence of coronary-artery disease. The last episode before death, I believe, was more likely to have been a pulmonary embolism than myocardial infarction, although the latter is possible.

In summary, then, I believe that this patient had coronary-artery disease, with congestive failure. I believe there is a good possibility, although no proof, that he had myocardial infarction. I still think that the later episodes were pulmonary infarcts despite the dicumarol therapy and venous ligation.

DR WYMAN: It is an unusual story for a pulmonary infarct to increase in size during the course of seven days. We are given the information that it lies against the pleural surface, but that is not entirely clear-cut from this film. I think an additional possibility that one might worry about is tumor of the lungs. I cannot exclude it from this examination.

DR MYERS: I am grateful for your suggestion. Certainly, if there was some enlarging process in the lung atypical of pulmonary infarction, a tumor might help to explain the troublesome fact of marked weight loss in a case in which otherwise there is no definite explanation for it. I suppose the tumor if present, could have been primary in the lung or possibly metastatic from somewhere under the diaphragm. In the latter case, it might explain the gastrointestinal symptoms that the patient had.

DR JOHN B. QUINBY: What would be the source of the pulmonary emboli?

DR MYERS: I suppose from the figures available one could bet on a 75 per cent chance, from the legs and a 25 per cent chance from the heart chambers—in which case the emboli would arise from a mural thrombus.

DR QUINBY: Even with ligation?

DR MYERS: Yes. Only the superficial femoral-vein ligation was performed, the profunda was not included, and also there is the possibility of clots in the iliac vessels and higher up in the pelvis.

A PHYSICIAN: In how many cases of myocardial infarction have you seen the electrocardiogram return to normal?

DR MYERS: I do not know exactly how many do.

A PHYSICIAN: It certainly does occur occasionally, but how many have you seen?

DR MYERS: I cannot answer that. Dr White has some excellent illustrations in his book showing the return of electrocardiograms to normal following myocardial infarctions.

## CLINICAL DIAGNOSES

Arteriosclerotic heart disease  
 Coronary thrombosis, with myocardial infarction  
 Phlebothrombosis of leg, with pulmonary embolism and infarction

## DR MYERS'S DIAGNOSES

Coronary-artery disease, congestive heart failure, probable myocardial infarction  
 Multiple pulmonary infarcts

## ANATOMICAL DIAGNOSES

*Coronary thrombosis, with myocardial infarction*  
 Mural thrombi, left ventricle and both auricles  
*Pulmonary infarcts, multiple, massive*  
 Coronary sclerosis, severe  
 Cardiac hypertrophy  
 Hydrothorax, bilateral  
 Central congestion of liver  
 Renal infarct

## PATHOLOGICAL DISCUSSION

DR CASTLEMAN Autopsy showed an enlarged heart, which weighed 500 gm. The coronary arteries were very severely sclerotic. The left had a pinpoint lumen throughout, and the right was also narrowed but, in addition, contained a recently organized thrombus. The anterior portion of the left ventricle was completely infarcted. The infarction involved the interventricular septum and extended through to involve the right portion of the septum, which is a relatively rare occurrence. There was a large mural thrombus over the infarct on the left side, but none on the right. A piece of this thrombus had apparently broken off and had produced an infarct to one of the kidneys, which may perhaps account for the red cells that were found in the urine. There were mural thrombi also in both auricles so that the emboli in the lungs could be accounted for by the right auricular thrombus. The lungs were the site of numerous infarcts and very large ones, much larger than we usually see. The infarct in the right upper lobe measured 7 cm. in diameter. The increase in size of the x-ray shadow between the two sets of films was due to an infarct in the right middle

lobe that occurred later, and its shadow was superimposed upon that of the upper-lobe lesion. Some years ago Dr. Hampton<sup>2</sup> showed that increase in size and changes in shape of infarcts may be due to other infarcts occurring close by, and that was true in the case under discussion. In addition, the entire upper portion or dorsal division of the right lower lobe and almost the entire left lower lobe were infarcted. These probably occurred after ligation, since they appeared to be redder and more recent than the others. I have the impression, and it is only an impression, that in patients with heart failure that have auricular mural thrombi as a source of emboli, the infarcts are larger than those observed when the emboli arise from the leg veins. This certainly could be borne out in this case.

The liver was enlarged and showed a severe degree of central congestion. It is surprising that he did not develop jaundice with that degree of pulmonary infarction in addition to fairly severe liver disease.

There was about 200 to 300 cc. of straw-colored fluid in the right pleural cavity, and a similar amount on the left. I think it is surprising that one cannot see anything in the left lower lobe that suggests infarct. It measured 16 by 20 cm. at autopsy. Of course, it might well have occurred during the six days between death and the time this film was taken.

DR MYERS How old was the myocardial infarct?

DR CASTLEMAN There were several areas of recent frank necrosis and also areas of granulation tissue. I believe that some foci of infarction could have been two months old.

DR MYERS Were the leg veins examined?

DR CASTLEMAN Yes. At the time of operation no thrombi were found in the superficial femoral veins, and at autopsy the sites of the ligation were perfectly negative. Both profundas were examined and found free from thrombus. We did find a thrombus in the popliteal vein on the right, which I think occurred following ligation.

## REFERENCES

1. White P. D. *Heart Disease*. Third edition. 1025 pp. New York: Macmillan Co. 1944.
2. Hampton A. O. and Castleman B. Correlation of postmortem chest teleroentgenograms with autopsy findings with special reference to pulmonary embolism and infarction. *Am J Roentgenol* 43: 305-326. 1940.

An index of the diagnoses and discussers of the Case Records for the year 1948 will be found elsewhere in this issue of the *Journal*

# The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established 1828

Official Organ of

THE MASSACHUSETTS MEDICAL SOCIETY

and

THE NEW HAMPSHIRE MEDICAL SOCIETY

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND

PUBLISHED WEEKLY UNDER THE JURISDICTION OF THE

COMMITTEE ON PUBLICATIONS

Richard M. Smith M.D. *Chairman*

James P. O'Hare M.D.

Conrad Wesselhoeft, M.D.

Oliver Cope M.D.

John Fallon M.D.

Joseph Garland M.D., Editor

Associate Editors

Thomas H. Lanman, M.D.

Donald Munro M.D.

Henry Jackson Jr., M.D.

Clara D. Davies Executive Editor

Robert O. Leary Assistant Editor

EDITORIAL BOARD

C. Guy Lane M.D.

Maxwell Finlaid M.D.

Henry R. Viets M.D.

James M. Faulkner M.D.

Robert M. Green M.D.

Carroll B. Larsoo M.D.

Dwight O'Hara M.D.

Francis D. Moore M.D.

Fletcher H. Colby M.D.

C. Stuart Welch M.D.

Robert L. Goodale M.D.

Vernoo P. Williams M.D.

Chester M. Jones M.D.

Benjamin Castleman M.D.

Harvey R. Morrissoo M.D.

Hugh R. Leavell M.D.

SUBSCRIPTION TERMS \$7.00 per year in advance postage paid for the United States (medical students, \$4.00 per year) Canada \$8.00 per year (Boston funds) \$9.50 per year for all foreign countries belonging to the Postal Union.

MATERIAL should be received not later than noon on Thursday three weeks before date of publication

THE JOURNAL does not hold itself responsible for statements made by any contributor

COMMUNICATIONS including those concerning classified advertising but not those regarding other advertising should be addressed to the New England Journal of Medicine 8 Fenway Boston 15 Massachusetts Telephone KE 6-2034

NEW ENGLAND ADVERTISING REPRESENTATIVE (except for classified advertising) Edwin B. Tyler 89 State Street, Boston Massachusetts Telephone LA 3 5516

This issue has been prepared in two sections

## A NEW YEAR

HUMILITY, best defined by Webster as "freedom from pride and arrogance," may be of various types and may constitute the mask that hides a variety of underlying patterns. Among these types are the self-debasing humility of the uncompensated inferiority complex, the sinister pseudohumility that characterizes the Uriah Heeps, the arrogant humility of conscious rectitude as expressed in Burton's *Anatomy of Melancholy* — "They are proud in humility, proud in that they are not proud."

There is also the honest humility of true magnanimity, fearless because it makes no pretence recognizing superior assets and capacities in others acknowledging powers higher than those that

humankind possesses, and admitting the likelihood that even the most capable person may sometimes be in error. It is a humility of the intellect free from pride and arrogance.

One of the errors to which any person of ambition may be liable — and the higher his road is built the deeper are the ditches that flank it — is the development of a belief in his own infallibility. Too often a genuine call to service turns with the passage of time and under the influence of personal prestige into a sense of superiority over those served. Too frequently a long period of unchallenged leadership may betray the leader into a belief in the permanence of his own position, even in his inability to make the wrong judgment. Obsessed with this feeling of unassailable righteousness, he unconsciously assumes the mantle of perfection and with it something in the way of self-bestowed divinity. In his estimation of himself he has caught up with God.

Especially vulnerable to this particular loss of perspective are those who have been drawn into fields of activity in which personal influence is a strong factor. Among these are politicians with their constituents, writers with their readers, teachers with their pupils, pastors with their parishioners, physicians with their patients. A penalty attached to their sometime loss of humility as expressed by an eminent preacher, is that they doubt God when it is themselves that they should doubt.

To them might be recalled the words of Cromwell to Parliament, the members of which he beseeched at one time to bear in mind that they "might be mistaken."

So for everyone a resolution with which to start a new year might be to bear in mind that he may be mistaken that true humility is a virtue that can be cultivated, and that conscious and outspoken humility is its own contradiction.

## MILESTONES

RELEASES from public-relations counsel at times seem like those from the butcher, replete with the lard of "significance" but shy of the lean of meaning. The copywriter's incomplete comparative is familiar: the better refrigerator, the better homes

and gardens, the better postwar automobiles Better than what? Attention is now invited by a Detroit committee of the automobile industry to a "significant" milestone, the production of a hundred million motor vehicles A significant milestone, it may be asked, on what road?

Since the first car, fifty-five years ago, production has been at an annual rate of nearly 2,000,000 vehicles until today more than 40,000,000 cars, trucks and busses crowd the nation's highways, one for every four persons in the United States Every minute of each working day sees 30 new cars and 10 new trucks and busses The second hundred millionth milestone should be reached in only twenty-five more years This informative committee avers that research and mass production have cut costs and increased sales, and in turn have increased employment, raised the nation's standard of living and expanded retail trade areas, indeed, whole new industries dependent upon this new flexible transportation tool have been developed Since the horseless-carriage tinkers have come out of their alleys and quit selling bicycles, the labor, the ingenuity and the lives of millions of Americans have been absorbed in the making, selling and servicing of automobiles Many thousands of other lives, it may be stated without exaggeration, have needlessly been sacrificed as a result of their labors

Comment has been made on accidents as a leading cause of death<sup>1 2</sup> The all-time prewar record for deaths from automobile accidents was nearly 40,000 in 1941 Although in actual numbers heart disease and cancer are the primary killers, Dickinson and Welker<sup>3</sup> question the adequacy of numbers of deaths as the sole measure of the relative importance of the various causes Two new measurements are suggested "life years lost" and "working years lost" When the latter was applied to the seven leading causes of death in four five-year periods, 1930 to 1945, accident, as a destroyer of working years, was third in 1930, second in 1935 and first in 1940 In 1945, during gas rationing, the working years lost from accidental death numbered 1,750,000, whereas those from heart disease were 1,680,000 The young white man, representing the productive strength of the country, was the

special victim It is not implied that all, but only that too many, accidental deaths are due to the automobile One hundred million cars, trucks and busses, and 40 more per minute! This significant milestone in the production line is also a marker on the broad way that leads to destruction

Free enterprise and fierce competition within the industry, the committee believes, is responsible for this triumph of mass production It is suggested, on the other hand, that the achievement marks a point on the errant road of reason Since that fall day in 1793 when a popular actress was crowned goddess of reason in Notre Dame—and in spite of the bad consciences of Robespierre and others—the modern world has believed in and depended upon reason alone In those early days revolutionary reason was most concerned with ends The ends were utopian truth, justice and enlightened self-interest would bring automatic harmony between individuals and society in nature As absolutism and authoritarianism were crushed, new creative activity was released, bringing rapid advances in politics, economics, education and technics With apparently complete success of republicanism and industrialism in the nineteenth century, revolutionary reason or the reason of ends was sacrificed to technical reason or the reason of means This technical reason has produced the present large-scale, industrial, competitive, mass-producing economy rising above physical nature and man himself and its heretical counterpart the totalitarian state with its "planning reason"<sup>4</sup> The hundred millionth motor vehicle is the crown of technical knowledge

This apogee of the assembly line, it is agreed, is a milestone of some sort Yet 40,000 deaths a year is only a pace on the way of man against himself, since the atom bomb can do twice or three times as well in the twinkling of an eye This record production of automobiles is a signal achievement on the road of technical reason, but this road remains the blind alley of men's hope Nevertheless, whatever road it is, the automobile industry should be joined in their self-congratulation on their milestone Let the public-relations counsel tot up the blessings of industrial culture at this season! One looks hopefully for a release from someone about a milestone,

however insignificant, on the straight and narrow path that leads to peace and good will among men

### REFERENCES

- 1 Editorial. Leading causes of death. *New Eng J Med* 239 71 1948
- 2 Editorial. Public health and diseases of old age. *New Eng J Med* 239 487 1948
- 3 Medical Economics. What is leading cause of death? *J A M A* 138 528 1948
- 4 Tillich P J. World situation. In *Christian Answer*. Edited by H P Van Dusen. 195 pp. New York: Charles Scribner & Sons. 1946

## HANDKERCHIEFS AND THE TRANSFER OF RESPIRATORY INFECTIONS

"Don't put a cold in your pocket" is a slogan used by manufacturers of disposable tissues and designed to sell the public on the idea of substituting their product for the traditional handkerchief. The use of the latter, however, has long been thought to be an effective means of protecting others from infections. A sneeze or cough not protected by a handkerchief has been considered by many as tantamount to a direct assault on the health of one's neighbors—a sort of peacetime version of bacterial warfare. Some recent considerations of the possible role of the handkerchief in the spread of respiratory infections may provide further ammunition for the sales talks against the handkerchief although they offer little solace when it comes to the virtues of the tissues.

In one of the latest studies to be reported in this connection,<sup>1</sup> an estimate was made of the number of bacteria-carrying particles that can be shaken into the air from the handkerchiefs of people with and without nasal discharge. The average number of such particles in a series of 211 handkerchiefs was about 130,000. The particles were large enough to suggest that they each carried a number of bacteria. The predominant organism recovered was *Staphylococcus aureus* and corresponded with those found in cultures of nasal swabs or of the skin of the same subjects. In some cases nonhemolytic streptococci similar to those of the throat and mouth flora were found.

This study was carried out at the Harvard Hospital in England, where investigations are being conducted on the transmission of the common cold. Interestingly enough, there was but small difference between the average counts of infected particles shaken from the handkerchiefs of persons without

nasal discharge and the counts of those with nasal discharge that was either slight, profuse or even purulent.

Because of the recent great interest in aerial disinfectants, studies were made of the effects of some of these agents on the bacteria shed from the handkerchiefs into the air. The infectious particles were found to be resistant to the action of several of the more potent of these aerial disinfectants, including ultraviolet rays and triethylene glycol, employed in the usual concentrations and at normal relative humidities.

Hamburger and Green<sup>2</sup> had previously called attention to the problem of the dangerous carriers of hemolytic streptococci when they found that large numbers of these bacteria could be recovered from the hands of nasal carriers. Hamburger<sup>3</sup> subsequently reported that literally hundreds of thousands of virulent hemolytic streptococci could frequently be recovered from the hands of such carriers. Furthermore, several hundred to almost 50,000 of these pathogens could be transferred to the hands of a noncarrier by an ordinary handshake. The greatest numbers were transferred by carriers who had just blown their noses into sterile handkerchiefs.

Although these experiments were not repeated with materials other than handkerchiefs, it is quite certain that the results would not have been very different had the subjects blown their noses into the best advertised of tissues and discarded them instead of using sterile handkerchiefs, which they would then have put into their pockets.

### REFERENCES

- 1 Dumbell K R, Lovelock J E and Lowbury E J. Handkerchiefs in transfer of respiratory infection. *Lancet* 2 185-185 1948
- 2 Hamburger M Jr and Green M J. Problem of dangerous carrier of hemolytic streptococci. IV. Observations upon role of hands of blowing nose, of sneezing and of coughing in dispersal of microorganisms. *J Infect Dis* 79 7-44 1946
- 3 Hamburger M Jr. Transfer of beta hemolytic streptococci by shaking hands. *Am J Med* 2 21-25 1947

## INFANT INVESTIGATOR

It is hard to realize that Dr Arnold Gesell, after thirty-seven years on the Yale faculty during most of which time he has been director of Yale's famous Clinic of Child Development, has retired—in order to expand his works still further. Some of Dr Gesell's books, of which there are a full two dozen,

have been the vade mecum of the intellectual young mother, determined that she will rear only superior children. All of them, reporting on territory explored largely by their author, have been enlightening texts on infant behavior and books of reference for the pediatrician and the psychologist.

If one lesson only that Dr. Gesell taught were to be selected as his greatest contribution, it would be that each infant is a person, with its own appetites and satisfactions, its own capacities and its own built-in timing mechanism.

Dr. Gesell, now that he has demonstrated to the world all there is at present to know about child behavior (from the age of four months on), will continue his investigations at Yale University in charge of a child vision research project, under a grant from the American Optical Company. Those who have taken to heart the injunction that where there is no vision the people perish will rejoice that this work is to be under such able direction. Dr. Gesell's pupils, disciples and other fans will wish him continued success in his new work. They may perhaps, looking a long way back, be reminded of another investigator in better vision to whom has been given the credit for the invention of spectacles—Roger Bacon, the Dr. Mirabilis of his day.

## MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

### CHANGES IN ISOLATION AND QUARANTINE REQUIREMENTS

The Department has recently made a number of changes in the list of reportable diseases and in the isolation and quarantine requirements. These changes will go into effect as soon as a printing of the revised regulations can be obtained and distribution made to boards of health, school departments, hospitals and other agencies.

To inform physicians of these changes, the following brief résumé is included in this column.

Infectious hepatitis has been added to the list of reportable diseases, hookworm disease, lobar pneumonia and suppurative conjunctivitis have been removed from the list.

Hereafter, there will be no differentiation in the handling of immune and nonimmune contacts of communicable diseases.

*Poliomyelitis* The term "poliomyelitis" will be used instead of the former designation, "anterior poliomyelitis." This will change the order of the disease in the list and in the table of isolation and

quarantine requirements. The deletion of the phrase "and thereafter until acute symptoms have subsided" leaves the isolation of the patient as a period of two weeks from the onset of the disease. All restrictions upon contacts, whether adults or children, have been removed. A placard will no longer be required for the disease.

*Chancroid* There will be no restrictions upon contacts of this disease.

*Chicken pox* The period of isolation will be seven days from the appearance of the eruption.

*Diphtheria* The minimum time limit of one week for isolation of the patient has been eliminated. The patient will be isolated until clinical recovery and the obtaining of negative cultures. There will be no restrictions upon adult contacts of diphtheria, but child contacts will be excluded from school for one week after the patient has been hospitalized or until the child has lived away from home for one week.

*Granuloma inguinale* There will be no restrictions upon contacts of patients with this disease.

*Infectious hepatitis* Patients will be isolated for the duration of fever. There will be no restrictions upon contacts.

*Leprosy* There will be no isolation of patients with leprosy.

*Lymphogranuloma venereum* There will be no restrictions upon contacts of patients with this disease.

*Meningitis, meningococcal* Patients will be isolated for only three days from the beginning of adequate sulfonamide therapy. There will be no restrictions upon contacts.

*Meningitis, other forms* No isolation will be imposed upon cases of meningitis due to organisms other than the meningococcus.

*Mumps* The patient with mumps will be isolated for a week from the onset of the disease, the reference to swelling of the salivary glands being eliminated from the regulations.

*Ophthalmia neonatorum* Infants with infected eyes will be isolated only until two negative smears or cultures to rule out gonococcal ophthalmia have been obtained.

*Salmonellosis* All paratyphoid infections will be included under this designation.

*Plague* The new regulations place restrictions upon contacts of patients with plague only in pneumonic cases, in which the contacts are quarantined for seven days after the last exposure.

*Scarlet fever* Isolation of both adults and children has been reduced to one week from appearance of the rash, and thereafter until clinically recovered, and until purulent discharges, if any, have ceased. Children may be allowed to go to school within one week after patient has been under adequate treatment, or the patient has been hospitalized.

*Whooping cough* There will be no restrictions upon contacts of patients with whooping cough.

## CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

The January schedule for Consultation Clinics for Crippled Children in Massachusetts under the provisions of the Social Security Act follows:

CLINIC	DATE	CLINIC CONSULTANT
Salem	January 3	Paul W. Hugenberger
Haverhill	January 5	William T. Green
Lowell	January 7	Albert H. Brewster
Greenfield	January 10	Charles L. Sturdevant
Gardner	January 11	Carter R. Rowe
Brockton	January 13	George W. Van Gorder
Springfield	January 18	Garry deN. Hough, Jr.
Pittsfield	January 19	Frank A. Slowick
Hvannis	January 20	Paul L. Norton
Worcester	January 21	John W. O'Meara
Fall River	January 24	David S. Grice

Physicians referring new patients to clinics should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

## CORRESPONDENCE

### A CORRECTION

To the Editor: In an excellent review of the book *Hodgkin's Disease and Allied Diseases* by Parker and Jackson in the December 2 issue of the *Journal* there are two factual errors. The review is clearly written by a man of experience and knowledge so that these errors may easily have slipped into the preparation of the manuscript. Nevertheless, I believe that they should be corrected. In the review it is stated that we suggest dropping the term endothelioma, which was not intended. We do require a complete autopsy before such a diagnosis is made, for endothelioma, frequent in Java, may very closely simulate undifferentiated carcinoma and unless this condition can be ruled out we believe a diagnosis of endothelioma is unwise. Secondly, the reviewer, though twice using the term giant-follicle lymphoma, once refers to giant-follicle lymphosarcoma. In our opinion "giant-follicle lymphosarcoma" does not and, indeed, cannot exist, even though practically all students of the subject agree that giant-follicle lymphoma frequently progresses, with the passage of time, into lymphosarcoma. The diagnosis, treatment and prognosis is then that of the latter condition — lymphosarcoma.

HENRY JACKSON, JR., M.D.

Mallory Institute of Pathology  
Boston City Hospital

## BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

*History of the Medical Society of the District of Columbia. Part II, 1833-1944.* History Committee. John Benjamin Nichols, chairman, William Johnston Mallory and Joseph Stiles Wall, eds., cloth, 357 pp., with 13 illustrations and frontispiece. Baltimore: Waverly Press, Incorporated, 1947.

This second volume of the history of the Society continues the narrative to approximately July 1, 1944. All the activities of the Society are covered, and a list of members from 1833 to 1911 is appended to the text. Two indexes with subjects and personal names conclude the volume. The book is well published and is recommended for history of medicine collections.

*Gardiner's Handbook of Skin Diseases.* Revised by John Kinnear, O.B.E., T.D., M.D., M.R.C.P. (Ed.), D.L., lecturer in diseases of the skin, St. Andrews University, physician for diseases of the skin, Dundee Royal Infirmary, and derma-

tologist, pre-school and school medical services, Dundee. Fifth edition, 12° cloth, 250 pp. with 80 illustrations and colored plates. Baltimore: The Williams and Wilkins Company, 1948. \$4.50.

This fifth edition of a popular manual, first printed in 1919, has been revised to bring it up to date since the printing of the third edition in 1939. The text was printed in Great Britain and bound in the United States. The volume reflects the British aspect of dermatology.

*The Year Book of Pathology and Clinical Pathology.* "Pathology," editor, Howard T. Karsner, M.D., professor of pathology, director of the Institute of Pathology, Western Reserve University, Cleveland, assistant editor, Herbert Z. Lund, M.D., assistant professor of pathology, Western Reserve University, Cleveland. "Clinical Pathology," editor, Arthur H. Sanford, M.D., professor of clinical pathology, University of Minnesota (The Mayo Foundation), and senior consultant, Division of Clinical Laboratories, Mayo Clinic. 12°, cloth, 558 pp., with 102 illustrations. Chicago: The Year Book Publishers, Incorporated, 1948. \$3.75.

*The Year Book of Pathology* ceased publication in 1941 because of war and post-war conditions. It has now been resumed, and the present volume abstracts the literature for the year 1947. The volume is well published and is recommended for all medical libraries and to persons interested in the subject.

*Ophthalmology in the War Years.* Edited by Meyer Wiener, M.D., professor of clinical ophthalmology, Washington University School of Medicine, and honorary consultant in ophthalmology, Bureau of Medicine and Surgery, United States Navy. Volume II (1944-June, 1946). 8°, cloth, 997 pp. Chicago: The Year Book Publishers, Incorporated, 1948. \$16.00.

This second volume attempts to include in the reviews everything of importance published during the period of two and a half years from 1944 to June, 1946. Thirty-seven persons have contributed to the volume. A few chapters not in the first volume have been added to make the work complete and up to date. Articles not discussed in the reviews have been listed in the bibliographies appended to the chapters. Comprehensive indexes of subjects and authors conclude the volume. The type and paper are good, and the printing excellent. The work is recommended for all medical libraries and ophthalmologists.

*Essentials of Fevers.* By Gerald E. Breen, M.D., B.Ch. (NUI Dub.), D.P.H., D.O.M.S. (R.C.P. Lond., R.C.S. Eng.). Second edition, 16°, cloth, 351 pp., with 23 illustrations and 17 plates. Baltimore: The Williams and Wilkins Company, 1948. \$4.50.

This second edition of a manual, first published in 1939, has been revised to include new sections on typhus glandular and undulant fevers, influenza and encephalitis lethargica. Additions have been made to the chapters on sore throat and food poisoning. The article on dysentery has been rewritten and expanded. Color plates have been included for the first time. The type, printing and paper are good (the book was printed in Great Britain). The manual should prove useful as a reference source for the general practitioner.

*Conference on Metabolic Aspects of Corroscence.* Transactions of the fifteenth meeting. Edited by Edward C. Reifstein, Jr., M.D., 8°, paper, 163 pp., with 35 illustrations. New York: Josiah Macy, Jr. Foundation, 1947. \$2.25.

This conference was featured by a symposium on the isotopes with fourteen persons participating. Eighteen other persons contributed discussions on various aspects of metabolism. The different conferences of the Macy Foundation should be in all medical libraries.

## NOTICES

JOSEPH H PRATT  
DIAGNOSTIC HOSPITAL

30 Bennet Street, Boston  
Lecture Hall, 9-10 a m

## MEDICAL CONFERENCE PROGRAM

Tuesday, January 4 — Vitamin B<sub>12</sub> Therapy in Pernicious Anemia Dr Abraham Frumin

Friday, January 7 — Carcinoma of the Cervix Dr Howard Ulfelder

Wednesday, January 12 — Pediatric Clinicopathological Conference Drs James M Baty and H E MacMahon

Friday, January 14 — Differential Spinal Block Dr Stanley J Sarnoff

Tuesday, January 18 — *Journal* review

Friday, January 21 — Simplified Blood Sugar Screening Method Dr Hugh L C Wilkerson

Tuesday, January 25 — The Clinical Use of Washed Red Cell Transfusions Dr Jacob Neber

Friday, January 28 — The Use of Tests that Measure Hepatic Excretory Functions Dr Albert I Mendeloff

On Tuesday morning, January 11, from 9 to 10 o'clock and on Wednesday mornings, January 5, 19 and 26, from 9 to 10 o'clock, Dr S J Thannhauser will give medical clinics on hospital cases. On Thursday mornings from 9 to 10 o'clock clinics will be given by Dr William Dameshek.

On the second and fourth Fridays of the month, January 14 and 28, therapeutic conferences will be held with round-table discussion from 2 to 4 o'clock (Dr Robert P McCombs, moderator). On the second and fourth Fridays, January 14 and 28, Dr Merrill Sosman will conduct x-ray conferences from 4 to 6 o'clock. On Saturday mornings from 9 to 10 o'clock surgical clinics will be given by Dr C Stuart Welch. Medical rounds are conducted each weekday except Saturday by members of the hospital staff from 12 to 1 o'clock.

All exercises are open to the medical profession

NEW ENGLAND HOSPITAL FOR  
WOMEN AND CHILDREN

The monthly clinical conference and meeting of the staff of the New England Hospital for Women and Children will be held on Thursday, January 6, at 7 15 p m in the classroom of the Nurses' Residence. Dr Cleveland Floyd will speak on the subject "Miliary Tuberculosis." Dr Pauline Luzackas will be chairman.

## NEW ENGLAND HEART ASSOCIATION

A meeting of the New England Heart Association will be held in the amphitheater of the Dowling Building, Boston City Hospital, on Monday, January 10, at 8 15 p m, Dr Laurence B Ellis presiding.

## PROGRAM

Functional Renal Insufficiency Precipitated in Patients with Congestive Failure by Sodium Depletion Drs Frank Drinan and Kermit H Katz

Mitral Stenosis, with Special Reference to Surgical Intervention

Clinical-Physiologic Correlations Drs Laurence B Ellis, J G Mebane, George Maresh, W K Long, and R A Bloomfield

Experimental Studies on Mitral-Valve Function Dr Leona R Norman

Surgical Aspects Dr Dwight E Harken

Thrombosis in Arteriosclerosis of the Lower Extremities Dr Edward A Edwards

Interested physicians and medical students are cordially invited to attend

NEW ENGLAND SOCIETY OF  
ANESTHESIOLOGISTS

A meeting of the New England Society of Anesthesiologists will be held in the Auditorium of Building A, Boston University School of Medicine, 80 East Concord Street, Boston, on Tuesday, January 11, at 8 00 p m. The scientific program will consist of the following:

Changes in Body Fluid Chemistry as They Affect Pre-operative and Postoperative Care Francis D Moore, M D

The Clinical Aspects of Pulmonary Atelectasis Cutting B Favour, M D

Pathologic Aspects of Postoperative Pulmonary Atelectasis Joseph D Boggs, M D

Aspiration Bronchoscopy in the Treatment of Post-operative Pulmonary Atelectasis William S Derrick, M D

Physicians and medical students are invited

## HARVARD MEDICAL SOCIETY

A meeting of the Harvard Medical Society will be held in the amphitheater of Building D, Harvard Medical School, on Tuesday, January 11 at 8 00 p m. The chairman for the evening is Dr Raymond D Adams.

## PROGRAM

The Correlation between Morphologic and Functional Disorders in the Motor-Nerve Cells in Poliomyelitis Derek E Denny-Brown and Joseph M Foley

An Encephalomyelitic Virus of Mice Causing Demyelinating Lesions of the Central Nervous System F Sargent Cheever, O T Bailey and A M Pappenheimer

Pathological Changes in Carbon Monoxide Poisoning Charles S Kubik

Subsequent meetings will be held on February 8, March 8, April 12 and May 10

## SUFFOLK DISTRICT MEDICAL SOCIETY

The third medicolegal meeting of the Suffolk District Medical Society and the Boston Bar Association will be held in Ware Hall, Boston Medical Library, on Wednesday, January 12, at 8 p m. Dr Alan R Moritz will speak on the subject "Scientific and Medical Tests in Legal Proceedings," which will be discussed by Mr Arthur F Bickford, prominent Boston trial lawyer.

## NEW ENGLAND PEDIATRIC SOCIETY

The annual meeting of the New England Pediatric Society will be held on Wednesday, January 26.

After the business meeting of the evening, Dr Bronson Crothers will speak on the subject, "The Position of the Pediatrician in Relation to Specialists of Various Categories, Present and Impending."

Further details concerning the meeting will be forthcoming at a later date.

UNIVERSITY OF WISCONSIN SYMPOSIUM ON  
SCIENCE AND CIVILIZATION

As part of the general celebration of the centennial anniversary of the University of Wisconsin, the University's History of Science Group is sponsoring a symposium on "Science and Civilization." This symposium will be held January 13-15 at the Memorial Union of the University of Wisconsin in Madison.

## MISSISSIPPI VALLEY MEDICAL SOCIETY

The annual meeting of the Mississippi Valley Medical Society will be held at the Jefferson Hotel, St. Louis, Missouri, from September 28 to 30, under the presidency of Dr Alphonse McMahon, of St. Louis University.

(Notices concluded on page vii)

## NOTICES (Concluded from page 1060)

## AMERICAN MEDICAL ASSOCIATION COUNCIL ON MEDICAL EDUCATION AND HOSPITALS

The forty-ninth annual congress on medical education and licensure will be held in the Red Lacquer Room, Palmer House, Chicago, on February 7 and 8. The fourth annual conference on rural health (sponsored by the Committee on Rural Health of the American Medical Association), will be held in the Red Lacquer Room, Palmer House, Chicago on February 4 and 5 from 9 30 a m to 5 00 p m. On February 6 the Advisory Board for Medical Specialties will hold an open meeting in the Crystal Room, Palmer House, Chicago (time to be announced later). From 9 30 a m to 5 00 p m the National Conference on Medical Service, sponsored by officers of state medical societies, will be held in the Red Lacquer Room, Palmer House, Chicago.

## MISSISSIPPI VALLEY MEDICAL SOCIETY 1949 ESSAY CONTEST

The Ninth Annual Essay Contest of the Mississippi Valley Medical Society will be held in 1949. The society will offer a cash prize of \$100.00, a gold medal, and a certificate of award for the best unpublished essay on any subject of general medical interest (including medical economics and education) and practical value to the general practitioner of medicine. Certificates of merit may also be granted to the physicians whose essays are rated second and third best. Contestants must be members of the American Medical Association who are residents and citizens of the United States. The winner will be invited to present his contribution before the Fourteenth Annual Meeting of the Mississippi Valley Medical Society to be held in St. Louis, Missouri, September 28, 29 and 30, 1949, the society reserving the exclusive right to first publish the essay in its official publication—the *Mississippi Valley Medical Journal* (incorporating the *Radiologic Review*). All contributions shall be typewritten in English in manuscript form, submitted in five copies, not to exceed 5000 words, and must be received not later than May 1, 1949. The winning essays in the 1948 contest appear in the January 1949 issue of the *Mississippi Valley Medical Journal*. Further details may be obtained from Harold Swanberg, M.D., Secretary, Mississippi Valley Medical Society, 209-224 W C U Building, Quincy, Illinois.

## SOCIETY MEETINGS AND CONFERENCES

## CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, JANUARY 6

## THURSDAY JANUARY 6

7 15 p m Monthly Clinical Conference and Staff Meeting New England Hospital for Women and Children Classroom of Nurses Residence

## FRIDAY JANUARY 7

9 00-10 00 a m. Carcinoma of the Cervix. Dr Howard Ulfelder Joseph H Pratt Diagnostic Hospital

9 00 a m -12 00 m. Combined Medical and Surgical Staff Rounds Peter Bent Brigham Hospital

12 00 m. X-Ray Conference Margaret Jewett Hall Mt. Auburn Hospital Cambridge

## MONDAY JANUARY 10

12 15-1 15 p m. Clinicopathological Conference Main Amphitheater Peter Bent Brigham Hospital

8 15 p m New England Heart Association Amphitheater Dowling Building Boston City Hospital

## TUESDAY JANUARY 11

12 15-1 15 p m. Clinicorontgenological Conference Peter Bent Brigham Hospital

1 30-2 30 p m. Pediatric Rounds Burnham Memorial Hospital for Children Massachusetts General Hospital

8 00 p m New England Society of Anesthesiologists Auditorium of Building A Boston University School of Medicine

8 00 p m Harvard Medical Society Amphitheater Building D Harvard Medical School

## WEDNESDAY JANUARY 12

9 00-10 00 a m. Pediatric Clinicopathological Conference Drs James M. Baty and H. E. MacMahon Joseph H Pratt Diagnostic Hospital

11 00 a m -12 00 m Medical Rounds Amphitheater Children's Hospital

\*12 00 m.-1 00 p m. Clinicopathological Conference (Children's Hospital) Amphitheater Peter Bent Brigham Hospital.

\*2 00-3 00 p m. Combined Clinic by the Medical Surgical and Orthopedic Services Amphitheater Children's Hospital

8 00 p m. Medicolegal Meeting Suffolk District Medical Society and the Boston Bar Association Ware Hall Boston Medical Library

\*Open to the medical profession

JANUARY 4-28 Joseph H. Pratt Diagnostic Hospital. Medical Conference Program Page 1060

JANUARY 6 New England Hospital for Women and Children Page 1060

JANUARY 7-APRIL 15 1949 American College of Surgeons Sectional Meetings. Page 11 issue of December 23

JANUARY 10 New England Heart Association Page 1060

JANUARY 11 Harvard Medical Society Page 1060

JANUARY 11 New England Society of Anesthesiologists Page 1060

JANUARY 12 Suffolk District Medical Society Page 1060

JANUARY 15 The Present Status of the Peptic Ulcer Problem Dr S Allan Wilkinson Pentucket Association of Physicians 8:30 p m Haver hill

JANUARY 13-15 University of Wisconsin Symposium on Science and Civilization Page 1060

JANUARY 26 New England Pediatric Society Page 1060

JANUARY 27-29 American Association of Schools of Social Work Page 984 issue of December 16

MARCH 7-9 American Academy of General Practice Page 728 issue of November 4

MARCH 28-APRIL 1 American College of Physicians. Page 158 issue of July 22

MAY 16-19 American Urological Association Biltmore Hotel Los Angeles California

MAY 24-26 Massachusetts Medical Society Annual Meeting Worcester Memorial Auditorium Worcester

MAY 26-28 American Gaiter Association Hotel Lorraine Madison Wisconsin

MAY 30-JUNE 3 International Congress on Rheumatic Diseases Page 500 issue of November 18

SEPTEMBER 28-30 Mississippi Valley Medical Society Page 1060

NOVEMBER 11-17 Third Inter American Congress of Radiology Page 158 issue of July 22

## DISTRICT MEDICAL SOCIETIES

## HAMPDEN

JANUARY 25 8 30 p m Academy of Medicine Springfield A Review of the Sterility Problem. Dr John Rock

APRIL 26 6 00 p m Hotel Highland Springfield. (Dinner Meeting) Convulsive Disorders Dr Douglas T Davidson

## HAMPSHIRE

JANUARY 5 4 30 p m. Experiences on a Medical Mission in Europe Dr Alexander M Burgess

MARCH 2 4 30 p m. The Present Status of Treatment of Coronary Disease Dr Clarence E de la Chapelle

MAY 4 Annual Meeting and Election of Officers.

## MIDDLESEX EAST

JANUARY 19

MARCH 23

MAY 11

## SUFFOLK

JANUARY 12 Joint Medicolegal Meeting with Boston Bar Association Ware Hall Boston Medical Library Scientific and Medical Tests in Legal Proceedings Dr Alan R. Montz.

## WORCESTER NORTH

FEBRUARY 25 Burnham Hospital Fitchburg

APRIL 27 Annual Meeting

## TWO-WAY PROTECTION

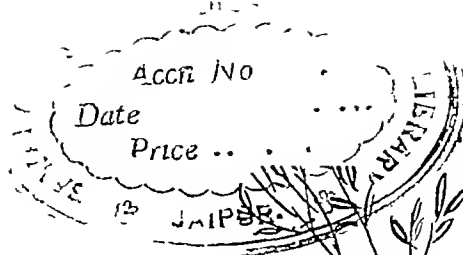
## Tablets FERROSATE (Kenmore)

(Ferrous Sulfate, gr 17)

are coated twice to provide a doubly protected Ferrous Sulfate offering these therapeutic advantages

- 1 Inner coating prevents premature oxidation in vivo
- 2 Outer coating increases palatability and aids in preventing tooth discoloration

Write Dept. A12 for professional sample  
Kenmore Pharmacy, Inc.  
500 Commonwealth Ave.  
Boston, Mass. U.S.A.



## Old Way...

### CURING RICKETS in the CLEFT of an ASH TREE

FOR many centuries,—and apparently down to the present time, even in this country—ricketic children have been passed through a cleft ash tree to cure them of their rickets, and thenceforth a sympathetic relationship was supposed to exist between them and the tree.

Frazer\* states that the ordinary mode of effecting the cure is to split a young ash sapling longitudinally for a few feet and pass the child, naked, either three times or three times three through the fissure at sunrise. In the West of England, it is said the passage must be "against the sun." As soon as the ceremony is performed, the tree is bound tightly up and the fissure plastered over with mud or clay. The belief is that just as the cleft in the tree will be healed, so the child's body will be healed, but that if the rift in the tree remains open, the deformity in the child will remain, too, and if the tree were to die, the death of the child would surely follow.

\*Frazer, J. G.: *The Golden Bough*, vol. 1, New York, Macmillan & Co., 1923.



It is ironical that the practice of attempting to cure rickets by holding the child in the cleft of an ash tree was associated with the rising of the sun, the light of which we now know is in itself one of Nature's specifics.

## New Way...

### Preventing and Curing Rickets with OLEUM PERCOMORPHUM

NOWADAYS, the physician has at his command, Mead's Oleum Percomorphum, a Council-Accepted vitamin D product which actually prevents and cures rickets, when given in proper dosage.

Like other specifics for other diseases, larger dosage may be required for extreme cases. It is safe to say that when used in the indicated dosage, Mead's Oleum Percomorphum is a specific in almost all cases of rickets, regardless of

degree and duration. Mead's Oleum Percomorphum because of its high vitamins A and D content is also useful in deficiency conditions such as tetany, osteomalacia and xerophthalmia.

\* \* \*

#### COUNCIL-ACCEPTED

Oleum Percomorphum With Other Fish Liver Oils and Viosterol. Contains 60,000 vitamin A units and 8,500 vitamin D units per gram and is supplied in 10 c.c. and 50 c.c. bottles; and in bottles containing 50 and 250 capsules.

MEAD JOHNSON & COMPANY, Evansville, Indiana, U S A

Please enclose professional card when requesting samples of Mead Johnson products to co-operate in preventing their reaching unauthorized persons.

